https://doi.org/10.15407/exp-oncology.2023.02.151

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EVALUATION OF CURRENT FACTORS OF RADIATION-ASSOCIATED CARCINOGENESIS

The widespread introduction of nuclear technologies in industry, medicine, science, etc. increases the number of professionals subjected to additional radiation exposure. Moreover, the problem of occupational cancer is the most complicated in occupational pathology due to the multifactorial nature of the etiology of this disease. The radiation accidents in Chornobyl and Fukushima-1 showed that nuclear reactors cannot guarantee absolutely safe operation. At present, the threat of nuclear terrorism is increasing. Occupational radiation exposure and its consequences are also of great concern worldwide. Based on the literature data and our own studies on the effects of various types of radiation exposure, especially stochastic effects of radiation, it seems reasonable to develop a scientific basis for the optimization of radiation protection of various categories of population, first of all, medical personnel and patients. The complex assessment of radiation risks and reconstruction of the total ionizing radiation dose from all types of irradiation will allow optimizing radiation protection of the population and reducing carcinogenic risk..

Keywords: radiation-induced carcinogenesis, irradiation, radiation therapy, ionizing radiation.

Systematic and in-depth studies of the effects of ionizing radiation (IR) on the human body and health began in the middle of the last century, 5 years after the atomic bombing of Hiroshima and Nagasaki in Japan. The First International Conference on the peaceful uses of atomic energy (Geneva, 1955) sparked the worldwide interest in the development of nuclear power plants (NPPs). This would eventually lead to a significant increase in the number of people exposed to radiation at their workplace and thus to the increased radiation and carcinogenic risks. In addition, the radiation accidents in Chornobyl and Fukushima-1 (Japan, Honshu Island) have shown that nuclear reactors cannot guarantee absolutely safe operation. At present, the threat of nuclear terrorism significantly increases the radiation danger to the population.

Citation: Domina EA, Kopylenko OL, Chekhun VF. Evaluation of the current factors of radiation-associated carcinogenesis. *Exp Oncol*. 2023; 45(2): 151-160. https://doi.org/10.15407/exp-oncology.2023.02.151

At present, the main components of human radiation exposure are recognized as the following:

- global fallout of nuclear test products — 0.77%;
- nuclear power generation — 0.03%;
- use of air transport — 0.1%;
- use of fluorescent products — 0.1%;
- IR sources in medicine — 34%;
- natural radiation background — 23%;
- indoor exposure due to radon and thoron decay products — 42%.

The carcinogenic effects of IR have been proven in numerous experimental and epidemiological studies. IR exerts potent immune suppressor and carcinogenic effects. Moreover, irradiation in the low dose range is capable of inducing genetic abnormalities that later cause the development of cancer. Therefore, accounting only for early post-irradiation changes with ignoring the effects of low-dose IR is not reasonable. The large-scale studies [1] on a cohort of liquidators of the consequences of the Chornobyl NPP accident confirm the main concept of radiation carcinogenesis, according to which low (above background) radiation doses represent a carcinogenic risk factor [2]. It should be noted that as a result of the Chornobyl NPP accident, issues of radiation hazards became a subject of close attention.

A number of radioecological issues should be considered. Particularly, the unpredicted level of formation of strontium-90 radionuclides, the impact of highly toxic americium-241, which is actively included in trophic chains with predominant accumulation in parenchymatous organs, the decay of fuel particles with the formation of easily accessible forms of radionuclides require permanent correction in the assessment of the radioecological situation. The transuranic elements deserve special attention, with their long-term negative effects on the health of the population. One should not exclude the increase in the radiation background in many regions due to the active development of the nuclear industry, nuclear fuel disposal, etc.

The widespread introduction of nuclear technologies in industry, medicine, science, etc. increases the number of professionals subjected to additional radiation exposure. Moreover, the problem of occupational cancer is without exaggeration the most complicated in occupational pathology due to its multifactorial etiology [3].

Thus, the radioecological situation that has developed in Ukraine highlights the necessity of updating the national program for overcoming the consequences of the Chornobyl catastrophe which should include the development and implementation of personalized programs for the prevention of radiation-associated diseases, including cancer.

The problems in the field of fundamental and clinical oncology are at the center of a complex set of socio-economic, medico-biological, technological, and moral-ethical problems that bring this pathology beyond the scope of purely medical problems. The socio-economic significance of the problem is determined by the fact that cancer reduces the life expectancy of the male and female populations by 3.6 and 2.5 years respectively.

The high cancer morbidity and mortality rates among people of reproductive and working age in Ukraine exceed the Western Europe's rates. Ukraine ranks second in Europe in terms of cancer incidence due to the problems in the organization of cancer care, inadequate material support, low availability of medical care, late diagnostics, and, consequently, the low efficiency of the treatment.

In order to reduce the cancer rates, the Ministry of Health of Ukraine created the «National Strategy for the Control of Cancer for the period up to 2030» that aims, among other things, to ensure the primary prevention of cancer by reducing the impact of carcinogenic risk factors, including radiation-induced ones.

Ukraine belongs to the countries with a rather high level of natural radiation background. However, currently, it is difficult to assess the role of the background impact of IR because the nuclear weapons tests conducted in the atmosphere and radiation accidents have led to a wide spread of radioactive substances, primarily of long-lived elements, and their deposition in the soil.

Based on the results of the literature and own studies [2, 4] regarding various types and characteristics of irradiation, it is reasonable to form a scientific basis for the optimization of radiation protection of various categories of population, first of all, medical personnel and patients.

Radiation exposure of patients and occupational exposure of medical personnel

The occupational radiation exposure and its consequences are of great concern worldwide regarding the radiation safety of medical personnel performing diagnostic examinations of various types using X-rays. The first to be exposed to occupational irradiation are radiologists, radiation oncologists, and invasive cardiologists [5]. Adverse medico-biological consequences of occupational irradiation depend on the exposure duration [6].

Currently, there is a global trend toward the development of various methods of radiation diagnostics of cancer. The most dangerous in terms of radiation risk for patients is computed tomography (CT) with the use of a contrast substance. The development and implementation of new technologies and the improvement of medical diagnostic devices reduce the dose load on patients. However, the collective dose of medical exposure is increasing due to the use of new highly informative high-dose examinations. The number of human chest CT scans has increased significantly in recent years due to the spread of COVID-19 infection. If a CT scan is prescribed regularly, then, according to international recommendations, the patient should be informed about possible radiation risks. Highly radiosensitive individuals require special attention. For example, about 10% of CT examinations are performed for children and adolescents under 18 years of age. In Germany and the United States, this figure is 13% and 20% respectively [7]. However, in most cases, the benefits of CT procedures may be incommensurably higher than the radiation damage. This should be kept in mind in the diagnostic examinations of Ukrainian patients in the setting of a long radioecological crisis after the Chornobyl catastrophe.

Recently, the number of interventional diagnostic procedures has increased. These examinations are performed by the puncture access followed by the X-ray control. The angiographic examinations, the duration and complexity of which depend on the individual characteristics of the examinees and the specific clinical situation, are characterized by high radiation exposure both for the staff and patients.

Due to the introduction of digital technologies into the practice of radiological diagnostics, the radiation load on the staff and patients shows a pronounced tendency to decrease. However, the problem of radiation-associated cancer undoubtedly remains the most challenging one [3]. The repeated examination of patients using modern highly informative radiological methods can serve as a promoter of radiation-induced carcinogenesis, especially for weakened patients. This highlights the need for a more balanced prescription of diagnostic radiation examinations.

Therefore, specialists in the field of radiation hygiene should pay attention to the additional radiation exposure of the population at the expense of radiation diagnostics, protection of vital organs and tissues with obligatory control of dose loads, and preventive measures of radiologic protection of professionals working in the fields of radiation medicine, nuclear power industry, uranium mining industry, as well as the residents of the radiation-contaminated areas of Ukraine.

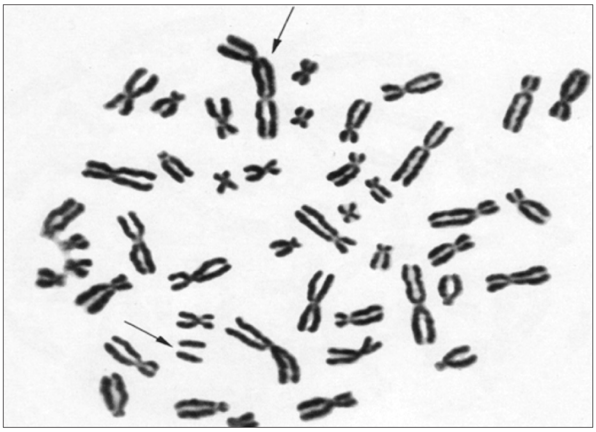

Fig. 1. Dicentric chromosome and accompanying pair fragment [8]

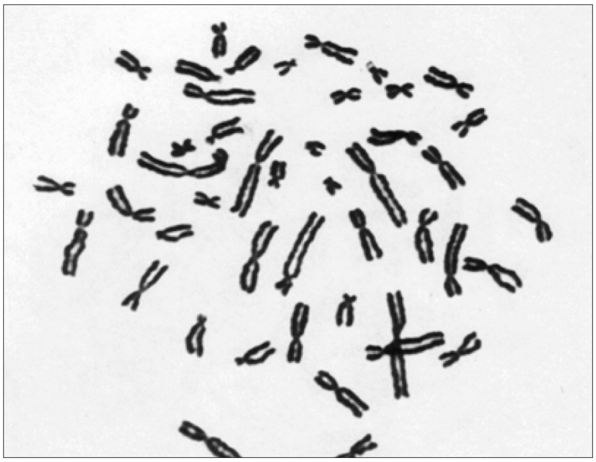

Fig. 2. Translocation (abnormal chromosome) [8]

The most vulnerable are professionals with high individual radiosensitivity (IRS) of the organism, carcinogenic risks of whom vary within wide limits [8]. In this context, employees of the Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine developed «Passport of Individual Human Radiosensitivity by Cytogenetic Indicators», which is approved by the Ministry of Health of Ukraine. The idea of the passport lies in determining the sensitivity of the organism of an individual professional to the effects of the radiation and is based on cytogenetic indices of peripheral blood cells using G_0- and G_2-tests, i.e. the analysis of the frequency and spectrum of the chromosome aberrations in human peripheral blood T-lymphocytes responsible for anti-tumor protection of the body and considered as the «golden standard» in bioindication/biodosimetry of radiation lesions [9]. A high mobility of lymphocytes in the bloodstream, the distribution of lymph nodes throughout the body, and the ability of lymphocytes to accumulate chromosome aberrations allow for evaluating the radiosensitivity of the organism in general. The increased spontaneous chromosome aberrations after irradiation provide information about the accumulation of mutations and radiation exposure received previously (G_0-test). The frequency of radiation-induced aberrations under the conditions of «provocative» irradiation of T-lymphocytes provides information about the genetically determined IRS of the examined individual (G_2-test). When an elevated spontaneous level of chromosomal rearrangements coincides with a high IRS, the greatest radiation and carcinogenic risk should be expected. Therefore, the passportization of professionals who are in contact with IR sources is a scientifically valid approach for determining their IRS [8].

We have examined groups of radiation professionals with various durations of work. The group with an increased occupational radiation risk was composed of industry veterans, i.e. radiologists with a long period of service. The cytogenetic examination showed a high incidence of spontaneous chromosome aberrations in their blood T-lymphocytes (8.3 ± 0.6/100 metaphases), which was more than twice higher than the average value of the index in the general population. The radiation markers (dicentrics and abnormal chromosomes) from 0.5 to 6.0/100 metaphases were observed in 38% of radiologists examined, indicating radiation exposure of the genome (Figs. 1, 2). Based on radiation carcinogenesis paradigms, the additional occupational exposures enhance the genomic instability in the cells of these individuals potentially contributing to the increased carcinogenic risk. This conclusion is supported by their IRS data [8]. In the group of professionals with a long history of occupational exposure to IR, the average chromosome aberration rate during «provocative» irradiation (G_2-test) was 80.2 aberrations per 100 metaphases. The total frequency of chromosome rearrangements varied from 45 to 140 aberrations per 100 metaphases. Thus, the results of cytogenetic examination of radiologists indicated a significant increase in genetic changes in immunocompetent blood cells, T-lymphocytes, which are specific biomarkers for determining the IRS and the carcinogenic risk and are also useful for individually justified primary prevention of radiogenic cancer.

The role of radiotherapy in cancer treatment is difficult to overestimate. It is applied at different stages of complex therapy as a separate method of treatment that in some cases can compete with surgery (stereotactic radiosurgery). The most equipped radiation oncology centers use highly effective techniques for combined individualized chemo- and radiation treatment and radiologic modification. However, high-quality radiotherapy is not available to all cancer patients in Ukraine. The slow pace of implementation of radiation therapy on linear electron accelerators and the continued use of outdated gamma therapy devices characterize radiation therapy in Ukraine as significantly lagging behind the obvious successes of Eastern Europe, the Baltic States, and Turkey [4].

The consequences of the irradiation of healthy tissues due to the radiation therapy of cancer patients, which reduces treatment efficacy and worsens their quality of life, deserve special attention [11]. Despite the conformal strategy of the current radiation therapy and the strict parameters of the dose delivery to the tumor, healthy tissues, including circulating blood pool cells, get into the irradiated volume. There are several reasons for this, the main of which are as follows:

- The malignant tumors form microscopic infiltrates in healthy tissues from their surroundings; it is important to include such areas in the volume of the irradiated field.
- The soft tissues, the blood vessels, etc. are irradiated at the same dose as the tumors.
- The healthy tissues at the entrance and exit of the ionizing radiation beam can be irradiated at sufficiently high doses.
- Finally, the increased IRS of the patient's body correlates with the occurrence of radiation complications.

Therefore, the therapeutic irradiation of cancer patients may in a number of cases cause the development of genomic instability of healthy cells and, as a consequence, the development of distant post-irradiation complications in normal tissues of the tumor environment and the occurrence of secondary cancer of radiation-associated etiology [2, 11—13].

A significant role in the development of the late radiation effects is played by the persistence of the cell ability to form reactive oxygen species (ROS), which is one of the early events occurring in the cell during irradiation. Among the most effective and low-toxic radioprotectors is amifostine, which acts as a «trap» of ROS [14, 15].

Occupational exposure of astronauts

The cosmic radiation is an extremely complex damaging factor in human exploration of extraterrestrial space. It consists of protons (85%), α-particles (14%), and heavy particles with a maximum energy of up to 200—500 MeV, among which the heaviest particles are Fe atoms (0.05%). At the same time, the professional dose limit for cosmonauts during a one-year flight is about 1000 mSv. The contribution of neutrons to the total radiation dose reaches 40%. Therefore, the physical dosimetry of space radiation is extremely complicated. The wide range of the proton power rate poses a big problem, and the dose difference over cosmonauts' bodies may vary by two to ten times. During long-lasting flights, there is a threat of cosmonauts' irradiation in doses that cause somatic (deterministic) and carcinogenic (stochastic) radiation-induced effects. The most difficult problem is the protection of cosmonauts from the action of heavy-charged particles (HCP) on the central nervous system. The mechanism of their action is unknown. There is information about HCP action on the cognitive and behavioral functions of animals in experimental research.

The most difficult and urgent problem is the protection of cosmonauts from the action of protons and HCP during the planned flights into deep space (Moon, Mars). Taking into account the prolonged radiation effects of high-energy protons in deep space, the mechanism of action of which is still unknown, it is necessary to focus the attention on the search and development of radioprotective means, first of all, radiomitigators, which enhance reparation processes in irradiated critical tissues.

For the prevention and relief of radiation reactions, the prescription of indralin and latran is recommended. The use of radiomitigator inosine and others under the conditions of proton radiation and increased solar activity will allow accelerating processes of the postradiation recovery of hematopoietic tissue. We have argumented, both theoretically and experimentally, the use of inosine during the action of IR in a wide range of doses for the prevention of the development of radiation reactions and radiogenic cancer. We attribute this effect to the activation of enzymatic repair processes. The radioprotective effect of inosine in human somatic cells is most expressed in the interval of low doses — the reduction of radiation-induced chromosome aberrations down to spontaneous values [16].

For pathogenetic therapy of acute radiation disease, the drug Neupomax has been proposed. However, so far no highly effective means of radiation protection for cosmonauts during long-term flights in space have been developed. Currently, the researchers are raising questions about the possible influence of HCP on the development of radiation carcinogenesis. From these positions, the continuation of studies of genetically determined individual radiosensitivity of the human organism and its modification under the action of extreme external factors will contribute to a better selection of candidates for cosmonauts with a radioresistant genotype.

Occupational exposure of miners

The creation and development of the nuclear industry began with uranium mines designed to extract uranium and radium and later to provide raw materials for the nuclear fuel cycle enterprises. Uranium has been mined in Ukraine since 1949. Miners are exposed to alpha-emitting dust (uranium-234, uranium-238, thorium-230, radium-226, polonium-210), and subsidiary products of radon decay (polonium-218, lead-214, polonium-214). Of all dose-forming factors, radon content in the air is the most significant for miners' health. Its contribution to the occupational total radiation dose achieves 40%—60% [17].

Dust-radiation working conditions, the presence of toxic exhaust gases in the inhaled air, and high temperatures are the main causes of occupational cancer among miners.

Epidemiological studies performed in different periods have revealed a stable relationship between the amount of absorbed dose and the risk of lung cancer in uranium mine workers [18].

For a number of years, the radiation dose to the personnel of uranium mines did not exceed 20 $mSv\text{-}year^{-1}$. The physical dosimetry was performed by a calculation method based on the periodic measurements of control parameters in the working area. However, according to the data of the State Supervision Service, which performed sampling control, the real radiation dose at workplaces may be much higher and exceed

50 mSv-year^{-1}. This forces the relevant specialists to question the reliability of the current system of personnel dosimetry. The radiation protection system must be radically revised and brought in line with the current international requirements. We believe that the physical dosimetry data should correlate with the results of biological dosimetry [10] performed using the «golden standard», that is, the analysis of the frequency and spectrum of the radiation-induced chromosome aberrations in the peripheral blood lymphocytes of the exposed persons.

Exposure to natural sources of ionizing radiation

Natural background radiation is a chronic exposure at low dose rates. The population in most countries lives in the conditions of an average natural IR background of 2.4 mSv/year. Natural background radiation constantly affects the human body and therefore its level is viewed as a criterion of acceptable irradiation. There is a real danger that it can be a potentially carcinogenic factor. Thus, in the USA, there is an inverse correlation between the radon concentration in the premises and the level of cancer morbidity, and in several departments of France — between the level of radiation background and mortality of children from leukemia, women from breast cancer, and men and women from thyroid and lung cancer.

About 80% of irradiation of the Earth's population occurs under the influence of natural sources of IR and only 20% — from artificial sources, used mainly in medicine. An important component of the former is formed by natural soil radionuclides. The most important source of natural radiation is radon and its decay products, which can account for ¾ of the annual individual effective irradiation dose. Radon is emitted from soil, especially in the areas of the shallow occurrence of crystalline rocks such as granites and basalts and accumulates in large amounts in the uranium deposits, during processing, concentration, and enrichment of uranium products, in uranium production wastes due to the industrial air pollution, etc. Being a heavy gas, it fills the low-lying areas such as the basements of houses and buildings. Moreover, the concentration of radon in residential areas can reach the levels that exceed the occupational exposure limits established by the International Commission on Radiation Protection. Radon also poses a radiation danger when it is present in drinking water. There is a high degree of radon migration in the form of gas molecules through the membranes of cells in the digestive tract and other organs. Up to 1% of bronchial epithelial cells may be exposed to alpha particles associated with the presence of radon in drinking water.

Numerous studies have proven that radon plays an important role in the occurrence of additional cases of lung cancer [19]. In some areas with high radiation levels (Brazil, India, China, Iran, Turkey), the level of exposure of residents is even higher than that of workers employed in the nuclear industry or radiation medicine. At the same time, the effective dose value significantly exceeds the dose allowed for the personnel working in the field of IR (20 mSv/year) [20]. When assessing the radiation danger in case of exposure to natural sources of IR, the national specificities of each country as well as the scale of irradiation of its population should be taken into account. One of the main tasks of oncology is the reduction of morbidity and mortality of the population from radon-induced lung cancer [21], the share of which is in the range of 3%—14% of the total lung cancer cases [22]. High radiosensitivity of the immune system and long-term persistence of radiation-induced genetic abnormalities in T-lymphocytes could cause immune dysfunction and tumor development [4].

Ukraine belongs to the countries with a rather high level of natural radiation background.

The average annual total effective individual radiation dose to the population from the sources of natural origin is 4.86 mSv, of which 80% is radon-222 in the indoor air. The radioecological crisis in the country necessitates an intensification of the radiation epidemiological studies of the impact of radon and its subsidiary products on cancer morbidity of the population.

The above-mentioned data is a brief illustration of the radiation hazard for humans resulting in the occurrence of stochastic effects including radiogenic cancer. Research on radiation and carcinogenic risks is being conducted all over the world. It has been repeatedly demonstrated that IR destabilizes the human genome, initiating a cascade of genetic events (the formation of micronuclei, increased level of point mutations, chromosome aberrations, etc.), which can persist in the cell population for a long time and induce cancer [23, 24]. To assess the state of radiation safety, the use of only one type of irradiation does not always guarantee the correct data. For example, during the examination of nuclear professionals seconded for the liquidation of the consequences of the Chornobyl NPP accident, the individual dose «history» during the period of work at the main production facility was not taken into account. This limited the ability to reconstruct the total radiation dose received by an individual.

Our review would be incomplete without mentioning the radiological consequences and lessons of the Chornobyl NPP and Fukushima-1 NPP radiation accidents. We should keep in mind that while deterministic effects of radiation accidents (somatic diseases with certain pathomorphosis) are realized to the level of decompensation in about a 25-year period, the stochastic (carcinogenic) effects have no limitations [2]. The major radiation incidents in the past associated with the release of products of nuclear reactions into the environment not only caused mass radiation exposure of people but also significantly increased the radiation background of the planet. In this context, it would be advisable to focus on reviewing certain paradigms of current radiobiology, among which the study of the carcinogenic unsafety of human exposure to low doses is of great importance. The experience accumulated during the examination and treatment of «liquidators» of the Chornobyl NPP accident consequences is valuable and unique. In particular, a diagnostic method has been developed for estimating the degree of acute radiation sickness (ARS) based on the data on cytogenetic examination of the victims, which can be used even in the course of intensive therapy [25]. A therapeutic tactic with bone marrow transplantation to ARS patients has been developed — the temporary replacement therapy [26].

The presented data along with many other developments of Ukrainian scientists in the post-Chornobyl period serve as a reference point for the continuation of studies on the specificities of different types of human radiation exposure, as well as their role in the etiology and pathogenesis of radiation-associated tumors [2—4, 27, 28].

The performed analysis of the literature data and our own epidemiological, experimental, and radiobiological studies allow us to conclude that the study of the effects of all types of IR sources on humans with regard to their total, i.e. cumulative, radiation dose is most topical. The necessity of calculating complex assessment of the radiation risks and the reconstruction of total IR dose from all types of irradiation will allow optimizing radiation protection of the population and reducing the carcinogenic risk.

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Submitted: June 1, 2023

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ОЦІНКА СУЧАСНИХ ФАКТОРІВ РАДІАЦІЙНО-АСОЦІЙОВАНОГО КАНЦЕРОГЕНЕЗУ

Широке впровадження ядерних технологій у промисловість, медицину, науку тощо збільшує кількість фахівців, що піддаються додатковому радіаційному опроміненню. Крім того, проблема професійного раку є без перебільшення, найскладнішою в профпатології, що зумовлено багатофакторністю етіології цього захворювання. Радіаційні аварії на Чорнобильській АЕС і Фукусіма-1 (Японія, острів Хонсю) показали, що ядерні реактори не мають гарантій абсолютно безпечної експлуатації. Наразі зростає і загроза ядерного тероризму. На основі результатів літературних джерел і аналізу представленого в них великого фактичного матеріалу та результатів власних досліджень щодо різних видів і характеристик опромінення доцільно сформувати науково обґрунтовану основу для оптимізації радіаційного захисту різних категорії населення, насамперед, медичний персонал і пацієнтів. Професійне опромінення та його наслідки викликають велике занепокоєння в усьому світі щодо радіаційної безпеки медичного персоналу та пацієнтів. Наведені в роботі дані –- це незначна ілюстрація до питання про стан радіаційної небезпеки для людини за різних форм опромінення і як наслідок, виникнення стохастичних ефектів, у тому числі радіогенного раку. Проведений аналіз літературних даних та власні радіаційно-епідеміологічні, експериментальні та радіобіологічні дослідження дозволяють зробити висновок, що найбільш коректним є вивчення впливу на людину всіх типів джерел радіації щодо їх сумарної, тобто кумулятивної дози опромінення. Необхідність розрахунку комплексної оцінки радіаційних ризиків, реконструкції сумарної дози іонізуючих випромінювань від усіх видів опромінення дозволить оптимізувати радіаційний захист населення країни та знизити канцерогенний ризик.

Ключові слова: радіаційний канцерогенез, променева терапія, іонізувальне випромінювання.