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CLINICAL, IMMUNOLOGICAL AND GENETIC RESEARCH ON THE PARTICIPANTS IN MITIGATING THE CONSEQUENCES OF THE CHERNOBYL NUCLEAR ACCIDENT

Liuba CORETCHI[1,2], Mariana GINCU[1], Ion BAHNAREL[2], Grigore FRIPTULEAC[2], Parascovia ROMANCIUC[1], Angela CAPATINA[1]

[1]National Agency for Public Health, Chisinau, the Republic of Moldova
[2]*Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova

Corresponding author: Liuba Coretchi, e-mail: coretchiliuba@gmail.com

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Keywords: *ionizing radiation, nuclear accident, chromosomal aberrations, immunological effects.*

Introduction. *The paper presents the results of research on the influence of IR sources on the health of professionally and accidentally exposed personnel. Particular emphasis is placed on: identifying the relationships between the level of radiation dose and the development of oncological diseases; use of contemporary biological dosimetry methods for retrospective analysis of irradiation doses; the impact of parental irradiation on the health of the offspring; the structure of morbidity, including oncological diseases in patients exposed to IR sources.*

Material and methods. *The study material was used by subjects professionally and accidentally exposed to IR sources: medical staff and PMCCNA born in the Republic of Moldova, Ukraine and the Russian Federation, as well as their descendants, victims of the accident at the Fukushima Daiichi nuclear power plant (Japan) and residents of the region. Chelyabinsk. Clinical, immunological and cytogenetic methods were used.*

Results. *A wide range of mental pathologies was observed at PMCCNA, at the victims of the accident at the Fukushima Daiichi nuclear power plant, etc. The structure of immune deficiency syndromes was dominated by allergic and autoimmune syndromes. Based on the analysis of stable chromosomal aberrations, exposure doses were established.*

Conclusions. *In the absence of dose information received by staff professionally/accidentally exposed to IR sources, assessment of stable chromosomal aberrations makes it possible to reconstruct the radiation dose for PMCCNA exposed to low doses of IR.*

Cuvinte cheie: *radiații ionizante, accident nuclear, aberații cromozomiale, efecte imunologice.*

CERCETĂRILE CLINICE, IMUNOLOGICE ŞI GENETICE ASUPRA PARTICIPANȚILOR LA DIMINUAREA CONSECINȚELOR ACCIDENTULUI NUCLEAR DE LA CERNOBÎL

Introducere. *În prezenta lucrare sunt descrise rezultatele cercetărilor influenței surselor de radiații ionizante asupra stării de sănătate a personalului expus profesional și accidental. În mod prioritar, în studiu se pune accent pe: identificarea relațiilor dintre nivelul dozei de iradiere și dezvoltarea maladiilor oncologice; utilizarea metodelor contemporane de dozimetrie biologică pentru analiza retrospectivă a dozelor de iradiere; impactul iradierii părinților asupra stării de sănătate a descendenților; structura morbidității, inclusiv a maladiilor oncologice la pacienții expuși la surse de RI.*

Material şi metode. *Ca material de studiu au servit subiecții expuși profesional și accidental la sursele de RI: personalul medical și PDCANC, născuți în Republica Moldova, Ucraina și Federația Rusă, cât și descendenții acestora, victimele accidentului de la centrala nucleară Fukushima Daiichi (Japonia) și locuitorii din regiunea Celiabinsk. Au fost utilizate metode clinice, imunologice și citogenetice.*

Rezultate. *O gamă largă de patologii psihice a fost observată la PDCANC, la victimele accidentului de la centrala nucleară Fukushima Daiichi etc. Structura sindroamelor de deficiență imună a fost dominată față de sindroamele alergice și autoimune. În baza analizelor aberațiilor cromozomiale stabile au fost determinate dozele de expunere.*

Concluzii. *În absența informațiilor privind doza primită de către personalul expus profesional/accidental la sursele de RI, evaluarea aberațiilor cromozomiale stabile face posibilă reconstrucția dozei de radiații pentru PDCANC expuși la doze mici de RI.*

ABBREVIATIONS: PMCCNA – participants in mitigating the consequences of the Chernobyl nuclear accident; **IR** – ionizing radiation; **CVD** – cardiovascular diseases; **MCB** – the microcirculatory bed; **CA** – coronary arteries; **AH** – arterial hypertension; **MFC** – the microvascular form of coronary artery disease; **AF** – atherosclerotic form; **CNA** – the Chernobyl nuclear accident; **DEP** – dyscirculatory encephalopathy; **FAC** – fractional anisotropy coefficient; **CG** – the control group; **AOA** – antioxidant activity; **WHO** – World Health Organization; **MN** – malignant neoplasms; **NRER** – National Registry of Epidemiology and Radiology; **CM** – congenital malformation; **OR** – the odds ratio; **NMR** – nuclear magnetic resonance; **DT-NMR** – diffusion tensor NMR; **IG** – the investigated group; **DNA** – deoxyribonucleic acid; **microRNA** – ribonucleic acid (micro – small molecules); **UNSCEAR** – United Nations Scientific Committee on the Effects of Atomic Radiation; **ICRP** – International Commission on Radiological Protection; **RHR** – relatively high risk of radiation exposure; **RSN** – radiation safety norms.

INTRODUCTION

The Chernobyl nuclear accident resulted in a significant contingent of people exposed to "low" doses (<100 mGy) of radiation, followed by the long-term development of various digestive, cardiovascular, neuropsychiatric and psychosomatic disorders. These violations subsequently led to disability and increased mortality among victims. The lack of information on the external exposure dose for many PMCCNA determined the need for retrospective dosimetry. The evaluation of the possibilities of using cytogenetic dosimetry methods to determine stochastic effects and external exposure doses in PMCCNA exposed to low doses of IR is of particular interest from a scientific point of view. A fundamental scientific interest presents the results of the clinical monitoring of the manifestation of stochastic effects, namely CVD and the particularities of their manifestation in PMCCNA who were exposed to "low" doses of ionizing radiation. An important role is to address the issues of the impact of IR on occupationally and accidentally exposed personnel, including medical personnel. It is worth highlighting the relevance of studying the stochastic effects of small doses of radiation, due to the increasing use of IR sources in various fields of scientific and practical human activity, including medicine. At the same time, scientific research is focused on the control and supervision of the health status of the PMCCNA descendants, in order to assess the immunological and genetic effects in the targeted contingent.

The aim of the paper consisted in conducting a synthesis of personal results and the respective literature of studying the influence of exposure to IR on the reaction of the human body at the individual, cellular and molecular level with the manifestation of stochastic effects.

MATERIAL AND METHODS

Subjects professionally and accidentally exposed to RI sources served as study material: medical personnel and PMCCNA born in the Republic of Moldova, Ukraine and the Russian Federation, as well as their descendants, victims of the accident at the Fukushima Daiichi nuclear power plant (Japan) and residents of the region Chelyabinsk, Russian Federation. Clinical, immunological and cytogenetic methods were used. The structure of morbidity and mortality, including oncological diseases, was studied. The immunological effects of those exposed to IR were studied by *flow cytometry* using monoclonal antibodies. Cytogenetic effects were studied by analyzing stable and unstable chromosomal aberrations, which later contributed to the reconstruction of the doses of those exposed to IR (1, 2).

RESULTS

Effects of IR on medical staff and PMCCNA

It has been shown that operating physicians working with IR sources often do not have a sufficient level of protection of the thyroid tissue against radiation. The vast majority of studies in the field of thyroid pathology in medical personnel working with X-rays are aimed at identifying the risks of thyroid cancer and do not take into account the pathology of non-tumor genesis. Based on the analysis of experimental data, it was established that under the influence of low-dose X-radiation, the intercellular contacts of thymocytes are disconnected, which can lead to a decrease in the synthesis of thyroid hormones and, as a result, to the development of hypothyroidism (3).

A wide range of mental disorders was observed in PMCCNA, in the victims of the accident at the Fukushima Daiichi nuclear power plant (Japan), etc. Of particular interest is the study of primary inci-

dence indicators of mental and behavioral disorders (F00–F09, F20–F99) for the period 2005-2018 of residents of the municipal districts of the Celiabinsk region (Kunashaksky, Krasnoarmeysky, Arga yashsky, Kaslinsky districts) exposed to radioactive contamination in years 1949-1951, and in 1957 as a result of the activities of the Mayak Production Association. These data were compared with indicators for the non-radioactively contaminated Etkulsky district, comparable in terms of population and nature of economic activity. Mental disorders were matched to the groups of the fifth class "Mental and behavioral disorders" according to the International Classification of Diseases, 10th revision (ICD-10). The calculation of morbidity cases was made per 10 thousand people or in 0/000. A descriptive analysis of statistical data was presented, which reflects the recorded primary incidence of mental disorders in the inhabitants of the mentioned districts of the Chelyabinsk region. The level of primary incidence of mental disorders in the Chelyabinsk region (49.1±3.6)0/000 significantly exceeded ($p<0.01$) the indicators in the Sverdlovsk regions (30.3±4.2)0/000, Kurgan (30.2±6.9) 0/000 and in general the average in the Russian Federation (32.9±3.8)0/000. In the remote time, the level of primary morbidity with mental disorders in a number of districts among the population living in radioactively contaminated territories was higher than among residents of the Etkulsky district, but it turned out to be significantly lower than the general indicators for the Chelyabinsk region ($p<0.001$) (4).

In order to summarize the results of a clinical examination of PMCCNA with diseases of internal organs, in the years 1996-2002, 117 participants were examined, who since June 1986, in 1987 and 1988 were engaged in various work operations in the emergency area of 30 Kilometres. The absorbed dose of external radiation varied between 50.0 and 270.0 mGy (average value being 163.06±9.54 mGy). The study demonstrated that the pathologic effect of IR consists of widespread SMC damage of variable severity, ranging from vasculopathy to the manifestation of productive vasculitis, established in right ventricular myocardium biopsy specimens. In the post-Chernobyl period, high mortality at working age was established in the mentioned cohort. Until 2002, death was caused by external factors and diseases of the circulatory system, later by diseases of the circulatory system and malignant neoplasms of the lungs (5).

Of particular interest is the analysis of the incidence and risk of cataracts caused by radiation. The results of the study demonstrated that the use of doses of different types of IR exposure on a person led to different values of cataract risk. An excess relative risk of 1 Sv suggests that cataracts caused by IR may be associated with senile cataract. Only the use of the total dose received as a result of occupational, medical, natural exposure and doses during work in the Chernobyl area will make it possible to correctly assess the risk of radiation-related cataract. For a correct analysis of the incidence and calculation of the risk of radiation-induced cataract, it is advisable to apply the diagnosis code "Radiation cataract" in ICD-10 (6).

402 PMCCNA were examined, of which 185 people were investigated for 15 years (1994-2009), undergoing primary and repeated cardiological examinations: CA angiography, endomyocardial biopsy, helical computed tomography of the CA, echographic examination (ultrasound) of the peripheral arteries , evaluation of hormonal and carbohydrate metabolism and the functional state of the cardiovascular system. The results show the predominance of AH – 70.3% and/or MFC – 58.9% among PMCCNA in the first monitoring stage (1995-1999). 10-15 years after the initial examination, the frequency of diagnosis of AH remained unchanged. The number of cases of AF of CVD has increased, including due to the development of CA atherosclerosis in patients with early-onset MFC. The severity of the clinical manifestations of CVD, their form and results depended on a number of factors: age, length of stay in the accident area, the dose of IR, and after returning – on the lifestyle and conditions of professional activity. Based on the study, the authors state that the stabilization of the pathomorphosis of AH and the prevention of the atherosclerotic evolution of MFC CVD was facilitated by the timely diagnosis of the early stages of vascular disorders and the appropriate measures of preventive interventions (7).

The clinical and epidemiological study of the in-influence of risk factors on the development of diseases of the circulatory system and cerebrovascular diseases in PMCCNA established that the probability of developing diseases of the circula-

tory system in the nominated contingent was much higher than in non-irradiated men in the control group. The priority pathology in the structure of diseases of the circulatory system returned to cerebrovascular ones, the proportion of which in the PMCCNA of 1986 was 1.7 and 3.6 times higher, respectively, than in the PMCCNA of 1987 and 1988. It was demonstrated that the diseases of the circulatory system and cerebrovascular disease in PMCCNA developed at a younger age than in unirradiated men in the control group, 7.5 and 12.8 years earlier, respectively. The age difference between the 1986 PMCCNA for cerebrovascular disease and men in the comparison group with the same diagnosis was 13.6 years. Positive correlations of cerebrovascular disease with radiation dose and hypertension were revealed, with a negative correlation with age. The influence of the radiation factor was confirmed by the results of neuroimaging and neurophysiological studies (8).

A clinical and laboratory study was carried out on a group of PMCCNA who manifested the main forms of bronchopulmonary pathology (pneumonia – 32, chronic bronchitis – 44, bronchial asthma – 34), being irradiated with an average dose of 25 R. The results of the study were compared with similar indicators of the control group – patients identical to the patients in the main group from the point of view of nosology, sex and age. It was detected that the pathology in the investigated patients – former PMCCNA was distinguished by concomitant violations of the disease underlying the functional state of the main homeostasis systems – immunological, hormonal, antioxidant, blood coagulation, which, apparently, determined its slowing down, progressive course, regardless of the nature of nosology (9).

Descriptions of the mental effects of the influence of extreme factors of CNA, the stages of formation and clinical forms of psychosomatic radiation sickness, the characteristics of its diagnosis, treatment and prevention occupy an important role in studying the medico-biological effects of nuclear accidents (1, 10).

Cytogenetic biological assay and biological dosimetry of IR was performed at PMCCNA 27-30 years after participation in liquidation works. Stable and unstable chromosomal aberrations in peripheral blood lymphocytes were analyzed. In the analysis of unstable chromosomal disorders in 45.1% of PMCCNA, radiation markers were identified with a frequency exceeding the control group, a fact indicating the impact of IR. In 18% of those examined, using analysis of chromosomal aberrations, biological exposure doses to IR were determined (2, 11).

In order to identify the peculiarities of the long-term changes of the cerebral tract in PMCCNA with DEP, using magnetic resonance imaging, a detailed examination of 41 patients in the PMCCNA groups and 49 patients in the control group with a history of stage II DEP was performed, whose average age was 68.0±6.9 years in the PMCCNA group, and 68.6±5.8 years in the control group. All patients underwent: routine MRI, diffusion tensor MRI (TD-MRI), clinical examination to identify DEP stage, presence of diabetes and AH. The proportion of diseases leading to cerebrovascular damage, such as diabetes and AH, in the structure of diseases in both groups was comparable. According to routine MRI, all patients in both groups had severe dyscirculatory changes in the brain – multifocal white matter lesions and periventricular leukoaraiosis, mixed substitution of hydrocephalus. The results denote that, compared to the control, the PMCCNA group demonstrated a decrease in FAC in the neocortex structures of the frontal and temporal lobes of the brain. FAC in the PMCCNA group was statistically significantly reduced in four brain tracts: in the superior longitudinal fasciculus ($p<0.02$); anterior parts of the radiant crown ($p<0.02$); in the anterior limb of the internal capsule ($p<0.01$) and in the inferior longitudinal fasciculus ($p<0.01$). The authors state that the structures of the neocortex of the frontal and temporal lobes responsible for cognitive functions are the most sensitive to the impact of the factors used to eliminate the consequences of a nuclear accident. The changes in these brain structures revealed in the main group are similar to those in the elderly with DEP, however, they are more pronounced clinically, supporting the hypothesis of early brain aging in PMCCNA (12).

Previous studies have shown that in PMCCNA, brain dyscirculatory changes were observed more often than in the general population. The assessment of the brain substance status in 45 PMCCNA (IG) in the remote period and CG – 49 patients of the same age and sex, who had no history of radioactive damage demonstrated that the level of severity of DEP in the groups was similar.

High-field magnetic resonance imaging was performed on a Magnetom Verio tomograph with a magnetic field strength of 3 Tesla. Brain morphological changes in IG were more pronounced than in CG. Thus, external substitution hydrocephalus in IG was visualized statistically more often than in CG, in 84% and 65% respectively ($p<0.05$), mixed – in 51% and 16% respectively ($p<0.005$). In 14.2% of CG cases examined, the changes were absent. In both groups, lacunae of the consequences of infarcts were identified as cysts in the area of the basal ganglia, surrounded by areas of gliosis. In IG, these changes occurred with a more pronounced frequency than in CG ($p<0.05$). The results of magnetic resonance imaging of the brain help to research the evolution of DEP in PMCCNA in the long term, but also to correct treatment and rehabilitation measures (13).

The comparative analysis of the main performance indicators of the Chelyabinsk Regional Interdepartmental Council of Experts for establishing a causal relationship between diseases and radiation exposure in the periods 1990-2009 and 2010-2015 is of interest. Annual reports on activities, standard meeting protocols and decisions of the Chelyabinsk Interdepartmental Council of Experts served as sources of information. During the analyzed period, there was a natural aging of all investigated population groups, the proportion of cases considered repeatedly increased, mainly due to the cases found as a result of the disability or death of the exposed persons. In the years 2010-2015, a causal relationship was established more often than in previous periods: 43.3% and 67.1%, respectively. Most frequently, positive decisions were made in relation to people with malignant neoplasms (62.9% of the total number of positive decisions made). The association of disability and death with radiation exposure in the years 2010-2015 was detected more frequently, while the share of classified causes decreased significantly (14).

Comparison of the effect of increased levels of IR on a number of agricultural animal species and bioindicator species of small murine rodents after CNA with the results of studies of human populations after CNA and Fukushima demonstrated that there is a similarity between the main identified targets of IR in humans and agricultural animals (cardiovascular system, kidneys) (15, 16, 17).

Recently, research on the possible mechanisms associated with the threshold of damage accumulation for the induction of DNA repair systems, changes in the ratio of young and old cell populations and mitochondrial dysfunctions is gaining momentum. The concept of horizontal and vertical consequences of increasing the level of IR for biological objects was introduced. The results indicate that in different species of murine rodents (*Microtus arvalis, Clethrionomys glareolus*) and lines of laboratory mice (C57BL/6, CC57W/Mv, BALB/c) under conditions of more than 100-fold increase of IR in bone marrow cells, an increase in the frequency of only those cytogenetic abnormalities is observed, the relatively increased variability of which was typical for the studied objects and in relatively "clean" areas. The main and apparently underestimated vertical consequence of increasing IR levels is a decrease in the reproductive success of irradiated animals. The importance of the transgenerational transmission of PTSD signs revealed in recent years and its mechanisms are discussed, including the transmission of microRNA (mediator of the stress response) through spermatozoa (18), changes in the microbiota of parents and offspring, as well as cultural heritage, to explain the complexity of observed radiobiological effects and their transmission over generations (19, 20).

Domestic and international approaches to standardizing exposure doses for personnel and individuals involved in mitigating the consequences of radiation accidents are of interest. For the purpose of standardization, on the example of the real accidents at the Chernobyl and Fukushima nuclear power plants, the problems of the influence of increased exposure on long-term consequences on the health of emergency personnel were considered. Standardization of existing IR dose and applicability of international criteria are discussed (21).

Evaluation of cytogenetic parameters and markers of oxidative stress (malondialdehyde, plasma AOA) in women who lived in the territories of Russia with various levels of radioactive contamination, as well as resettled in 1991 from the areas recommended for relocation to the "clean zones" demonstrated the increased individual frequency of dicentrics and the significant decrease in the level of plasma AOA ($p<0.005$) in women residing in localities with increased radioactivity, compared to the control group and emigrants (22).

Analysis of structural damage of chromosomes in workers of the Mayak enterprise, exposed to occupational combined irradiation using the modern molecular cytogenetic method mFISH, demonstrated that the frequency of stable chromosomal aberrations in the group of workers exposed to external gamma irradiation with the total absorbed dose in the red bone marrow of over 0.2 Gy was statistically significantly higher, compared to the frequency of stable chromosomal aberrations in a group of workers exposed to radiation at a dose lower than 0.2 Gy, due to the increased frequency of translocations – biological markers of external exposure. In the group of workers with a content of 239Pu in the body greater than 1.48 kBq, the frequency of stable chromosomal aberrations was statistically significantly higher due to a significant number of cells with complex chromosomal rearrangements. Linear dependences of the frequency of translocations on the absorbed dose of external gamma radiation and the frequency of complex chromosomal rearrangements on the content of 239Pu in the body were established. The frequency of chromosomal aberrations (complex chromosomal translocations and rearrangements) detected by mFISH has been shown to be an effective biological indicator of combined exposure (23).

Some researchers studied the identification of the biological dose in a group of employees of the Ministry of Emergency Situations of the Russian Federation who participated in the work in Japan in connection with the accident at the Fukushima-1 nuclear power plant and several journalists who covered this event. The authors conclude that there is no significant overexposure of this contingent during their stay in Japan, however, it is necessary to perform a preliminary analysis of chromosomal aberrations if it is assumed that the assay of biological dose will be performed when people return from the area of possible exposure (24).

An analysis of the incidence of thyroid cancer among PMCCNA (men), residents of Russia, was performed for the observation period 1992-2010. It was shown that the contribution of exposure to 131I in the development of thyroid cancer among PMCCNA, who worked in May 1986, was 53% (25). Thus, a special emphasis is placed on protecting health and preventing diseases associated with IR (26).

In the period 1992-2019, by the collaborators of the National Registry of Radiology and Epidemiology, a study was carried out on the assessment of the risks caused by IR using the indicators: morbidity/mortality from solid malignant neoplasms, and morbidity from leukemia (excluding chronic lymphocytic leukemia) in the PMCCNA cohorts. The number of subjects in the cohort was more than 65 thousand, the average age at the time of entering the Chernobyl zone was 34 years, the average accumulated dose of external gamma irradiation of the whole body during the working period of the liquidator was approximately 0.133Gy. Results denote statistically significant radiation risks of solid cancer morbidity and solid cancer mortality that increased with increasing cohort observation period (27).

Mathematical models of IR risk forecasting and their calculation methods are currently at the stage of scientific research and have not yet been standardized for solving practical risk forecasting problems. At the international level, radiation risk models have been developed by UNSCEAR, ICRP and WHO, using epidemiological data (28).

Statistically significant radiation risks of solid malignancies, including radiation risk of breast cancer in women, were not identified for the population in the most radioisotope-contaminated territories. The radiation risk of leukemia among the population was also not revealed, although for the male population the average value of the excess radiation risk still exceeded zero. Further observations of a cohort of people who lived in territories contaminated with radioisotopes will help to increase the statistical power of epidemiological studies in the research of radiation effects and will refine estimates of human radiation risks during chronic exposure to low doses (29).

To identify the group with relatively high risk of radiation exposure (RHR), special studies were conducted on the incidence of solid malignant neoplasms in the reference cohort of PMCCNA, registered in the NRER. It is recommended that the value of the absolute/relative risk factor criterion does not exceed 10% (30).

In the period 1986-2019, an interesting study was carried out on the PMCCNA contingent with a view to the radio-epidemiological classification of the incidence of MN according to the diagnosis, using statistical relationships between the incidence and the radiation dose. Cancer incidence

data on PMCCNA men who were in the exposure area during 1986-1987, accumulating an average total external gamma radiation dose of 0.128 Gy, were analyzed. The total number of cases was 9542. The average age at diagnosis was 57.4 years. The data were accumulated in the NRER. The authors conclude that in order to clarify the cause-effect relationship between the incidence of malignant neoplasms and radiation dose, further assessment of radiation risks using more precise methods of epidemiologic study of stochastic effects is needed (31).

In order to study the possible impact of the IR on the life expectancy of PMCCNA, the mortality monitoring of people enrolled in the NRER was carried out. The analysis of the obtained results demonstrated that when studying the impact of exposure on changes in life expectancy, it is necessary to consider the contribution of each of the main causes of death, even if it was not related to the exposure. In PMCCNA who received a radiation dose of 150 mGy or more, there was a radiation-related decrease in life expectancy due to mortality from solid malignancies. During 27 years of follow-up, the reduction in life expectancy was 0.3 years per unit dose (32).

A criterion was developed, demonstrating the existence of radiation risk, determined from cohort observational data under a linear multiplicative hazard model (in terms of radiation dose). Based on the calculation, according to the PMCCNA cohort data observed in the NRER from 1986 to 2019, a list of diseases was developed, the mortality from which is statistically associated with the radiation dose. The criterion developed for the excess of average doses for deaths over doses averaged with weighted observation times over the entire cohort was a sufficient condition for the existence of radiation risk in a linear multiplicative model. The use of the developed threshold criterion made it possible to formulate two new hypotheses about patterns of radiation risks of human mortality. (i) For the radiation risk of mortality from solid malignancies, the existence of two time phases for the implementation of this stochastic effect (up to 9 years and beyond 24 years after exposure) was demonstrated for the first time. Further testing of the statistical significance of the observed dependence on risk is required – the time. (ii) For the first time, the existence of an irradiation risk for mortality from diseases of the digestive system and the presence of a latent period for this risk of approximately 9 years was demonstrated (33).

The calculation of the damage caused by radiation was carried out for the population currently living (year 2020) on the territories of the Russian Federation contaminated with ^{137}Cs after the Chernobyl accident in 1986. The damage caused by radiation was calculated in two ways: according to the original ICRP methodology and by the method of using as the product of a nominal risk coefficient RSN-99/2009 per effective dose (nominal radiation damage). For ICRP calculations, equivalent doses were estimated using dose factors from the US Environmental Protection Agency. The number of the studied population from the contaminated territories at the beginning of 2020 was 142,676 people (65,205 men and 77,471 women). Basically, this constituted the population of Bryansk and Tula regions: 85.5%, and 10% of the total number, respectively. The mean cumulative effective dose for the population was 30.6 mSv, and the maximum individual cumulative dose was 707 mSv. In 2020, for 44-year-old men and 55-year-old women, the nominal radiation damage was approximately equal to the amount of radiation damage calculated using the ICRP methodology. At the same time, the nominal damage was significantly (up to 2.3 times) underestimated for the young and overestimated for the older ages. In 2020, the critical population groups with the maximum accumulated doses and maximum radiation damage were men aged 34 and women aged 35. For these population groups, the average cumulative effective doses were 35.3 and 39.2 mSv, and the average radiation damage was 2.6×10-3 and 4.2×10-3 respectively for men and women. For 11.8% of the population (8.3% men, 14.8% women), individual radiation damage calculated using the ICRP methodology exceeded the value of 3.5×10-3, which corresponds to the RSN-99/2009 for normal conditions of exposure. The maximum radiation damage of 3.9×10-2 was found for a 37-year-old woman from Krasnogorsk district of Bryansk region with an effective accumulated dose of 392 mSv. The results of the study in question can be used in the preparation of recommendations for health authorities to improve the medical monitoring of citizens living in territories contaminated with radionuclides, as well as in the development of regulatory documents for the provision of targeted medical care to people from groups at increased risk of radiation exposure that use personalized medicine methods (34).

Current studies are focused on the comparative analysis of modern risk assessment models for exposure to IR, developed by UNSCEAR, ICRP and WHO (35).

In the period 1992-2017, based on the NRER, the assessment of IR risks of mortality from solid cancers was carried out in a PMCCNA cohort in 1986-1987 (36).

Using the method of statistical relationships, work is being done on the radio-epidemiological classification of the causes of death by malignant neoplasms of the population most contaminated with radionuclides due to CNA in Bryansk, Kaluga, Tula and Oryol regions. Data on mortality from malignant neoplasms for the observation period 1993-2017 were used. The number of men who died during the observation period was 30,771 people (5,407 deaths from cancer), women – 29,033 people (3,472 deaths from cancer). The results show that for the population of the four regions, being the most polluted as a result of CNA, no statistically significant relationships were found between the causes of death by malignant neoplasms and the radiation dose both for the entire class of malignant neoplasms and for the ICD-10 rubrics of three digits in this class. Statistically significant relationships with radiation dose were observed for certain diagnoses of the causes of death: among the male population – for gastric cancer of unspecified location (C16.9) and for pancreatic cancer, unspecified (C25.9); in the female population – for stomach cancer (C16.9) and for lung cancer of unspecified locations (C34.9). These diagnoses of the causes of death should first of all be subject to a more sensitive and specific radio-epidemiological analysis, taking into account possible risk factors. The presented methodology defines the priority areas of research for a more precise radio-epidemiological analysis of dose-effect relationships among the population living in areas contaminated with radionuclides as a result of CNA. The methodology and the results of its use can be useful in the work of expert councils to establish a causal relationship between a disease (death) and the impact of man-made factors (37).

Research evaluating median survival time of the subjects after diagnosis of solid cancers in a cohort of PMCCNA exposed to IR is of interest. Individual medical and dosimetric information of male subjects for the observation period from 1991 to 2015 was analyzed. The cohort size in 1991 was 142,871 individuals. These were the participants, who worked in the area in 1986-1987. The number of solid cancers with documented stages of the disease was 7,652 cases, of which deaths constituted 5,085 (4,351 people died from cancer). The internal classification of cancer prevalence stages was used in the research. The median survival time after diagnosis of solid cancers (ICD-10: C00-C80.9) with documented tumor prevalence stages for the period 2000-2015 was 4.73 years; for malignant neoplasms of respiratory organs (ICD-10: C30-C39.9) – 2.57 years and for malignant neoplasms of digestive organs (ICD-10: C15-C26.9) – 3.55 years. The median survival time during the observation period was continuously increasing, despite the aging of the cohort and the increase in overall mortality. The dependence of the median survival time on the stage of tumor development was studied. In the case of solid cancers, the survival time when moving from stage 1 to stage 4 decreased 7 times (from 8.62 to 1.22 years). The dependence of the median survival time in cases of solid cancers on the radiation dose was studied. Two dose groups were considered: ≤100 mGy (average dose 56.6 mGy) and >100 mGy (average dose 187.9 mGy). The median survival time was 4.66 and 4.72 years, respectively, and their difference was not statistically significant. Studies conducted in a cohort with a changing size and age structure were relevant in the context of assessing the consequences of the impact of man-made factors on the health of individual populations and groups of people (38).

Effects of IR on children whose parents were irradiated

The review of data from the literature on the issue of hereditary effects in offspring due to parental contact with mutagenic risk factors highlighted various agents that cause adverse effects on the hereditary apparatus, including chemical, infectious, physical and biological (39).

The CM analysis in the offspring of Mayak Production Association employees who accumulated preconception doses of external gamma radiation is of a fundamental scientific interest. A retrospective study was conducted on 1190 children born in 1949-1969, of which 238 were descendants of workers in an enterprise with a high risk of radiation exposure. Maximum comparability of

groups formed from the infant population of Ozyorsk was achieved by selection by gender, year of birth and age of parents at birth. CM frequency comparison was performed using the χ^2 test, Fisher's exact test. The OR was calculated with a 95% confidence interval. To identify the latent factors, factor analysis was applied, using the method of principal components, followed by the normalized Varimax rotation. The range of external gamma irradiation doses to the gonads of workers at the Mayak Production Association was 0.09-3523.7 mGy; the average cumulative dose was 373.6±34.2 mGy. In the group of offspring of irradiated mothers, every tenth child was born to a mother who had a cumulative preconception dose of external gamma irradiation to the gonads (ovaries, sex glands) of more than 1 Gy. The comparative analysis did not reveal statistically significant differences between the groups regarding the incidence of CM, including the nosological forms. The OR indicator as a whole was 0.86 (0.46-1.59), in boys it was 0.88 (0.35-2.2), and in girls – 0.84 (0.36-1.94). Differences in the CM structure were noted: CM of the nervous system, respiratory organs (23% each) and CM of the musculoskeletal system (15.3% of all defects) predominated among the offspring of irradiated mothers; among children of intact parents, CM of the musculoskeletal system (23.3%) and nervous system (21.7%) were predominant. Gender differences in CM structure were observed in the compared groups. Chromosomal pathology was not recorded in both groups. In the cohort of offspring of exposed mothers, CMs were diagnosed in children whose mothers accumulated preconception doses of external gamma irradiation to the gonads in the range of 1.9–1635.5 mGy, with an average dose of 307.5 mGy. The factor analysis in the group of offspring of workers in the nuclear risk area revealed four factors that characterize the mothers' pre-conception exposure (21.5% of the variance), the antenatal period of the offspring (17.1% of the variance), the obstetric and gynecological antecedents (12.9% of the variance) and mothers' bad habits – alcohol consumption and smoking (11.0% of the variance). Considering the identified characteristics, it is necessary to continue the study with the expansion of the group of descendants and the period of their observation (40).

Scientific studies demonstrate that during intrauterine development, the developing organism is particularly sensitive to adverse effects. Radiation-mediated immunological disturbances play an important role in shaping not only the early but also the long-term effects of exposure. The structure of immune deficiency syndromes was dominated by allergic and autoimmune syndromes. Immune status has been studied most fully in individuals who lived in the Techa River Basin and were subjected to chronic radiation exposure as a result of liquid radioactive waste spills from the Mayak Production Association. During the long-term follow-up period, various disorders of innate and adaptive immunity were recorded in this group of individuals. It is of interest to evaluate the composition of the lymphocyte subpopulation in individuals exposed to intrauterine irradiation in the long-term post-irradiation period, using flow cytometry. In the study, the main subpopulations of lymphocytes were analyzed in 56 subjects: 29 being exposed to intrauterine irradiation (23 women and 6 men) and 27 from the control group (25 women, 2 men). The age of the people examined varied from 52 to 72 years. Results show that there were no deviations in the absolute and relative content of lymphocyte subpopulations. A tendency to decrease the number of lymphocytes expressing the early activation marker CD25 was established as a function of the increase in the total dose of external γ-irradiation of the mother during pregnancy. The data obtained on the composition of the lymphocyte subpopulation were consistent with the results of a survey of people who lived in the Techa River basin and were subjected to intrauterine exposure as a result of liquid radioactive waste spills from the Mayak Production Association, during which no changes were also detected in the composition of the lymphocyte subpopulation in prenatally irradiated individuals. The tendency to decrease the relative number of lymphocytes expressing the early activation marker CD25 in individuals exposed to intrauterine irradiation as a function of the increase in the total dose of external γ radiation absorbed in the bone marrow during maternal pregnancy was consistent with the results of experimental studies. Thus, the authors note that the study of people exposed to intrauterine irradiation did not detect abnormalities in the main lymphocyte subpopulations. A tendency to decrease the relative number of lymphocytes expressing the early activation marker CD25 in individuals exposed to intrauterine irradiation was observed as a function of the increase in the total dose of external γ radiation absorbed in the

bone marrow during the mother's pregnancy (41).

The author's data on the genetic consequences on the population of the reproduction of various mammal species under conditions of high levels of ionizing radiation following the accident at the Chernobyl and Fukushima nuclear power plants were also taken into account. Such conditions contribute to the genomic instability of the parental population, which was directly exposed to increased doses of ionizing radiation, and to the basic reproduction of offspring with a relatively increased stability of the chromosomal apparatus. It is assumed that the use of the relative reproductive "success" of carriers of increased genomic stability under conditions of environmental change as an integral indicator of resistance to the selective action of environmental stressors can be used to identify radioresistant individuals.

The importance of transgenerational transmission of PTSD features and its mechanisms, including microRNA transmission through sperm, changes in parental and offspring microbiota, and cultural inheritance, are discussed to explain the complexity of observed radiobiological effects and their transmission across generations. Man-made accidents (such as Chernobyl and Fukushima) and more frequent economic crises pose the risk of biosocial consequences in the fabric of society, based on the legacy of epigenetic, cultural and micro/macrobiotic changes (42).

The assessment of the effect of ionizing radiation on the offspring of exposed parents is one of the most discussed problems in the epidemiology and radiobiology of radiation effects research. In the last three decades, the main focus of research on the radiological consequences on the descendants of people exposed to radiation as a result of the Chernobyl accident has focused on the studies of the possible relationship between the development of congenital malformations and their dependence on the radiation dose received by their fathers – liquidators of the consequences the Chernobyl nuclear accident. The study of 11,698 liquidating fathers and 15,450 of their children did not detect an effect of fathers' exposure. No statistically significant risks of radiation morbidity were found for most disease classes and headings, including the classes "All neoplasms" and "Congenital anomalies (malformations), deformities and chromosomal disorders". It should be noted that the average external gamma irradiation dose of the fathers was 130 mGy. Three methods of statistical analysis were used in the study: descriptive analysis in dose comparison groups, a method for determining statistical relationships based on data mining, and morbidity modeling (43).

Research conducted in Japan after the Fukushima nuclear accident detected a significant association between effective external dose rate and thyroid cancer detection rate in youth and adolescents living in Fukushima prefecture: the detection rate ratio per μSv/h was 1.065 (44), the same trend being observed in studies performed on PMCCNA children (45).

The epidemiological study of the incidence of thyroid cancer in the Russian Federation after the CNA established that only the population of children in the territories of the country contaminated with radionuclides, which received a thyroid dose of more than 100-150 mGy due to the incorporated exposure to 131I, should be included in the radiation risk group. Taking into account data from Chernobyl and the recommendations of the International Commission on Radiological Protection, predictive estimates of the occurrence of an increased incidence of thyroid cancer in the Japanese population living near the Fukushima-1 nuclear power plant were made. The authors conclude that large-scale studies conducted and included in the National Epidemiological Radiation Registry found that only children who received radiation doses greater than 100-150 mGy due to incorporated irradiation of the thyroid gland with the radionuclide 131I should be included in the group at high risk of radiation exposure for additional induction of thyroid cancer. Taking into account post-Chernobyl epidemiological data and accepted international standards, a forecast was made for a possible additional incidence of thyroid cancer among the Japanese population living near the Fukushima-1 nuclear power plant, depending on the radiation doses received (20).

DISCUSSIONS

The mechanisms of action of high doses on the human body were elucidated by studying the acute effects. To detect the action of small doses, a series of researches were carried out on PMCCNA, victims of the accident at the Fukushima Daiichi

nuclear power plant (Japan), residents of the Chelyabinsk region, etc. and important fundamental results were achieved. Thus, it was shown that the mental morbidity of the population in areas that were exposed to accidental radioactive contamination more than 70 years ago now reflects the general trend of deterioration of the mental health of the population of the Chelyabinsk region. It can be assumed that the incidence of mental disorders in the population of the Chelyabinsk region is determined by a complex set of interacting factors (socio-economic, individual-psychological, radiation, informational, etc.), among which the most important are from a social point of view, determining the mechanisms of formation of mental pathology.

As a result of occupational exposure of the thyroid gland to low-dose IR sources, under the influence of X-rays, the intercellular contacts of thymocytes are disconnected, which can lead to a decrease in the synthesis of thyroid hormones and, as a result, to the development of hypothyroidism – the pathology of non-tumor genesis. An adequate approach to the problem in question is missing in the literature.

During the post-Chernobyl period in the targeted cohort, a large number of deaths at working age were established, determining that until 2002, mortality was caused by external factors and diseases of the circulatory system, later by diseases of circulatory system and malignant neoplasms of the lungs. It can be assumed that damage to MCB vessels of the brain and heart has important targets of the harmful effect of "low" doses of IR. Their changes in the remote period from the accident exacerbate (intensify) the psychosomatic maladjustment of these patients and can explain the high mortality from various external causes and diseases of the cardiovascular system (5).

The problem of hereditary effects in offspring, due to parental contact with mutagenic risk factors, highlighted those of a chemical, infectious, physical and biological nature. At the same time, the influence of smoking and parents' age on the occurrence of *de novo* mutations is essential. The role of the radiological factor in the genesis of hereditary disorders in the offspring of parents exposed to IR has been demonstrated. The stages of the development of radiation genetics, the evolution of ideas about IR damage by presenting the results of experimental, cytogenetic, molecular genetic and epidemiological studies, analyzing the contribution of parental exposure to inherited pathology in offspring were described. Attention is focused on the "non-target" effects of radiation, with evidence being presented about the possibility of transgenerational transmission of genome instability. The special contribution of the studies of the descendants cohort of the victims of the atomic bombings of Hiroshima and Nagasaki should be noted, being considered the main scientific platform for radiation risk assessment. Hereditary effects are known in the descendants of people who suffered as a result of radiotherapeutic exposure, that is, had professional contact with IR, or were exposed to radiation as a result of CNA, nuclear weapons tests at the Semipalatinsk test site, chronic exposure on the territory of the radioactively contaminated Techa River and areas with increased natural radioactivity. Despite numerous confirmations of radiation-induced effects in offspring through experimental and genetic-molecular studies, the results of epidemiological research remain contradictory. We can consider possible reasons for explaining these discrepancies: the evolution of views on legacy effects in the international radiation safety system; the ICRP new approach to hereditary risks; the dynamics of the weighting factor for gonads in the evaluation of the effective dose; methods of evaluating hereditary effects (direct method and double dose method). In order to reduce the uncertainties in the modern assessment of radiation genetic damage, further study of radiation-induced heritable effects is probably necessary. It is worth highlighting the possibility of analyzing the inherited effects on the example of a cohort of descendants of the workers of the production association "Mayak" – the first enterprise in the nuclear industry of the Russian Federation (39).

The study of radiation-induced effects in children of persons exposed to radiation at work is important for the standardization of man-made exposure doses of persons of reproductive age and for predicting the adverse effects of parental exposure in offspring.

The current environmental situation imposes the priority of the protection of the genome and the human body as a whole over the action of IR. Primary disease prevention is a priority component of human health protection. In some localities, the primary prevention of radiogenic cancer in the post-Chernobyl period was insufficiently carried characterized by frag out, and certain stages of its

development are mentation, the lack of a scientific basis, etc. The global distribution of radiation sources, modern ideas about the aetiology and pathogenesis of radiogenic cancer indicate the dominant carcinogenic risk of low doses of radiation. The scientific and practical aspects of the primary prevention of radiogenic tumors are of interest. This reduces the carcinogenic risk in people with increased individual radiosensitivity. Such a strategy should be carried out in parallel with general preventive measures aimed at reducing the incidence of cancer (46).

The lack of information on external exposure dose for many PMCCNA necessitated retrospective dosimetry. Evaluation of the possibilities of using cytogenetic dosimetry methods to determine external exposure doses for PMCCNA exposed to low doses of IR in a remote period of time is of particular interest from a scientific point of view. Biological cytogenetic indication and biological dosimetry of ionizing radiation were performed at PMCCNA 27-30 years after participation in liquidation works. Stable and unstable chromosomal aberrations in peripheral blood lymphocytes were analyzed. In the analysis of unstable chromosomal rearrangements in about 50% of PMCCNA, radiation markers were identified with a frequency exceeding those of the control group, which indicates the impact of IR. In the absence of information on the received dose of external exposure, the assessment of stable chromosomal aberrations makes it possible to reconstruct the radiation dose for PMCCNA exposed to low doses of ionizing radiation, which can be the basis for solving the problem of compensation for the damage caused to their health (2, 11).

Some researchers say that the structures of the neocortex of the frontal and temporal lobes, responsible for cognitive functions, are the most sensitive to the harmful factor of a nuclear accident. Changes in these brain structures revealed in PMCCNA were similar to those in the elderly with DEP, however, they are more pronounced clinically, supporting the hypothesis of early brain aging in PMCCNA (12).

CONCLUSIONS

1. The studies carried out on PMCCNA originating from the Republic of Moldova, Ukraine, Belarus, the Russian Federation and the Baltic countries; victims of the accident at the Fukushima Daiichi nuclear power plant (Japan), residents of the Chelyabinsk region, etc. highlight the harmful impact of ionizing radiation on the health of the exposed, manifested by clinical, genetic and immunological effects.
2. Important fundamental results were obtained in establishing the mechanisms of action of small doses of ionizing radiation, with the identification of biological markers of the radiation factor.
3. The analysis of the results of studies of clinical, immunological and genetic effects in those exposed to occupational/accidental ionizing radiation and their descendants, highlight significant fundamental results and emphasize the importance of investigations aimed at elucidating some markers of the radiological factor and the priority of biological dosimetry in ascertaining exposure doses.
4. The study of ionizing radiation-induced effects in children of persons exposed at work or accidentally is important for the standardization of man-made exposure doses for persons of reproductive age, as well as for predicting the adverse effects of parental exposure in offspring.
5. The lack of information on external exposure dose for many PMCCNA necessitated retrospective dosimetry. Evaluation of the possibilities of using cytogenetic dosimetry methods for determining external exposure doses for PMCCNA exposed to low doses of ionizing radiation in a distant period of time is of particular interest from a scientific point of view.
6. Considering the importance of the problem and the possibility of new radiation accidents, studies in this field urgently need to be continued.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICAL APPROVAL

Approval from the Research Ethics Committee no. 87 of 27.06.2017, *Nicolae Testemiţanu* State University of Medicine and Pharmacy, of the research topic, the project protocol, the informed consent.

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