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# THE ESTIMATION OF THE LONG-TERM EFFECTS CAUSED BY LOW DOSES OF IONIZING RADIATION. REVIEW

#### Summary

The objective of this review is to analyze the current state of the issue of the long-term effects caused by chronic low-dose irradiation. Unfavourable impact a certain degree correlated with age at the time of exposure to ionizing radiation and its dose and for certain types of diseases characterized by a long latency period. The relevance of research prompted by the fact that in modern radiobiology and radiation medicine is no clear answer.

**Key words:** long-term effects, radiation exposure, small doses radiation.

**Background.** In recent years all over the world have greatly increased the number of studies devoted to a detailed study of the events taking place at all levels of biological organization under the action of ionizing radiation in the range of low doses [1–3]. This is due to a significant decreasing of interest in work have become less actual in the field of the harmful effect of radiation and increased attention to the effects of low doses. Radiation and biological effects at low doses and low dose rates - the subject of special interest of researchers in various fields.

**Purpose** of this study was carried out literature review of modern sources of information, followed by an analysis of data as the issue of the long-term effects caused by chronic low-dose irradiation.

**Methods:** To achieve this purpose, the analysis of data in the literature indexed in the databases MEDLINE, Embase, e-library, Google Scholar for the last 10 years (2002 to 2013), the systematization of materials science data on the following subject categories were carried out:

- 1. The long-term genetic effects caused by ionizing radiation;
- 2. Cytogenetic effects of ionizing radiation on human lymphocytes;
- 3. Long-term somatic effects caused by ionizing radiation

**Results and discussion.** The long-term genetic effects caused by ionizing radiation.

Due to technological progress, the development of nuclear power engineering and extensive use of sources of ionizing radiation in the national economy and radiopharmaceuticals in clinical practice are primary the problem of pollution and study its effects on human heredity [4].

The sources of knowledge of the effects of ionizing radiation in small doses are experimental and theoretical and radiation epidemiology study. Each of these sources has its advantages and disadvantages. The experiment can well control and vary the conditions of the experiments, to achieve statistical significance of the increase in the number of objects or experiments. However, there is a problem the eligibility of transferring experimental results on human [5]

Radiation-epidemiological studies, it would seem, should give a straight answer about the dangers of ionizing radiation or harmlessness, but limited the surveyed groups and inaccuracies in the estimates of individual doses, lead to incorrect conclusions [6].

As some researchers believe the most important for the next generation of the descendants of victims of ionizing radiation exposure are genetic changes [7; 8].

It is known that the genetic effects of radiation are non-stochastic, which on the one hand, is often observed

"superlinear" output effect, on the other hand - the stimulating action of radiation, so-called hormesis. One of the most interesting phenomena of hormesis it is radiation-induced reaction adaptive response in which small doses of radiation adapted cell system by inducing or stimulating the reparative proliferation. The consequence of DNA repair may be a reduction in the frequency of spontaneous cancer, or the likelihood of its occurrence only in the subsequent re-radiation [9].

It is suggested that the hypothesis of the mechanisms of radiation stimulation is intensification of the DNA repair and recombination of oxygen free radicals at low dose rate radiation [10]. However, a number of researchers in their studies have convincingly shown that even when stimulating doses of ionizing radiation against rapid cell division and observed adverse mutagenic effects, especially increasing in the number of chromosomal aberrations [11].

Genetic effects of radiation are also divided into early and late. The early consequences, according to some researchers should be classified those effects that occur: 1) The death of the offspring parents which are exposed by radiation at different stages of ontogenesis 2) the appearance of some of congenital malformations (CM), and 3) a breach of fertility in the parents. As early and somatic effects, they are associated with tissue destruction due to cell death caused by genetic effects, for example, blockade of stage specific genes. This process turns out to be fatal for the organism (prenatal and early postnatal death) and damage to organs and tissues (CM, reduced fertility). To the distant genetic effects of radiation include increased risk of carcinogenesis, hereditarily determined CM and physiological inferiority progeny of irradiated parents [12]. The difference between these genetic effects similar to somatic effects, it is blocked with the same intensity of radiation exposure doses, which is apparently due to elimination of individuals with severe defects in the early stages of ontogenesis and survival of only those who is phenotypically and physiologically irrelevant species deviate from the norm.

Cause of outlying somatic and genetic effects of radiation are induced recessive mutations in the heterozygous state, as well as epigenetic disorders, conditional destabilization of the hereditary apparatus and increasing of probability of activation of proto-oncogenes and functional deficiency of the cell genome [13].

For today all of the genetic effects of ionizing radiation can be divided into three groups: the mutagenic, teratogenic, carcinogenic. Genetic effects as well as tumorigenesis, referred to as stochastic, which may involve more or even a single cell and no threshold dose [14]. As highlighted in a publication prepared for the 30th anniversary

of the UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) "this is the most serious effect on the consequences of all the known effects of exposure of the human fetus."

To this day, there is uncertainty as to refference of teratogenic effects to "pure" genetic. Teratogenic effects referred to genetic, mean of the common misconception that the mechanism of occurrence of deformities and other birth defects involved the mother has exposed by radiation during pregnancy. In fact, it is well established that teratogenic effect is a consequence of direct exposure of the fetus.

Exposure at early stages embryogenesis typically leads to fetal death, and in the middle stages – to the death of newborn [15]. The impact during the period of organogenesis is the main variety of malformations, fetal exposure – radiation sickness, and in the long-term period – malignant tumors.

It is known that the effects of ionizing radiation on the body structure induced genetic mutation at all levels of genes generation: chromosomal and genomic [16]. Mutations in somatic cells may be the progenitors of carcinogenesis, destabilize the genome, causing a decrease in functional and reparative activity, the resistance of the body and limiting adaptive capacity [17]. Mutations that occur during radiation exposure in germ cells, affecting individual genes, chromosomes or sets of chromosomes can occur in a number of generations in the form of chromosomal disease, and hereditary diseases. At the same chromosome and dominant mutations appear in the first generation, but later found recessive [18].

One example of chromosomal abnormalities in the reproductive cells of the parents is Down syndrome. Relationship between the frequency of Down's syndrome and exposure to pregnant women has been demonstrated in several studies [19–21].

Svyatovaya G.S. conducted genetic studies of populations of Abay and Beskaragai regions of the East Kazakhstan region [4]. It is known that these areas are zones of emergency radiation risk, where during the testing of nuclear weapons, the radiation dose to the population was 100> sSv. The highest incidence of Down syndrome is detected in a population of Abay district, which was 1,85 ± 0,10 per 1000 live births, which was significantly higher than that of all the tested areas and control regions 0,78 ± 0,01 per 1000 births. For Beskaragai district, the figure was  $0.97 \pm 0.11$  per 1000 births, which is also significantly higher than in the control area, but the difference was only approaching statistical significance (t = 1,73; p > 0.05). It should be noted that the incidence of Down syndrome in a population of Abai district srednepopulyatsionnuyu exceeded not only their frequency in the cities of the Republic of Kazakhstan, but also data from the International Register of EUROGAT 0,70-1,40 per 1,000 births of nondisjunction of chromosome 21 in meiosis.

Of the current epidemiological approaches: biochemical monitoring, cytogenetic testing, the study of specific phenotypes, the most acceptable to the accounting for congenital malformations. Using the CM as an indicator of the harmful effects of the environment on man is determined by the frequency of this disease in the newborn total of 2% or more of deaths of children – 25%. Advantages excluding CM lies in the fact that they occur with high frequency in the population, genetic disorders play a significant role in their origin and in the majority of clinically recorded. It is possible to survey large numbers of people without the use of sophisticated methods of investiga-

tion and comparison with the results of retrospective studies [22]

Foreign authors which are studying the problem of radiation-induced CM showed no increase in the frequency of CM after the accident at the Chernobyl nuclear power plant in Western Europe, except for some cases of spinal hernia. In 9 countries of Western Europe was conducted epidemiological study of frequency and dynamics of the CM after the accident at Chernobyl [23].

An epidemiological study of the health of newborns in the contaminated areas of the Ryazan region of the Russian Federation has shown that the incidence of stillbirth from CM in the whole region in the post-accident period compared to the pre-accident is practically unchanged at 8.7 and 8.8 per 1,000 live births [24].

Cytogenetic effects of ionizing radiation on human lymphocytes.

Cytogenetic methods are currently the most objective research to quantify damage in cells caused by radiation exposure. It is proved that radiation exposure is a factor in destabilizing the chromosomes of human, accelerating the aging process and thereby shorten the lifespan.

Cytogenetic studies conducted 40 years after the atomic bombing of Hiroshima, showed that stable chromosome aberrations are an indicator of radiation exposure and dose [25; 26]. Currently, there is a point of view that the spectrum of chromosomal transformations and their frequency are comparable to the acute and chronic exposure [27].

Is widely accepted that cytogenetic markers of radiation exposure are exchange-type chromosome aberrations. They are divided into 2 groups: the unstable and stable aberrations. Was established that cells containing unstable aberration (dicentric and ring chromosomes, acentric fragments). The presence of accompanying dicentrics and rings paired fragments indicate that the cell entered in the first postradiation mitosis.

The group of stable chromosome aberrations include translocations, inversions, deletions, insertions. According to the nomenclature of ISCN (1985) all allocated nine kinds of stable chromosome rearrangements. The frequency of symmetrical exchanges (translocations) is the most reliable marker of radiation exposure even in remote periods after radiation exposure. These aberrations are stored in cell division, did not lead to mitotic cell death, not eliminated over time, accumulate during long-term effect of radiation and persist even decades after acute exposure [28; 29].

Widely used to assess genetic changes at the chromosomal level after the effect of low doses of ionizing radiation is the method of accounting of chromosomal aberrations in human peripheral blood lymphocytes. Cytogenetic technique originates from development in 1960, cultivation techniques and obtain metaphase preparations of human peripheral blood lymphocytes and the subsequent papers in which it was first shown that the yield of chromosomal aberrations induced by X-rays in vitro, depending on the radiation dose [30].

For detection of chromosomal aberrations in metaphase cytogenetics lymphocytes using various methods: a simple method for staining and fluorescence in situ hybridization (FISH) etc. Each method has its advantages and disadvantages. Simple staining method allows you to quickly and accurately estimate the frequency of unstable chromosome aberrations. The use of FISH-method, which uses fluorescent dyes can detect chromosomal aberrations as a stable and unstable type. The advantage of this

technique to a simple painting of chromosomes is, above all, is that it allows you to quickly and correctly assess the frequency of stable aberrations, exploring for a short time a large number of cells. Pantsentromernye probes used in combination with chromosome probes to distinguish from the dicentric reciprocal translocations [31]. Application of this method can accurately estimate the ratio of stable and unstable aberrations in the decades after the exposure.

Currently, it is sufficient amount of work on the spontaneous frequency of chromosome aberrations in human lymphocytes [32]. The results of these studies are as follows. Human peripheral blood lymphocytes are characterized by very low frequency of spontaneous chromosomal aberrations (average 0.01-0.02 per cell), the average frequency of aberrant cells was 1.2%, the level of spontaneous aberrations in cultured human peripheral blood lymphocytes is a pretty solid performance, not beyond the control of any individual, nor of the sexual characteristics of individuals, but is dependent on the age of the person. With increasing age, the frequency of aberrations in cells increases - in those over 60 years old to 0.05-0.06 aberrations per cell. The establishment of a sufficient level of accuracy of spontaneous chromosomal aberrations in cultured lymphocytes has allowed greater use of this method in determining the effect of environmental factors on human heredity and to predict the effects caused by pollution. Therefore, the use of analysis of chromosomal aberrations in human lymphocytes conclusively proven in many local and foreign studies and documents recommended by WHO, IAEA for practical use [33]. In the analysis of data on the spontaneous level of unstable aberrations impression that their frequency varies in different cohorts of people.

Suggest that exposure to low doses of radiation at the level of the background leading to the emergence of longterm effects in the form of increased frequency of chromosomal aberrations [34]. A study conducted in a group of 200 people in the Brazilian village of Guarapari, where due to the monazite sands average dose, excluding the dose from radon is 6.4 mSv /year, found an increased frequency of chromosomal aberrations in the amount of peripheral blood lymphocytes compared with a similar the control village. In studies of British scientists demonstrated a significant increase in the frequency of chromosome aberrations in the average group, which is positively correlated with the duration of exposure and cumulative dose [11]. They are suggested to determine the coefficient of the output of dicentric chromosomes at 1 sGy in chronic exposure, of course, such chromosomal aberrations is not inherited.

Long-term somatic effects caused by ionizing radiation The sources of information of exposure to ionizing radiation on the health effects at different groups exposed are: persons exposed to radiation during nuclear tests [35; 36]; persons exposed to radiation during accidents and incidents at nuclear power plants, reprocessing plants, storage of radioactive waste during transportation of radioactive sources [11]; the victims of the atomic bombing of Hiroshima and Nagasaki [37; 38]; professional staff whose activities are connected with the possibility of significant radiation doses (radiobiology, radiation experts hazardous industries, miners, etc.) [39]; patients receiving relatively high radiation doses in a variety of therapeutic purposes [40; 41]; population living in normal conditions near nuclear plants and test sites [42]; population areas with high natural background radiation.

The cause of death of the overwhelming majority of the victims of the atomic bombings were the blast and thermal effects. At a distance of 1.5 km to the epicenter of the number of survivors was an order of magnitude less than the number of victims. Since the absorbed dose at this distance was about 0.1 Gy, then the majority of those who have survived the bombing, the radiation doses were low. Doses less than 0.1 Sv received 77% of the survivors of the bombing. From here atomic bombing of Japan is an interest in light of the question of the influence of small doses. The most frequently observed leukemia, the incidence of which has increased three years after the bombing, and reaching a maximum in 1951-1952, became gradually decline. Was less than the age of the bombardment, the greater was the risk factor at the peak, the earlier and steeper increase was faster and the risk ratio decreases with time after the peak [43]. New facts on the physics of nuclear explosions and forced dosimetry in 1965 and 1986 overestimate the dose as tissue, including bone marrow, and the dose dependence of radiationinduced leukemia in the exposed populations of Hiroshima and Nagasaki. In both cases was confirmed by the dependence of the frequency of leukemia from the radiation dose. In the group exposed at the age of 20 years, the incidence of leukemia was twice as high as expected at a dose of 10-40 Rad, and in those over 35 years - with a dose of 40-75 Rad. A higher risk of disease and death was observed in the irradiated in childhood. In children, the most significant was the predisposition to granulocytic leukemia. Of particular interest is the work, highlighting the impact of exposure of pregnant women to the health of the offspring. It was shown that exposure of pregnant women increased the frequency of stillbirth, early infant mortality in children with delays mental and physical development. Irradiation in the early stages of pregnancy at doses of 1.47 Gy caused the development of microcephaly. The highest level of microcephaly and mental retardation established by irradiation at 8-15 week of fetal development, particularly at high doses. Thus, at a dose of 1 Gy microcephaly observed in 72.2% of cases, mental retardation - in 46.2%. The combination of microcephaly and mental retardation when irradiated at 8-15 weeks of pregnancy was noted in 44.4% of cases. Typically, the small dimensions of the head detected at the same time substantially reducing other anthropometric indices, namely, height, weight, chest circumference. Mental retardation have been reported based on the use of IQ-test and evaluation of progress in achieving these children age 10-11 years [38].

The sources of information on the impact of atmospheric nuclear explosions on population data are Nevada and Semipalatinsk test site, the testing in the Marshall Islands. The most famous are the studies on the incidence of leukemia.

In a study of the Brookhaven National Laboratory in the U.S. has been detected at high risk of cancer and benign tumors of the thyroid gland, especially for the residents as well. Rongelap, received the maximum dose (up to 2 Gy in children under the age of 1 year with average values in this age of 0.57 Gy). Tumor frequency and latency period depended on the dose and age. Thus, among the inhabitants of a. Rongelap exposed at the age of 10 years, they were revealed in 59% of the patients, aged 10-18 years - 25% in the more mature age - at 14%. Atrophy of the thyroid gland is described in 2 exposed boys at Rongelap [44].

From 1949 to 1962 at the site was made 111 atmospheric nuclear explosions. For air explosions radioactive contamination occurred in the center of the blast, and at a considerable distance from the epicenter, where possible touch the bottom edge of the cloud of explosion surface.

In Gusev B.I. works is detected the range of effective equivalent radiation doses as appropriate sSv 7-200. The nature of exposure for the majority of the population corresponded to repeated acute external gamma radiation in combination with acute and chronic internal exposure [45]. The peculiarity of the formation of public exposure is that the vast majority of the dose was created relatively short-lived radionuclides (zirconium-95, 97, niobium-95, 97, molybdenum-99, ruthenium-103, iodine-131, 135). Therefore, this kind of public exposure rightly regarded as primarily an acute, in which the biological effects of ionizing radiation is higher than in chronic irradiation.

The external dose accumulated in a relatively short period of time: for the first four days since the loss of radioactive products formed about 70% of the total dose, and within a year - up to 96%. Internal dose accumulated more slowly. As a result of their stay on the trail of the explosion (atmospheric) within one year after the test cumulative total dose of about 96% of the dose that would get people living in the area for 50 years.

Medical examinations of the population were first launched after ground nuclear explosion 08.24.56, when the Ministry of Health of the USSR received information on radioactive contamination of some areas adjacent to test site. In 1956-58 was examined more than 310,000 people from 22 villages. No cases of acute or chronic radiation sickness has been identified. Hematologic studies showed instability in the peripheral blood was observed reticulocytosis, thrombocytopenia and leukopenia due to granulocytes.

Since 1961, clinic number 4 Semipalatinsk started to implement program on study long-term effects of low doses of radiation on the human body. For register was taken of 10,000 people out of the three most affected during the period of nuclear testing in the atmosphere areas of the Semipalatinsk region. These studies have stated there are no differences in the health status of both adults and children, irradiated with a dose of less than 100 sSv. Only in irradiated at a dose of more than 100 sSv showed cytogenetic markers of exposure and symptoms of low immunity 1461

Low material-technical base, the conditions strictest secrecy, lack of health professionals in rural areas are the cause of the fact that over the years 1947-1954 information is not available and in the next few years it is incomplete. Contaminated sites in the area and water sources are not subjected to decontamination, the population was not provided with means of protection and control, food was significantly contaminated [47].

In the early 90's of the 20th century were declassified the first quantitative data on the local deposition of radio-active products at the landfill site which showed that the most significant radioactive contamination of Semipalatinsk, Pavlodar and Karaganda regions and partially Altai Russia [48].

The study of the health of more than 40,000 residents of the Republic of Kazakhstan for 1957-1993 years., Who were in the area of radiation exposure Semipalatinsk test site, in comparison with a control group of 12,000 people found no increase in mortality among exposed from non-malignant diseases of various organs and systems, in-

creased mortality from malignant tumors observed in a cohort exposed at a dose of 100 or more sSv [42].

**Conclusion.** Analysis of the literature showed that the results of scientific studies on the genetic effects of radiation, revealed the high sensitivity of the fetus and the mother during pregnancy. The results of the study of the frequency of malformations ambiguous and revealed significant fluctuations in this disease in children, due to various reasons, including a lack of standardized methods for estimating population frequencies.

On the basis of the existing data in the literature is necessary to continue the accumulation of information about the frequency of unstable and stable cytogenetic markers of human exposure and the search for new genetic indicators to reconstruct the radiation dose for acute and chronic radiation exposure, as well as predict the stochastic effects caused by ionizing radiation.

Recently published a lot of information on the health effects of prolonged radiation exposure on the health of those directly exposed to radiation and their descendants in the Semipalatinsk region that have established the significant increase in somatic diseases, changes in immune status, genetic factors influence the effects of radiation nature. However, the question of studying long-term effects when exposed to low doses of ionizing radiation is still open.

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#### Тұжырым ИОНДАУШЫ СӘУЛЕЛЕРДІҢ ШАҒЫН ДОЗА ӘСЕРІНІҢ КЕЙІНГІ ЗАРДАПТАРЫНЫҢ БАҒАЛАУ (ӘДЕБИЕТТЕРГЕ ШОЛУ) М.Р. Мадиева

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Аталған шолудың міндеті, иондаушы сәулеленудің аз мөлшерінің сқзылмалы әсерінен кейінгі ұзақ уақыттан кейінгі әсерін бағалау. Кері әсері иондаушы сәулеленудің әсер еткендегі жасына, мөлшеріне және латентті периодына байланысты сипатталады. Қазіргі заманғы радиобиология және радиационды медицинада біркелкі жауаптың болмауы зерттеу өзектілігігін құрайды

**Негізгі сөздер:** сәулеленудің ұзақ ұақыттан кейінгі әсері, радиационды әсер, аз мөлшермен сәулелену.

#### Резюме ОЦЕНКА ОТДАЛЕННЫХ ЭФФЕКТОВ ПРИ ВОЗДЕЙСТВИИ МАЛЫХ ДОЗ ИОНИЗИРУЮЩЕГО ИЗЛУЧЕНИЯ (ЛИТЕРАТУРНЫЙ ОЗОР) М.Р. Мадиева

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Задачей данного обзора является анализ современного состояния вопроса об отдаленных эффектах, вызываемых хроническим низкодозовым облучением. Неблагоприятные влияния в определенной степени соотносятся с возрастом на момент воздействия ионизирующего излучения, его дозой и по отдельным видам патологии характеризуется длительным латентным периодом. Актуальность исследования продиктована тем, что в современной радиобиологии и радиационной медицине пока нет однозначного ответа. Обзор составлен в рамках НТП (2012-2014 г.)

Ключевые слова: отдаленные эффекты облучения, радиационное воздействие, облучение малыми дозами.

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## ВЛИЯНИЕ КУРЕНИЯ НА РИСК РАЗВИТИЯ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА. ОБЗОР ЛИТЕРАТУРЫ

#### Аннотация

Литературный обзор посвящен влиянию курения табака на состояние сердечно-сосудистой системы, микроциркуляторного русла и эндотелий у молодых здоровых людей и больных ишемической болезнью сердца. Рассмотрены также отдельные аспекты лекарственной терапии ишемической болезни сердца.

Ключевые слова: микроциркуляторное русло, табакокурение, сердечно-сосудистая система, эндотелий.

По данным многофакторного анализа, относительный риск развития ишемической болезни сердца (ИБС) у курящих женщин составляет 4,2, тогда как у прекративших курение — 1,4 и не отличается от показателей, наблюдаемых у никогда не куривших женщин. Курение у женщин является существенным фактором риска развития сахарного диабета вне зависимости от веса тела [20]. Несмотря на то, что среди курящих больше мужчин, женщины гораздо реже отказываются от курения [22, 26]. Этот тревожный факт был установлен проектом Всемирной организации здравоохранения (World Health Organization MONICA), цель которого состояла в том, чтобы определить современные

тенденции течения ИБС по отношению к классическим коронарным факторам риска за 10 лет при обследовании 38 популяций населения в 21 стране на 4 континентах [22]. По некоторым характеристикам в комбинации с курением табака женщины заняли преимущественное место относительно более высокого риска ИБС, чем мужчины. Согласно исследованию NHANES I курение табака повышает на 45% риск развития хронической сердечной недостаточности (ХСН) у мужчин и на 88% — у женщин [23].

Выяснено, что риск развития атеросклероза и ИМ при курении увеличивается 1,5 – 6 раз [1, 6, 7]. Курение табака также является фактором риска атероскле-