ASSESSMENT OF THE EFFECT OF CHRONIC EXPOSURE ON PREMATURE AGING OF HUMAN T-LYMPHOCYTES BASED ON UNSTABLE CHROMOSOME ABERRATIONS

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For more than 60 years, residents of the villages on the Techa River have been chronically exposed to combined radiation, receiving a wide range of doses. Red bone marrow (RBM) is the critical system in the exposure conditions. This study aimed to assess the effect of chronic exposure on premature aging of T-lymphocytes based on the frequency of unstable chromosome aberrations; the subjects were the residents of the Southern Urals that have been chronically exposed to radiation. The increased frequency of occurrence of dicentrics and rings in T-cells of the exposed persons was the marker of cellular aging, with the associated doses to the red bone marrow (RBM dose) at 0.5–2.5 Gy. The participants (RBM donors), both exposed and non-exposed, were divided into three age subgroups: 40–59 years old, 60–69 years old, 70–79 years old. The differences in the RBM dose among the exposed individuals were insignificant. In the exposed group, unstable chromosome aberrations (UCA) were recorded significantly more often than in the control group (p = 0.04). The age group of 40–59 years was the one where the exposed donors had significantly more frequently occurring chromosome aberrations compared to the non-exposed participants. There were no such differences registered in other age groups. The age-associated increase of the amount of chromosome aberrations was registered in the non-exposed group only. Chronic exposure to radiation indirectly promotes premature aging of T-lymphocytes: 1) in the long term, the exposed individuals had UCA significantly more often; 2) compared to the control group, the 40–59 years age subgroup of the exposed group had increased cytogenetic index. In the context of this study, the number of dicentrics and rings was not registered as increasing in the older age subgroups of exposed individuals, which may be due to the specifics of the donor inclusion criteria, which, for the elderly, may favor radioresistant individuals.

Keywords: unstable chromosome aberrations, dicentrics, rings, Techa River, aging of T-lymphocytes, chronic radiation exposure, Southern Urals

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Compliance with ethical standards: the study was approved by the ethics committee of the Urals Research Center for Radiation Medicine (Minutes № 5 of December 20, 2022); all the cytogenetic study participants signed a voluntary informed consent for blood sampling and further analysis.

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ОЦЕНКА ВЛИЯНИЯ ХРОНИЧЕСКОГО ОБЛУЧЕНИЯ НА ПРЕЖДЕВРЕМЕННОЕ СТАРЕНИЕ Т-ЛИМФОЦИТОВ ЧЕЛОВЕКА НА ОСНОВЕ НЕСТАБИЛЬНЫХ ХРОМОСОМНЫХ АБЕРРАЦИЙ

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Более 60 лет жители прибрежных сел реки Теча подвержены хроническому сочетанному облучению в широком диапазоне доз. Критический орган при облучении — красный костный мозг (ККМ). Целью работы было оценить влияние хронического облучения жителей Южного Урала на преждевременное старение Т-лимфоцитов на основе частоты нестабильных обменных аберраций хромосом. Маркером клеточного старения была повышенная частота дицентриков и колец в Т-клетках облученных лиц (дозы на красный костный мозг — 0,5–2,5 Гр). Сформированы три возрастные подгруппы (40–59 лет, 60–69 лет, 70–79 лет) среди облученных и необлученных лиц. Подгруппы облученных лиц по дозам на ККМ достоверно не различались. Нестабильные хромосомные аберрации (НХА) в клетках облученных лиц отмечены достоверно чаще, чем в группе сравнения (p = 0,04). Достоверно повышенную частоту хромосомных аберраций выявили у облученных доноров в возрасте 40–59 лет при сравнении с необлученными донорами такого же возраста. В двух других возрастных периодах различий нет. Только у необлученных доноров выявили возрастную динамику увеличения хромосомных аберраций. Хроническое облучение оказывает опосредованное влияние на преждевременное старение Т-лимфоцитов: 1) достоверно повышена частота НХА у облученных лиц в отдаленные сроки; 2) выявлено увеличение цитогенетического показателя у облученных лиц в возрасте 40–59 лет по сравнению с лицами, не подвергавшимися аварийному облучению. Отсутствие динамики увеличения дицентриков и колец в старших возрастных группах у облученных лиц может быть обусловлено особенностью критериев для включения доноров в цитогенетическое исследование. В старшем возрасте критерии могут способствовать включению лиц с радиорезистентными характеристиками.

Ключевые слова: нестабильные хромосомные аберрации, дицентрики, кольца, река Теча, старение Т-лимфоцитов, хроническое радиационное воздействие, Южный Урал

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Over 70 years ago, several accidents happened at the Mayak Production Association facility; as a result of these accidents, more than 100,000 residents of the Southern Urals were chronically exposed radiation. For several decades now, specialists of the Urals Research Center for Radiation Medicine have been monitoring health of the exposed people, studying the effects of ionizing radiation on the organs and tissues of the body and providing medical and psychological assistance to the affected and their offspring. Residents of the Techa riverside villages were exposed to combined radiation: internally, the sources of radionuclides were the food and water consumed (mainly ^{89,90}Sr), and externally there was the γ radiation from the water of the river into which the Mayak PA discharged the liquid radioactive waste. It is important to note here that strontium, being similar to calcium, replaces it in bone tissue and bombards bone marrow cells with β particles, affecting hematopoiesis and immunity of the exposed person. This thesis is confirmed by the results of the published immunological, clinical, cytogenetic, and epidemiological studies that involved population of the Techa riverside villages [1].

In the recent decades, a cohort of residents of the Techa riverside villages has naturally stepped into the late phase of life, which allows starting investigation of the effect chronic radiation exposure has on human aging. Mechanisms of aging is research problem currently tackled by scientists and medical professionals around the world. The goal is to preserve the quality of life of an elderly person and, considering the increasing life expectancy in the developed countries, enable the older generation to fully participate in the life of the society [2].

In addition to studying the natural mechanisms of body aging at all system levels (cellular, tissue, organ, etc.), it is important to investigate the influence of adverse factors that can accelerate the processes leading to aging or trigger its mechanisms earlier, leading to what can be called premature (unnatural) aging of the studied systems or the body as a whole [3]. Hence, studying the effect ionizing radiation has on premature aging of biological systems is an urgent scientific problem, since radiation is one of the factors peculiar to the modern civilization.

Exchange-type chromosome aberrations (dicentric and circular chromosomes) are a generally accepted marker of cell aging; they are characteristic for the processes associated with instability of the human genome [4, 5]. The exchange between different chromosomes is the result of breaks of the DNA's two strands (less often — one strand) and the subsequent incorrect repair thereof. On average, a cell sees about 8.8 breaks of two strands and 55,000 breaks of one strand of the DNA in a day [2]. The efficiency of repair of such breaks and/or elimination of cells with unrepaired DNA damage decreases with age, consequently, the frequency of occurrence of chromosome aberrations increases.

In biodosimetry studies, the increased frequency of occurrence of dicentrics and rings in cells is perceived as a marker of exposure to ionizing radiation. The dose-effect dependencies for X-ray, gamma and other types of radiation have been studied well; this background enables assessing the radiation dose received by a person based on the frequency of unstable chromosome aberrations (UCA) if several months have passed since the exposure. In the long term, the increased frequency of UCA is a biomarker of exposure to ionizing radiation [6].

For over 40 years, the phytohemagglutinin-stimulated peripheral blood T-lymphocytes sampled from the exposed residents of the Southern Urals have been studied in the context of a cytogenetic investigation [7, 8]. Over the entire follow-up period, the chronically exposed persons had significantly elevated levels of UCA compared to the individuals that did not suffer such fallout of the accidents. However, the analysis of the dynamics of the UCA occurrence has shown a two-fold decrease of the frequency thereof, 25 and 50 years since the beginning of the exposure [9], which can be explained by the elimination of cells with unstable aberrations during mitosis due to violation of chromosome segregation into daughter cells. The presence of unstable rearrangements indicates that the cell with an aberration has entered its first mitosis *in vitro* or is a daughter of a precursor cell. It was shown that in the second mitosis, cells with dicentrics occurred 50% less often, but in the third mitosis, despite the 70% drop in the occurrence frequency, such cells were still present [10]. Dicentrics with closely spaced two centromeres had a noteworthy higher chance of surviving the cell cycle.

Numerous radiobiological studies have shown that the frequency of exchange-type chromosome aberrations correlates with age of the person. There were no dicentric chromosomes found in the phytohemagglutinin-stimulated T cells sampled from the newborns, but such did appear and became more common with age [11]. The UCA were obviously growing more frequent in groups of people divided by age with 10-year increments [12]. Thus, an increased frequency of UCA is a marker of exposure to ionizing radiation and cellular aging [13]. Based on the above, it can be assumed that exposure to ionizing radiation leads to the formation of additional chromosome aberrations in cells. Therefore, a greater frequency of chromosomal damage in exposed individuals compared to the same-age non-exposed people will indicate premature aging of cells under the action of radiation.

This study aimed to investigate the effect of ionizing radiation on premature aging of human peripheral blood T-lymphocytes based on the frequency of UCA with red bone marrow as the critical system affected by chronic exposure.

METHODS

Study Design

This work was based on the results of cytogenetic studies of samples taken from 800 exposed individuals (RBM doses from 0.001 Gy to 4.1 Gy, age from 40 to 89 years) and 100 non-exposed people; the tasks were to form age subgroups among the exposed and the unexposed, analyze the frequency of chromosome aberrations in each age subgroup and intercompare the indicators, assess the age-related dynamics of chromosome aberrations, and, based on the results, make a conclusion about the effect of chronic exposure, as suffered by the residents of the Southern Urals, on premature aging of T-cells in the long term.

Characteristics of the donors

The exposure of residents of the Techa riverside villages to combined sources of radiation began in the 1950s, when Mayak Production Association facility discharged radioactive wastes into the river system. The external sources of γ-rays were bottom sediments and floodplain soils contaminated with radionuclides. The internal sources of β-rays were radionuclides that entered the body with river water and locally produced food. The internal exposure doses were estimated based on the measured content of ^{89,90}Sr radionuclides in the body; external exposure doses were calculated based on the duration and frequency of presence of the participants (by age subgroups) in contaminated areas. The study relied on

the red bone marrow (RBM) exposure doses calculated at the biophysics laboratory of the Urals Research Center for Radiation Medicine using the TRDS-2016 system [14].

The cytogenetic study that involves local residents chronically exposed to radiation continues currently; the cytogenetic database receives regular updates. The inclusion criteria for the study are: residence in the Southern Urals (exposed and non-exposed); no history of autoimmune, oncological, chronic inflammatory diseases in the acute phase; for an exposed person — calculated cumulative exposure dose factoring in internal (β-rays) and external (γ-rays) sources [14]. People who underwent X-ray examination less than 6 months before blood sampling were excluded from the study. Same criteria applied to the control group gathered from the residents of uncontaminated areas.

Calculated exposure doses are significantly uncertain (30–60%), therefore, it was decided to include donors with RBM dose from 0.5 to 2.5 Gy. The age of the participants was 40 through 79 years. Thus, ultimately, the exposed group included 343 people (138 male and 205 female), and the control group 83 people. Three age subgroups were formed within each group, spanning ages 40 through 59 years, 60 through 69 years, 70 through 79 years. A fundamentally important fact is that the RBM doses did not differ significantly throughout the age subgroups. Table 1 shows the distribution of participants (donors) into age subgroups.

Thirty-eight of the exposed individuals underwent cytogenetic examination several times. After distribution of the participants into age subgroups, we found that we could follow the dynamics of indicators of only 15 people in different subgroups, and the remaining 23 participants that previously had been examined several times belonged to the same subgroup. Seven people in different age subgroups had zero chromosome aberrations; we did not include them in the analysis of the dynamics of indicators. Thus, we can show the dynamics of the UCA occurrence frequency for 8 people only, and since they were in different age subgroups, Table 2 disregards specific age and cites "early" and "late" age periods.

Preparation and analysis of the slides with metaphase chromosomes

We made cytogenetic preparations of the phytohemagglutinin-stimulated peripheral blood T-lymphocytes following the protocol adopted by the Laboratory of Radiation Genetics of the Urals Research Center for Radiation Medicine. This protocol includes four successive stages: cell cultivation to the metaphase condition (duration — 52 hours, colcemid administered 3 hours before the end, ultimate concentration of 0.1 mg/mL); hypotonic treatment of metaphase cells (1 hour before fixation); fixation of metaphase spreads (freshly prepared fixative: 3 parts of ethanol and 1 part of glacial acetic acid); preparation of the slides with metaphase chromosomes. Metaphase chromosomes were stained with 2% Giemsa solution for 10 minutes, then the stain was washed off and the slides were dried at room temperature [7, 8].

We used AxioImager A2, Z2 microscopes to analyze the preparations (no karyotyping): took 46-chromosome cells with 1–2 overlaps, marked dicentric and circular chromosomes and acentric rings. The number of cells analyzed from each participant ranged from 100 to 500.

Statistical methods

The obtained results were processed using the variation statistics methods: we calculated the median and the 25th and 75th percentiles, as well as the mean per 100 cells (if the percentile values were equal to 0, they were not put into the data table). Kolmogorov-Smirnov test enabled verification of normalcy of distribution of the indicators. Since the data we collected tended to distribute abnormally, we used the nonparametric Mann–Whitney test to compare values in the groups. The χ^2 test allowed assessing dynamics of the individual indicators of exchange-type aberrations. STATISTICA 10.0 software package (StatSoft Inc.; USA) was used to statistically process the data obtained.

RESULTS

Comparing the indicator data gathered from all exposed and all non-exposed individuals, we registered a significant excess of cells with metabolic UCA in the exposed individuals ($p = 0.04$). However, no linear correlation dependence of the studied parameters on the RBM dose was established in the group of exposed persons (all age subgroups) ($R = 0.125$; $p = 0.005$).

Table 1 presents the results of the study of dependence of the chromosomal aberrations occurrence frequency in different age subgroups.

It should be noted that exchange-type UCAs are rare events. In all subgroups (no exceptions), the median was zero, therefore, Table 1 shows the mean value. Absence of the range of 25th and 75th percentiles also reflects zero values. In the control group, the studied indicator grows with age (0, 0.18 and 0.30 per 100 cells). In both "60–69 years old" and "70*p*79 years old" age subgroups of the non-exposed group the frequency of chromosome aberrations was significantly higher than in the "40–59 years old" subgroup ($p^1 = 0.06$, $p^2 = 0.02$). There were more exchange-type events registered in the "70–79 years old" age subgroup, but the differences with the "60–69 years old" subgroup did not reach significance.

As for the frequency of occurrence of chromosome aberrations in the subgroups of the exposed group, the studied indicator did not grow with age. On the contrary, the respective values were the same in all three age subgroups ($p^1 = 0.69$, $p^2 = 0.37$), which constitutes another proof of the lack of linear correlation between frequency of chromosome aberrations and age ($R = 0.002$, $p = 0.76$).

Comparison of the frequencies of occurrence of exchange-type aberrations between the age subgroups of unexposed and exposed persons revealed a significant increase of the indicator's value in the "40–59 years old" subgroup of the exposed group ($p = 0.038$). In the exposed individuals aged 60–69 years, we detected cells with chromosome aberrations more often, but the differences were not significant. As for the oldest donors, there were no differences in cytogenetic parameters registered between the exposed and non-exposed groups.

Table 2 presents the analysis of dynamics of individual indicators reflecting frequency of occurrence of unstable exchanges in 8 exposed individuals.

The frequency of occurrence of chromosome aberrations has grown with age in 5 out of 8 examined participants, but the differences were not significant. However, it is noteworthy that the median frequency of UCA increased with age from 0.375 in the "early" group to 0.775 in the "late" group, while the RBM dose did not change significantly, (second figure after the decimal point).

DISCUSSION

Investigation of the human aging mechanisms is a scientific problem made urgent by the change in the world's age balance:

Table 1. Frequency (%) of unstable chromosomal aberrations in the examined groups (median, 25 and 75%)

Age subgroups	Control group median / mean 25–75%		Exposed individuals RBM dose 0.5–2.5 Gy median / mean 25–75%	
	n M : F	exchanges, %	*n* M : F	exchanges, %
40–59 y.o.	17 5 : 12	0 / 0	55 23 : 32	0 / 0.23 $p = 0.038$
60–69 y.o.	44 14 : 30	0 / 0.18 $p^1 = 0.06$	191 77 : 114	0 / 0.25 0–0.2 $p = 0.427$ $p^1 = 0.69$
70–79 y.o.	22 8 : 14	0 / 0.30 0–0.625 $p^2 = 0.02$	97 38 : 59	0 / 0.24 0–0.225 $p = 0.973$ $p^2 = 0.37$

Note: *p* — statistical differences in indicators between similar age subgroups of the exposed and control groups; p^1 — statistical differences in indicators between age subgroups "40–59 years old" and "60–69 years old"; p^2 — statistical differences in indicators between age subgroups "40–59 years old" and "70–79 years old"; M — male; F — female.

the number of elderly people is growing, by 2050, there will be about 1.6 billion people over 65 [15]. Understanding the basics of the body's aging program, inter alia, rests on research looking into the patterns of aging with the environmental factors accounted for. Such research requires a reliable set of tools: markers, methods, approaches, which eventually form a methodology for the respective studies. A living organism is a multilevel system, therefore, the processes and effects of aging are studied at several levels: subcellular, cellular, levels of tissue, organ, organism [16].

We chose the cytogenetic method that allows assessing the state of chromosomal DNA to study the possible effect of ionizing radiation on premature aging of human cells. Our work focused on the unstable exchange-type chromosome aberrations in the phytohemagglutinin-stimulated peripheral blood T-lymphocytes. The choice of this object was not accidental: in addition to γ beams, precursors of T-cells were also exposed with osteotropic ^{89,90}Sr radionuclides in the bone marrow. Currently, the youngest exposed individuals are 60 years old. It is known that after the age of 25, human thymus begins to involute, but there is a high probability of retaining UCA in cells that have not entered mitosis in the body or cells that survived 1–2 mitoses with aberrations. Circulating lymphocytes have been and are still exposed to the internal sources of radiation [17].

In the group of non-exposed participants, we detected an age-driven increase of the frequency of occurrence of cells with unstable metabolic aberrations. Moreover, this indicator was significantly higher in both the "60–69 years old" and "70–79 years old" age subgroups than in the "40–59 years old" subgroup. The regularities we discovered are consistent with the data from previously published papers, which have also noted the dependence of the amount of dicentric and ring chromosomes on age [11, 12]. However, we registered no such dependencies when analyzing the data describing chromosome preparations made from samples collected in the exposed group. In the three age subgroups, we have not detected the expected age-dependent increase in the frequency of chromosome aberrations. All indicators (Table 1) were similar and maximum for this study.

We revealed the influence of chronic exposure on the frequency of chromosome aberrations only in "40–59 years old" subgroup. Contrary to the expectations, the oldest participants (70–79 years old) from the exposed group had the indicators at the same level as that calculated for non-exposed donors. Thus, we registered that chronic exposure affects premature cellular aging in the residents of the Techa riverside villages aged 40–59 years only. Examining older exposed individuals, we found them to have similar indicator values as those from the control subgroups of the same age.

There is an explanation to the data that, at the first glance, looks "contradictory": the cytogenetic study inclusion criteria may bias the selection and fill the exposed group with the most radioresistant donors. For example, to participate, a person should have had a medical history without oncological, autoimmune diseases, diabetes mellitus. Such restrictions allow excluding the effect diagnostic and therapeutic measures may have on the frequency of occurrence of the studied cytogenetic indicators. Given that the above diseases more often begin to manifest in older ages, it is quite possible that the exposed radiosensitive individuals had the effects of irradiation triggering disorders in them earlier in life and, consequently, met the study exclusion criteria. There is a study that provides an indirect confirmation of this assumption: there, researchers noted that individuals with an increased frequency of chromosome aberrations were more likely to develop cancer in the future

Table 2. Dynamics of frequency (%) of unstable exchange-type chromosome aberrations in the same exposed individuals examined in different age subgroups

Number of the person	1	2	3	4	5	6	7	8	Total. Median 25–75%
Early indicator	0	1	0.98	0.75	0	0	0.85	0.8	0.375 0–0.9
Late indicator	0.6	0	0	1	0.25	0.5	0	1.5	0.775 0–0.9 $p = 0.8$

Note: *p* — statistical differences in the final indicators as registered between subgroups.

[18]. Taking into account all of the above, we can assume that while the younger groups participating in the cytogenetic research were comprised of people with a diverse genetic potential in terms of response to exposure to ionizing radiation, the older groups (above 60 years of age) included the so-called "radioresistant" individuals.

Despite some controversy in the results of the analysis, having conducted this study, we can conclude that chronic exposure did have an indirect effect on the premature aging of T-lymphocytes. The confirmations are, firstly, the significantly increased frequency of UCA registered in the exposed individuals in the long term, and secondly, the significantly more frequent occurrence of UCA in the exposed individuals aged 40–59 years compared to that found in their peers from the non-exposed group.

Thus, this article attempted to present the design of a cytogenetic study aimed at assessment of the effect of *in vivo* chronic ionizing radiation on the premature aging of human T-lymphocytes, as well as the subsequent analysis of the results of the study with its participants divided into three age subgroups. Ultimately, we cannot discount the possible effect of the inclusion criteria that may fill the exposed group with the most radioresistant individuals, which eventually may lead to "contradictory" results. This is a debatable topic; the investigation should be continued with a larger sample (both groups) and a greater number of the analyzed metaphase spreads.

CONCLUSIONS

Relying on the cytogenetic index, we registered the effect of chronic exposure on premature aging of T-cells in the residents of Southern Urals that were 40–59 years old at the time of the examination.

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