ESTIMATION OF THE IMPACT OF CHRONIC RADIATION EXPOSURE ON TELOMERE LOSS IN WOMEN'S T LYMPHOCYTES

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Residents of the Techa Riverside villages were chronically exposed to the wide range of doses more than 60 years ago. Telomeric regions of metaphase chromosomes in the cultured peripheral blood T-lymphocytes were the subject of the research. The study aimed to assess the impact of chronic exposure on telomere loss in exposed women of the Southern Urals using a fluorescent staining method. Chromatid and chromosome telomere loss was determined in three dose subgroups: comparison group (0–0.01 Gy), group of exposed individuals with the dose of 0.2–0.9 Gy, and group of the exposed individuals with the dose of 1–4.6 Gy. In the sample of female residents of the Southern Urals chronically exposed in the range of absorbed doses to RBM of 0–4.6 Gy, it was shown that there were no differences in telomere loss between the comparison group and the group exposed to the dose exceeding 1 Gy ($p > 0.33$), while the group of individuals exposed to medium doses of 0.2–0.9 Gy was statistically significantly different ($p < 0.05$). Statistically significant differences between all groups were reported for chromosome telomere loss ($p < 0.05$). According to the data obtained, telomere loss was found in 99.85% of donor cells. The loss of telomere region on one of the chromatids occurred statistically significantly more often in all the groups. Thus, in the group exposed to the dose of 0.2–0.9 Gy, the average rate of chromatid telomere loss was higher, it was statistically significantly different from that of the other groups of females of the studied age.

Keywords: ionizing radiation, T-lymphocytes, telomere, chromosome, telomere loss, FISH

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ОЦЕНКА ВЛИЯНИЯ ХРОНИЧЕСКОГО РАДИАЦИОННОГО ВОЗДЕЙСТВИЯ НА ПОТЕРЮ ТЕЛОМЕРНЫХ УЧАСТКОВ ХРОМОСОМ В Т-ЛИМФОЦИТАХ У ЖЕНЩИН

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Более 60 лет назад жители прибрежных сел реки Теча были подвержены хроническому облучению в широком диапазоне доз. Предметом исследования были теломерные районы в метафазных хромосомах культивированных Т-лимфоцитов периферической крови. Целью исследования было оценить влияние хронического облучения на потери теломерных участков хромосом у облученных женщин Южного Урала с применением метода флуоресцентного окрашивания. Определяли хроматидные и хромосомные потери теломерных участков хромосом в трех дозовых подгруппах: группа сравнения (0–0,01 Гр), группа облучения дозой 0,2–0,9 Гр и группа облучения дозой 1–4,6 Гр. В выборке жителей Южного Урала женского пола, подвергшихся хроническому облучению в диапазоне поглощенных доз на КМК от 0 до 4,6 Гр, было установлено, что хроматидные потери теломер для группы сравнения и группы облученных в дозе более 1 Гр статистически не различимы ($p > 0,33$), в то же время группа облученных средними дозами 0,2–0,9 Гр статистически отличается от них ($p < 0,05$). Для хромосомных потерь установлено статистически значимое различие между всеми группами ($p < 0,05$). Согласно полученным данным, теломерные потери присутствуют в 99,85% клеток доноров. Достоверно чаще во всех группах встречались потери теломерного участка на одной из хроматид. Таким образом, в группе с дозой 0,2–0,9 Гр среднее число потерь хроматид выше и статистически значимо отличается от других групп женского пола в исследуемом возрастном диапазоне.

Ключевые слова: ионизирующее излучение, Т-лимфоциты, теломеры, хромосомы, потери теломер, флуоресцентная *in situ* гибридизация

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Ionizing radiation affects human life everywhere: diagnostic medical procedures, travelling by planes, exposure to natural ionizing radiation in the areas with elevated background radiation. In addition to the planned and controlled radiation exposure, there is also accidental radiation exposure due to accidents and incidents involving the ionizing radiation sources. Investigation of mechanisms underlying the effects of radiation on human health is an important and relevant task.

More than 60 years ago more than 100,000 people who lived in the Southern Urals were chronically exposed at a wide

range of cumulative doses. Intake of ^{89,90}Sr radionuclides with food and water caused internal exposure, while external exposure resulted from the proximity to the banks of the Techa River contaminated due to liquid radioactive waste discharges (γ exposure). Changes in the status of multiple body systems were reported after the long-term follow-up of individuals exposed in the Southern Urals [1, 2].

The effects of ionizing radiation on chromosomal rearrangements have been proven by many studies. DNA structure in the cell is altered under exposure to ionizing radiation yielding the compounds capable of damaging DNA. For example, reactive oxygen species, lipid peroxidation products, etc. As a result, interatomic bonds are broken in the sugar-phosphate backbone, which leads to the DNA molecule continuity impairment. When there is no or insufficient repair, such breaks can become an event initiating aging and carcinogenesis [3, 4]. There can be single-strand breaks (when one DNA strand is broken) and double-strand ones (when both strands are broken).

Telomeres, the repeated nucleotide sequences, are responsible for maintaining stability of chromosomes and genome in the nucleus. The study of human chromosome telomeric regions is a pressing scientific issue due to proven involvement of telomeres in such processes, as aging, malignant transformation of cells. A number of genetic disorders are associated with alteration of chromosome telomeric regions.

The earlier studies of chromosome telomeric regions using fluorescence in situ hybridization (FISH) revealed qualitative chromatin changes in exposed individuals. It was reported that telomeric signals were observed in the chromosome arms, which resulted from inversions involving telomeric regions [5]. Significant telomere length reduction in some chromosome arms was also reported in exposed individuals compared with non-exposed ones [6]. When conducting research, the fact was noticed that not all metaphase chromosomes in the cell had four telomeres at the ends; in some chromosomes, telomere regions were not visible at all.

Telomere loss can occur due to gradual telomere shortening during cell division, or as a result of stochastic events, during which the repeated telomere sequences are lost, for example, as a result of terminal deletion or double-strand break within the subtelomeric region [7]. Some studies of tumor cell lines show that such spontaneous telomere deletions are typical of cancer cells [8, 9].

Telomere loss is important for human evolution. Many genetic disorders, such as mental retardation and muscular dystrophy, result from alterations occurring near the ends of chromosomes [10]. Furthermore, women with infertility showed a more pronounced telomere loss, than patients of the control group [11].

Ionizing radiation can also cause loss of chromosome telomeric regions. The underlying mechanism is still a matter of debate for scientists and cannot be clearly defined. Due to the fact that telomeres constitute only 0.02% of the entire human genome, the direct effect of radiation causing chromatid break and telomere loss is unlikely. The literature review suggests that the effects of reactive oxygen species can lead to formation of modified bases and breaks in certain DNA strands, including in telomeric regions [12]. The guanine-rich telomeric DNA sequences (-TTAGGG-) become a target of oxidative damage, since it is guanine that has the lowest oxidation/reduction potential among all nitrogenous bases. Guanine is easily oxidized to 8-oxoguanin considered to be a major oxidative stress biomarker [13]. Single-strand breaks in the G-rich strands regenerate poorly and persist in telomeres for longer period of time [14]. The double-strand breaks can occur near the telomeres under exposure to ionizing radiation, which can result in chromosomal rearrangements. This represents one of the mechanisms underlying replicative aging of normal human cells caused by ionizing radiation. Cellular alterations affecting the effeciency of the DNA replication mechanism can contribute to replication fork stalling in telomeres and telomere loss [15].

There are also studies showing that chromosome telomeric region losses can result from the effects of different proteins, such as TZAP (telomeric zinc finger-associated protein) with 11 zinc fingers able to bind specifically to telomeres of the chromosomes and truncate them [16].

The use of FISH and locus-specific probes makes it possible to find alterations in telomeric regions of chromosomes. Telomere loss can affect one arm or both arms (chromosome telomere loss in sister chromatids).

The objective of the pilot study was the assessment of the telomere loss in peripheral blood lymphocytes of women exposed on the Techa River using the fluorescent staining method.

METHODS

Characteristics of examined individuals

Since the study of telomere loss was a pilot study conducted in the Urals Research Center for Radiation Medicine of FMBA of Russia for the first time, it was decided to limit the groups based on sex and assess the studied effect in the groups of women only at the initial stage. Inclusion criteria: female residents of the territories contaminated with radionuclides born in 1939–1959, who were chronically exposed at a wide dose range; women of the comparison group, who were not accidentally exposed.

Information about the studied sample and health status of the exposed individuals was provided by the "Database "Man" Department. Individualized cumulative external and internal doses (hereinafter referred to as doses) to RBM were calculated using the TRDS-2016 in the Biophysics laboratory [17]. The data on the history of cancer in the examined individuals were provided by the Epidemiological laboratory of the Urals Research Center for Radiation Medicine. Exclusion criteria: history of autoimmune diseases, cancer, exacerbation of chronic inflammatory diseases; history of taking cytostatics, antibiotics; individuals born in 1961 and later.

A total of 32 women were examined. The comparison group (hereinafter referred to as group 1) consisted of 10 individuals, among them six women had the absorbed doses to RBM within the range of 0.0001–0.01 Gy and four ones were not accidentally exposed. A total of 10 women were chronically exposed to the radiation doses of 0.2–0.9 Gy (hereinafter, group 2); the average dose was 0.64 ± 0.21 Gy. The group of individuals exposed to high doses (hereinafter referred to as group 3) included 12 women with the cumulative doses to RBM exceeding 1 Gy, since cytogenetic effects most often emerge under high-dose exposure [1]. The range was 1.01–4.6 Gy, and the mean dose was 1.7 ± 0.9 Gy (Table 1).

Obtaining the peripheral blood T-lymphocyte metaphase chromosome preparations

The cytogenetic study involved metaphases of the peripheral blood T lymphocytes stimulated with phytohemagglutinin (PHA). The chromosome preparations were obtained in accordance with the protocol accepted in the laboratory: cells were cultured for 54 h. Colcemid was added to a final concentration of 0.1 mg/mL three hours before the end of the cultivation period.

Table 1. Characteristics of examined women

Group	Number of donors, *n*	Mean age, years (range)	Mean Dose, Gy
Group 1 (comparison) (0–0.01 Gy)	10	65.4 ± 3.3 (62–71)	0.003 ± 0.003
Group 2 (exposed) (0.2–0.9 Gy)	10	74.5 ± 4.6 (69–81)	0.64 ± 0.21
Group 3 (exposed) (1–4.6 Gy)	12	74 ± 2.6 (71–80)	1.7 ± 0.9
All donors (0–4.6 Gy)	32	71.4 ± 5.4 (62–81)	

Hypotonic treatment of metaphase cells was performed 40–50 min before fixation with warm (37 °C) KCl solution (0.55%). Then the mixture was centrifuged. After that the metaphase plate fixation was performed (three parts of 95% ethanol: one part of glacial acetic acid) and chromosome preparations were made [18].

When pipetting the cell suspension on the glass slides, we sought to minimize excess spreading and overlap of chromosomes to achieve the best results, for each metaphase to be suitable for analysis. After the cell suspension was pipetted, the glass slides were heated on the slide dryer at 42 °C and then fluorescent staining was performed.

Method of telomere region staining by fluorescence in situ hybridization (FISH) with locus-specific probes

Probes from the Telomere FISH Kit/Cy3 (Dako; Denmark) were used. Chromosomes were stained in accordance with the probe manufacturer's protocol. The probe stains telomeric regions of chromosomes only, it does not recognize subtelomeric sequences [19]. The manufacturer produces this probe using the Cy3-conjugated peptide nucleic acid being a synthetic DNA analog capable of binding to DNA of chromosomes in accordance with the base pairing rules.

Fluorescently stained preparations were analyzed using the Axio Imager Z2 microscope (Zeiss; Germany) with the DAPI and SpO filters and the Isis software. The Metafer system for metaphase plate search and digitization was configured to automatically acquire images of five frames for the SpO channel, which would differ in height from each other by half a micron. After Metafer took five frames, areas with the highest contrast were automatically selected in each frame in the background mode. This resulted in the final image, where all signals were sharp and high contrast, which improved accuracy of the analysis results. Thus, features of the ISIS software allow one to reliably determine the lack of telomeric signal in any chromatid. For that the digitized image is viewed using the DAPI-SpO filters, along with the black and white inverted image of the chromosome of interest.

When conducting analysis, telomere losses were divided into two types: chromatid and chromosome. Chromatid telomere loss was determined, when there was no telomeric signal in one of sister chromatids, while the other one was intact. Fig. 1 presents the chromosome 5 pair: all four telomeres can be seen in the left chromosome; in the right chromosome it can be seen that one q arm telomeric region is absent. When there were no telomeric signals in both sister chromatids, the telomere loss was considered to be chromosomal (Fig. 2). The lack of two signals in unpaired chromatids or in different arms of the same chromatid were considered as two single chromatid telomere losses.

Metaphases containing 46 chromosomes without overlapping or artifacts were included in the analysis. All the chromosomes were analyzed in each cell. A total of 25–100 cells per donor were counted. The data on telomere loss were entered in the analysis record.

Statistical data processing

Thus, the results of assessing 1,560 cells of 32 individuals aged 62–81 divided into three groups based on the exposure dose were used as baseline data for statistical analysis. All 46 chromosomes were examined in each cell, and the facts of chromatid or chromosome telomere loss were reported for the cell. The results were analyzed using the STATISTICA 10 software package (StatSoft; USA).

RESULTS

Baseline data by dose groups for both telomere loss variants (chromatid and chromosome) are provided in Fig. 3. The studied phenomenon (telomere loss in various dose groups) cannot be represented using normal distribution (Fig. 4), so the nonparametric Mann–Whitney U test was used for intergroup comparison of obtained results.

The lack of differences in the number of telomere losses (chromosome or chromatid) in individual cells between the dose groups was accepted as the null hypothesis. It was found that chromatid losses in the comparison group (group 1) and the group exposed to high radiation doses (group 3) were statistically significantly similar ($p > 0.33$), while the group exposed to medium doses (group 2) was statistically

Fig. 1. Example of finding telomere loss in the red-blue filter and inverted image. All four telomeres are visible in the *left* cnromosome. An example of telomere loss in one q arm chromatid is provided on the *right*

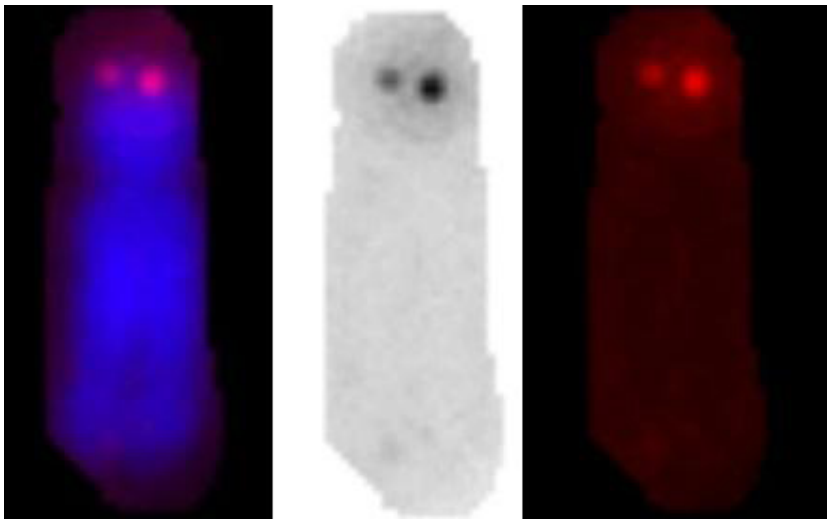

Fig. 2. Example of finding chromosome telomere loss in the red-blue filter and inverted image. No telomeres can be seen in both q arms

significantly different from these two groups ($p < 0.05$). Statistically significant differences between all groups were reported for chromosome telomere loss ($p < 0.05$). Thus, it can be concluded that the average number of chromatid losses in the second group is higher and is statistically significantly different from that in other groups.

Fig. 5 presents box plots of baseline data for each exposure group (rectangles represent the 5th and 95th percentiles, the central point represents the median, and whiskers correspond to minimum and maximum values). Table 2 contains the data of each studied subgroup for the chromatid and chromosome telomere loss: relative content in the cells, median, percentiles 5%–95%, minimum and maximum.

Loss of at least one telomeric region was found in 99.85% of the assessed cells.

Telomere loss in one of the chromatids was significantly more common, than chromosome telomere loss, in all groups ($p < 0.05$).

DISCUSSION

One function of the telomere is ensuring stability of the chromosome. That is why understanding the causes of changes in telomeric regions will shed light on the mechanisms underlying the development of cancer, human genetic disorders, infertility, and aging of the body [20]. The ionizing radiation effects on human cells can cause alterations at chromatin level, such as DNA strand breaks, improper reunion of which can result in chromosomal rearanngements. These events lead to redistribution of chromatin across the arms of chromosomes and can affect distribution of genes in chromosomes, alter gene expression and, therefore, lead to development of various biomedical effects, which will eventually influence human health [21].

The pilot project presented in this paper is part of the study focused on assessing the telomeric regions of chromosomes conducted at the Laboratory of Radiation Genetics of the Urals Research Center for Radiation Medicine. Such parameters, as the telomere length and rate of inversions involving telomeric regions, were estimated previously in individuals chronically exposed at the Techa River [5, 6]. In this study, telomere loss in metaphase chromosomes of cultured peripheral blood T lymphocytes of the exposed residents of the Southern Urals was the research subject. Fluorescent staining of telomeric chromosome regions was used for this purpose. Analysis of the impact of radiation factor on the loss of chromosome telomeric regions was conducted. According to the data obtained, telomere loss is found in 99.85% of donor cells. It

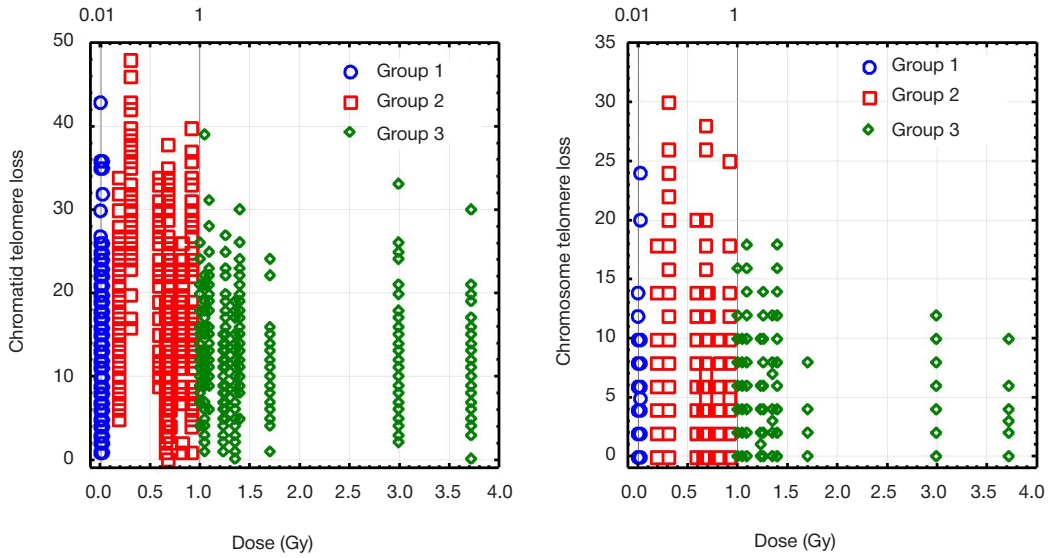

Fig. 3. Baseline data by dose groups

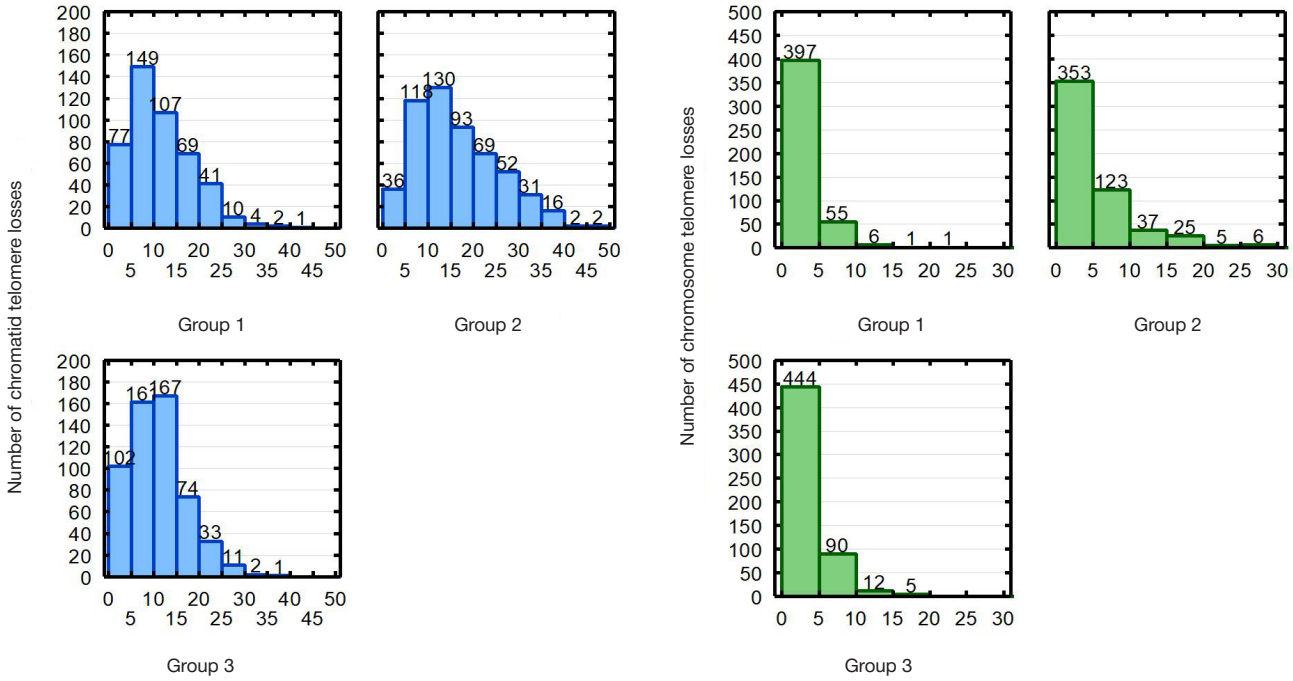

Fig. 4. Rate of chromatid and chromosome telomere loss observations in various exposed groups

has turned out that telomere loss in one of the two chromatids is statistically significantly more common in all groups. The loss of one sister telomere can result from replication defects in the S phase of the cell cycle, while chromosome telomere loss is likely to result from the loss in the pre-synthetic phase, when the chromosome represents one chromatid that is subsequently duplicated in the synthetic phase (consequently, the region with telomere loss is also duplicated yielding chromosome telomere loss) [22, 23]. Furthermore, low rate of chromosome telomere loss compared to chromatid telomere loss can be explained by the fact that these events occur with different probabilities. The chromosome occupies a certain space in the nucleus and normally does not overlap with chromatin of other chromosomes, therefore, the most common alterations are reported within the same chromatid. The ends of arms of sister chromatids lacking telomeric regions can be a marker of cell death. This means that the cell with the large number of telomere losses will be eliminated during cell division in order to preserve genome integrity.

Our study showed that single chromatid losses in the comparison group and the group exposed to high radiation doses were statistically significantly similar ($p > 0.33$), while the group exposed to medium doses was statistically significantly different from these two groups ($p < 0.05$). Statistically significant differences between all dose groups were reported for chromosome telomere loss ($p < 0.05$). Thus, it can be concluded that the average number of chromatid losses in the second group is higher and is statistically significantly different from that in other groups.

Against all expectations, the rate of telomere loss in the group of women exposed to the highest radiation doses showed no statistically significant differences from that in the comparison group. Yet we see that chronic exposure has some effect on the number of telomere losses, based on the results reported for group 2 showing a statistically significantly higher rate of chromosome and chromatid telomere loss compared to women of the comparison group who lived in similar socio-economic conditions but did not have doses of chronic exposure

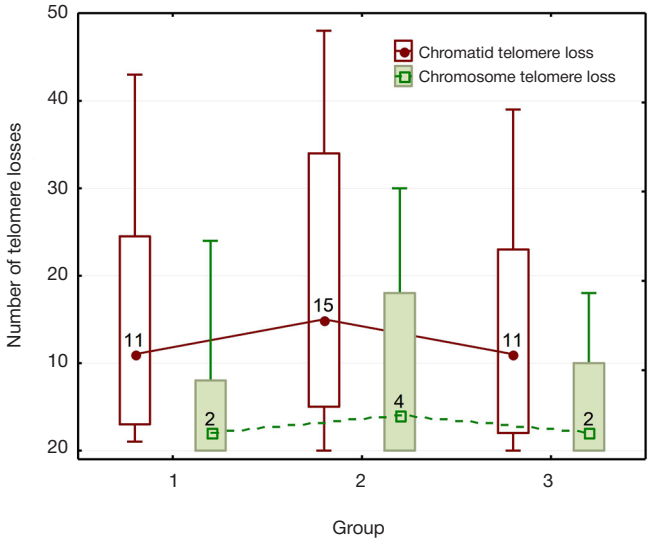

Fig. 5. Median, 5th and 95th percentiles, minima and maxima of baseline data for different exposure groups

Table 2. Median (5% and 95%) telomere loss in T-lymphocytes of exposed women of the Southern Urals

Chromatid telomere loss						
Group	Loss rate, %	Median	Minimum	Maximum	5%	95%
1	7	11	1	43	3	24.5
2	9	15	0	48	5	34
3	6	11	0	39	2	23
Chromosome telomere loss						
1	2	2	0	24	0	8
2	5	4	0	30	0	18
3	3	2	0	18	0	10

exceeding 0.01 Gy. It is likely that damaged chromosomes are eliminated from the cell after certain critical level is reached, As a result, the values of the comparison group and the group of donors exposed to the doses exceeding 1 Gy are at the same level and show no significant differences.

Such paradoxical data actually do not contradict the results of other cytogenetic studies, in which it was assumed that the criteria for selection of donors for cytogenetic testing can contribute to selection of the most radioresistant donors among exposed individuals, who have no autoimmune diseases, cancer or diabetes mellitus in their old age and do not take medicinal drugs that can affect the cytogenetic testing results. This is indirectly confirmed by the studies reporting that the rate of chromosomal aberrations in exposed individuals was equal to that calculated for non-exposed donors [24].

Thus, understanding the mechanisms responsible for the susceptibility of telomeric regions to the effects of external factors will provide new insights into the causes of human genetic disorders, infertility, aging, and cancer. Further investigation of chromosome structure using cytogenetic methods is important to understand the interplay between genes. It is necessary to continue this study and increase the size of the sample in order to confirm the findings, as well as to assess the impact of non-radiation factors.

CONCLUSIONS

In the sample of female residents of the Southern Urals with the combined chronic exposure within the range of absorbed doses to RBM of 0–4.6 Gy, it was shown that chromatid telomere losses reported for the comparison group and the group exposed to high radiation doses exceeding 1 Gy were statistically significantly similar ($p > 0.33$), while the group exposed to medium doses of 0.2–0.9 Gy was statistically significantly different from these two groups ($p < 0.05$). Statistically significant differences between all dose groups were reported for chromosome telomere loss ($p < 0.05$). Thus, the average telomere loss in the second group was higher and was statistically significantly different from that reported for the other groups of females of the same age range.

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