The Follow-up Study of Chromosomal aberrations in Chernobyl Clean-up Workers

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Abstract

A cytogenetic study was carried out on 359 clean-up workers who worked at the Chernobyl station in 1986-1989. The investigation was performed 6-12 years after irradiation. Chromosome type damages, i.e. double fragments, dicentrics and rings were significantly increased in the clean-up workers compared to the control. Chromatid exchanges were found only in the clean-up workers. A temporal change of radiation makers was also investigated based on the data of 243 persons who worked at Chernobyl in 1986. The temporal variation of dicentric frequency shows an inexplicable tendency towards the increase of dicentrics rate for the period of 8-12 years after irradiation. The association between the frequency of different types of chromosomal aberrations and such variables as smoking habits, coffee, tea, alcohol consumption, *etc.* was also analysed using a stepwise multiple regression analysis. A statistically significant association was only observed between smoking and chromatid exchanges. This type of aberrations was significantly higher in the smoking subgroup than in the non-smoking subgroup of the clean-up workers. The fact of an increased level of unstable chromosomal aberrations in a remote period after irradiation allows us to suppose that other pathways of genomic burden may exist in addition to straight radiation action at the time of irradiation.

Introduction

Chromosome damage induced in human lymphocytes is often considered a sensitive indicator of radiation exposure [1-3]. An increased level of structural chromosomal aberrations in the clean-up workers soon after the Chernobyl accident has been reported [4,5]. It is known that the frequency of radiation markers (dicentric and ring chromosomes) decreases in time [6,7]. So, it is expected that the frequency of chromosomal aberrations (CA) in the clean-up workers, who suffered from low doses of radiation, would become as low as the control level some years after the accident. However, increased rate of chromosomal aberrations in the clean-up workers was demonstrated 4-6 years after the Chernobyl accident [8-11]. A follow-up study of Chernobyl clean-up workers has been carried out at All-Russian Centre of Emergency and Radiation Medicine Emercom of Russia (ARCERM) since 1992 in order to assess the consequences of low doses of ionising radiation on their health. Cytogenetical investigation was carried out simultaneously with clinical examination.

The goal of this paper is to present the results of the follow-up study of cytogenetical damage in the peripheral blood lymphocytes from the clean-up workers in a remote period (6-12 years) after the Chernobyl accident.

Materials and methods

A cytogenetic study was carried out on 359 clean-up workers who worked at the Chernobyl station in 1986-1989. The investigation was performed 6-12 years after irradiation. 281 persons had official dose of irradiation, estimated by dosimetric service at Chernobyl. Most of them received up to 25 cGy, but 30 persons received from 25.1 cGy to 100 cGy. Thus, the mean dose of irradiation for clean-up workers who

worked at the station in 1986 was 20.3±1.01 cGy; 13.4±1.71 cGy for clean-up workers of 1987 and 5.2±0.88 cGy for clean-up workers, who worked at the station in 1988-89.

The control group comprised 48 persons matched for similarity of age and health status, with no history of irradiation.

Lymphocyte cultures (48 h) were set up. Culture medium consisted of RPMI 1640 (Sigma) supplemented with 15% fetal bovine serum (Sigma), phytogaemaaglutinin P (Difco), antibiotic. 5-Bromdeoxyuridine was added 24 h from the beginning of cultivation at a final concentration of 10 μg/ml to permit fluorescence plus Gimsa staining so that cells could be scored at the first in vitro metaphase. Chromosome preparation was stained by standard procedures. At the beginning of our investigations we analyzed no less than 100 metaphases per individual. Later the number of metaphases was increased to 200-500. Cells with 45-46 chromosomes were analyzed. All types of unstable chromosome aberrations (CA) were analysed: chromatid breaks (discontinuities more than the weight of a chromatid and without visible connecting material), chromatid exchanges (tri- and quadriradials), acentric fragments, dicentrics and rings were registered.

For micronucleus test cytochalasin B (Sigma), at the final concentration of 6 μg/ml, was added within the last 28 h to the cultures to be harvested for micronuclei, and the total cultivation time was 72 h. At least 500 cytokinesis-blocked binucleated cells for each individual were scored in the micronucleus test.

For all subjects, modified questionnaires, based on the method proposed by Carrano and Natarajan [12], were filled in.

During the 6-yr period of observation the same microscopists performed cytogenetic investigations. All slides were coded and distributed between two microscopists.

For each group dicentrics and rings yields from each individual were tested for homogenity using the chi-squared test. Mean yields and their standard errors were calculated taking into account any lack of homogeneity. Average values were weighted taking into account different number of cells per person. Various statistical methods (ANOVA test, chi-squared test, stepwise multiple regression analysis, Spearman Rank correlation test) were used according to the nature of data and type of analysis needed. Calculations were performed with a software package, Statistics for Windows.

The frequencies of various types of chromosome aberrations in the clean-up workers

The main frequencies of various types of chromosome aberrations are given in Table 1 along with

Table 1. Frequencies of chromosomal aberrations in the clean-up workers and the control individuals (1992-1998).

	Clean-up workers	Control
Number of individuals	359	48
Total number of cells scored	50771	7175
Aberrant cells (%)	2.71 ± 0.13	2.08 ± 0.25
Chromatid breaks (%)	1.36 ± 0.09	1.59 ± 0.23
Chromatid exchanges (%)	0.15 ± 0.03 [a]	0.00 ± 0.02
Chromosome breaks (%)	0.84 ± 0.06 [a]	0.42 ± 0.11
Dicentrics, rings (%)	0.25 ±0.03 [b]	0.03 ± 0.02
Atypical chromosomes (%)	0.12±0.02	0.03 ± 0.03

[a] Significantly greater frequency than in control at the 0.05 level of significance. [b] at the 0.01 level of significance.

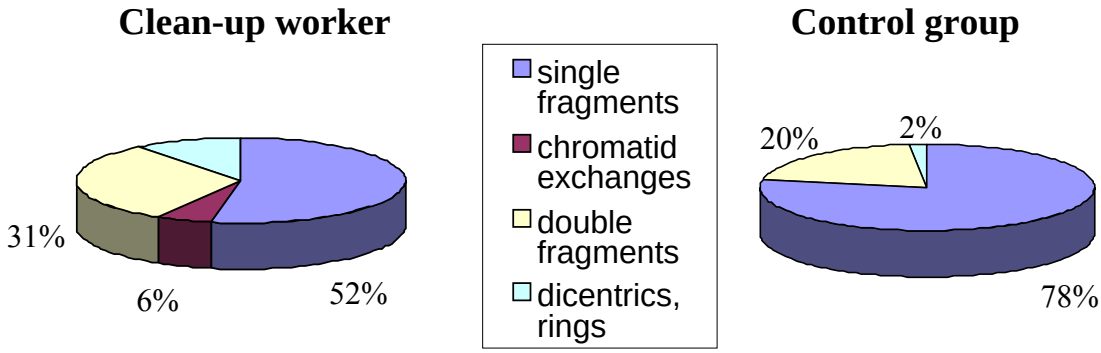

Figure 1. The spectrum of chromosomal aberrations in the clean-up workers and control group.

their standard errors. These data was obtained from blood taken 6-12 years after irradiation. The total frequency of chromosomal damage in the clean-up workers, whilst being higher than the controls, was not so high as at the 5% criterion for significance. The total damage was dominated in both groups by single or chromatid breaks, which, whilst being higher in the controls, were again not significantly in excess. Chromosome type damages, i.e. double fragments, dicentrics and rings significantly increased in the clean-up workers. Chromatid exchanges were found only in the clean-up workers. The ratios of various types of chromosomal aberrations in two groups are given in Figure 1.

It is possible to see in Fig 1 that the predominant type of damage in the controls is chromatid aberrations (78%), whilst double fragments comprise 20% and dicentrics and rings 2%. The relative proportion of chromatid aberrations in the clean-up workers is lower at 58 %. The chromosome types are higher at 42% of which 11% are dicentrics and rings.

Table 2 indicates a significantly larger proportion of individuals with dicentrics and rings, and with chromatid exchanges in the clean-up workers than in the controls.

The micronucleus (MN) test in the clean-up workers

The MN test were performed simultaneously with CA investigations. For 22 clean-up workers and 14 controls (presented in Table 1) MN and CA assays were used in parallel on peripheral blood lymphocyte cultures.

Table 3 presents the frequency of MN and CA in the clean-up workers and in the controls. Analysis of Table 3 shows that the clean-up workers and the controls do not differ in terms of MN test, while the

Table 2. Frequency of individuals with exchange aberrations.

Type of exchange aberrations	359 clean-up workers Number of subjects (%)	48 controls Number of subjects (%)
Dicentrics + rings	95 (26.4) [a]	3 (6.2)
Chromatid exchanges	58 (14.7) [a]	0 (0)

[a] Significantly exceeds the control value at the 0.01 level of significance.

Table 3. Results of the analysis of MN and CA assay in parallel cultures.

	Clean-up workers	Control
Number of individuals	22	14
MN frequency (%)	1.23 ± 0.12	1.06 ± 0.17
CA frequency (%)	2.18 ± 0.31[a]	1.00 ± 0.23

[a] Significantly exceeds the control value at the 0.01 level of significance.

rate of CA is significantly higher in the clean-up workers.

The results of micronucleus test did not demonstrate significantly higher damage in the clean-up workers than in the controls. Kolubaeva et al. [13] and Wuttke et al. [14] also could not find an increase in micronucleus frequency 5 years after the Chernobyl accident. So these data could be provided as an argument for that the application of the micronucleus test as a cytogenetic monitor of radiation effects in a remote period is not effective. The chromosomal aberration test was found to be more sensitive than the MN assay as a cytogenetic monitor of the remote radiation effects.

The temporal changes of radiation markers in the clean-up workers

A total of 243 persons who worked at Chernobyl in 1986 were selected from database in order to consider the temporal changes of radiation markers. Clean-up workers were divided into 6 groups according to time of blood sampling. The data is presented in Table 4.

As it can be seen from the data presented in Table 4, frequency of dicentrics and rings did not decrease during the 6 year period of observation and exceeded the control level even 12 years after irradiation.

There is a commonly held opinion that the frequency of unstable chromosomal aberrations in lymphocytes decreases with the time from irradiation. There are some publications devoted to the estimation of lifespan of human lymphocytes and temporal changes in the yield of chromosomal aberrations [7,15-17]. The most common opinion is that the half-life of lymphocytes is about 3 years [18]. If so, it means that the initial frequency of chromosomal aberrations decreases by half in 3 years. Schevchenko and co-authors [19] have published that the initial yield of chromosomal aberrations in the Chernobyl clean-up workers estimated in 1986 soon after the irradiation in different groups was: 0.27±0.10 dicentrics per 100 cells in a group of medical personnel, 0.32±0.08 in drivers, 0.44±0.09 in builders of sarcophagus and 0.48±0.17 in dosemetrists. Therefore, taking into account the suggested half-life of lymphocytes, one would suppose the frequency of dicentrics and rings of 12 years, ie. four half-lives, after irradiation has returned to essentially the control level.

However, the results of our investigation lead to a conclusion that 6-12 years after the irradiation the yield of dicentrics and rings did not decrease to the control value. The existence of a residual level of induced dicentrics and rings at long times, ie. decades, after irradiation has been reported although these have generally been observed in persons exposed to high doses of radiation [7, 20-25]. Few data have been reported on exposure to low doses. Thus a particular interest is imposed on our own investigations

Table 4. Dicentrics and rings frequency in clean-up workers by the years after the accident and homogenity testing on individuals within the year bands

Years after the accident	Number of subjects	Number of cells	Number of Dic+Rings (Rings)	Chi-squared	DF	Yield ± SE (per 100 cells)
6	14	1573	2 (0)	8.23	13	0.13±0.07
8	100	10180	25 (1)	146.13	99	0.25±0.05*
9	63	11869	29 (7)	80.11	62	0.24±0.04**
10	35	5821	26 (4)	35.89	35	0.45±0.10***
11	12	2125	10 (1)	14.42	11	0.47±0.15***
12	19	3711	14 (3)	20.52	18	0.38±0.12***
control	48	7175	3 (0)	41.55	47	0.04±0.02

Difference of the yield of dicentrics and rings between the clean-up workers and the control group is significant at * - $p<0.05$, ** - $p<0.01$ and *** - $p<0.001$ levels.

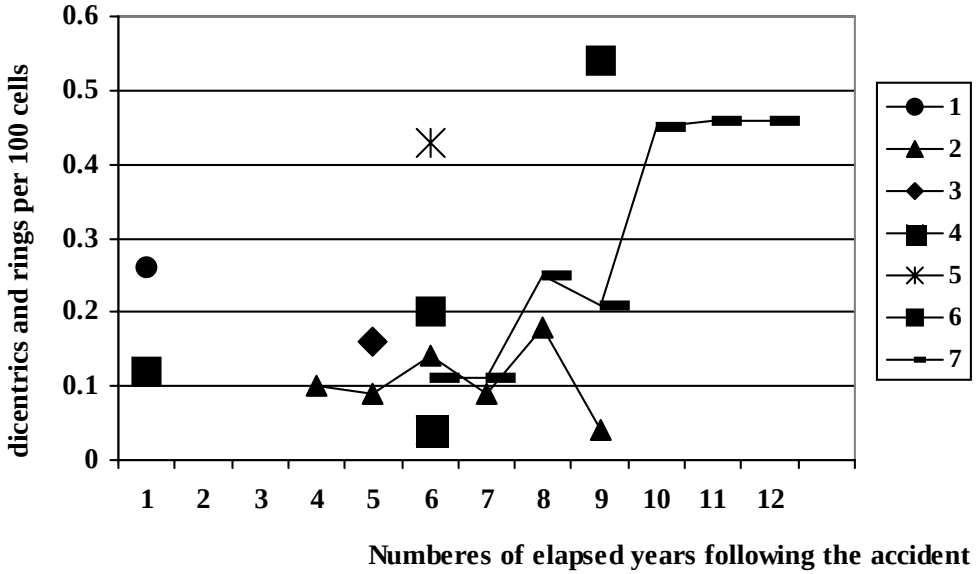

Figure 2. The yield of dicentrics and rings determined in clean-up workers in elapsed different years after the accident (the data of literature).

1.Semov et al., 1994 [4] 2. Schevchenko et al., 1995 [19] 3.Snigireva et al., 1994 [28]
4. Pilinskaya et al., 1994 [26] 5.Lazutka, 1996 [29] 6.Komar et al., 1997 30]
7. Slozina et al, present paper

which were carried out on a large group of such persons. Analysis of our data and the values reported by other laboratories who also examined the frequency of unstable chromosomal aberrations in the clean-up workers at different times after the Chernobyl accident [26-31] suggest that the levels of dicentrics found long afterwards is close to the initial levels reported in the studies carried out immediately after the accident. This is depicted in Figure 2, showing that the yields of dicentrics in the post-irradiation period do not become lower than the initial value (with only one exception; a point determined by Shevchenko et al. [19]. Later, an increased level of dicentrics was again found by this research group (personal communication).

In our investigation we found some temporal variation of dicentric frequency, which shows an inexplicable tendency towards the increase of dicentrics rate, 8-12 years after irradiation (Table 4 and Fig.2). No differences are seen in the scenario of irradiation, health status or the life style factors among the groups of people in different years of observation.

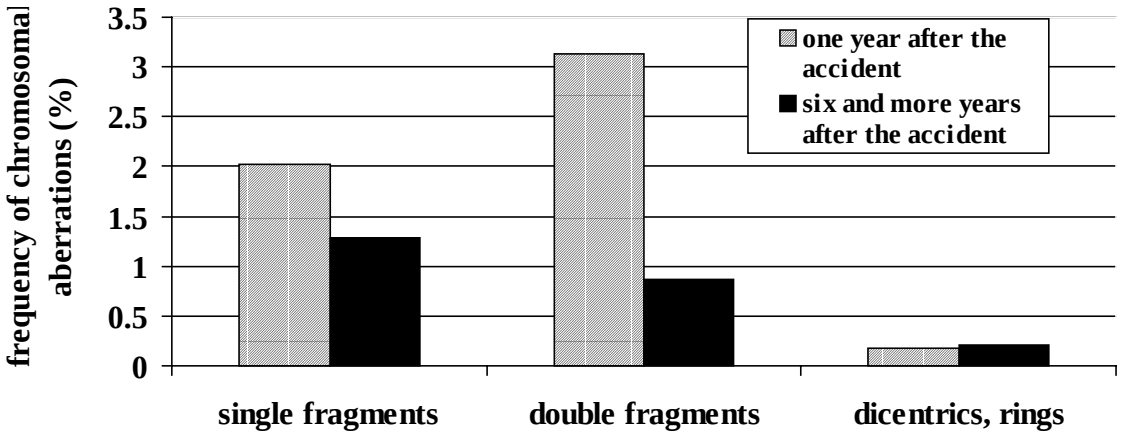

Figure 3. Frequency of chromosomal fragments and dicentrics + rings 1 year and 6-10 years after the Chernobyl accident.

We analysed temporal changes of chromosomal and chromatid fragments, the initial data of which had been obtained 1 year after the Chernobyl accident [32].(Fig 3). The frequencies both of single fragments and double fragments have clearly decreased 6-10 years after the accident.

It could be possible to put forward some suppositions about the persistence of dicentrics in the clean-up workers:

Long-life lymphocytes

Most lymphocytes have a half-life of about 3 years; however, some lymphocytes have a life span of several decades [6]. So it is possible to suppose that some asymmetrical exchanges have been found in long-life lymphocytes.

Stem cells

Although the clean-up workers were exposed to relatively low doses of ionising radiation, blood stem cells were also exposed to external -γ-irradiation. Some stem cells may survive many decades without undergoing proliferation and start to divide several years after irradiation. So it is possible that a part of dicentrics arises from these cells. It is also known that some dicentric chromosomes are able to pass through mitosis successfully and persist through cell divisions [33]. We cannot exclude that a certain fraction of the dicentrics is permanently produced by blood stem cells.

Radionuclides deposited

Several studies have shown that radioisotopes may cause chromosomal damage in peripheral lymphocytes after incorporation in man [34,35]. Radionuclides might have been incorporated by the clean-up workers during the accident. Some radioactive compounds have long physical half-lives and are retained in the body for a long period of time. So we cannot rule out the possible effects of internally deposited radioactive materials on chromosome aberrations in a remote period after the Chernobyl accident.

Chromosomal instability

It is also possible to assume that chromosomal instability could be induced by ionising radiation [36].

Association between the frequency of different types of chromosomal aberrations and the questionnaire information

The association between the frequency of different types of chromosomal aberrations and such variables as smoking habits, coffee, tea, alcohol consumption, history of current chronic illnesses, use of medicines and diagnostic X-rays was also analysed using stepwise multiple regression analysis in a group of clean-up workers. On the occasion to collect blood sample and fill out the questionnaire, we had the opportunity to inquire the doner whether he had specific anamnestic or environmental factors responsible for the existence of cytogenetic markers No statistically significant associations were observed due to any of these parameters except smoking. We have found the association of smoking with chromatid exchanges.

Table 5. Comparison of smoking and non-smoking liquidators.

	Smokers	Non-smokers
Number. of individuals	60	39
Total number. of cell scored	10071	6726
Aberrant cells (%)	2.97 ± 0.31	2.28 ± 0.34
Chromatid breaks (%)	1.13±0.19	0.96±0.21
Chromatid exchanges (%)	0.29 ± 0.07 [a]	0.03 ± 0.02
Chromosome breaks (%)	0.92 ±0.12	0.70 ± 0.12
Dicentrics, rings (%)	0.52 ± 0.09	0.31 ± 0.09
Atypical chromosomes (%)	0.08 ± 0.03	0.28 ± 0.13

[a]oSignificant at the 0.001 level.

This type of aberrations was significantly higher in the smoking subgroup than in the non-smoking subgroup of the clean-up workers (Table 5).

Although most chemical agents induce chromatid-type aberrations, the frequencies of chromatid exchanges are reported to be rare even in the smokers [37,38]. Concerning the high frequency of chromatid exchanges observed among the smokers in the Chernobyl clean-up workers, we cannot rule out the possible synergistic effects of smoking and previous radiation exposure.

The persistence of dicentrics and reconstructing doses

The long time persistence of dicentrics and rings should be considered in relation to the possibility to use the data for retrospective dose reconstruction. As an illustration, we have attempted to reconstruct the radiation doses using the yields of dicentrics and rings per cell obtained 6, 9, 12 years after irradiation. Assuming the half-life of lymphocytes 3 years [18] and taking account of the time between the irradiation and blood sampling we calculated what the initial frequency of dicentrics and rings could have been. Doses were then calculated using an *in vitro* calibration curve; $Y=0.0005+1.64*10^{-4}*D+4.92*10^{-6}*D^2$ taken from IAEA, 1986 [39]. The dose calculated 6 years after irradiation (~160mGy) is in a good agreement with the dose estimated in a similar group of clean-up workers soon after irradiation [40]. The dose derived 9 years after irradiation (~480mGy) seems a little overestimated, whilst the data derived 12 years after radiation exposure (~980mGy) is quite unrealistic for this cohort.

Conclusion

Results of these long-term investigations of so-called unstable chromosomal aberrations in the clean-up workers who suffered from low doses of ionizing radiation at Chernobyl suggest that the yield of dicentrics and rings does not change significantly over a long period of time following irradiation. This is an unexpected finding because it is at variance with the commonly accepted view of the persistence of dicentrics.

The results reported here demonstrate the presence of elevated chromosomal disturbances in lymphocytes of the clean-up workers in a remote period after the Chernobyl accident. Follow-up studies on individuals exposed to genotoxic agents have clearly demonstrated the predictive value of high chromosomal damage for subsequent cancer risk [41,42]. The fact of an increased level of unstable chromosomal aberrations in a remote period after irradiation allows us to suppose that other pathways of genomic burden may exist in addition to straight radiation action at the time of irradiation.

Considering the results of our investigations, we can conclude that the clean-up workers represent a high risk group that deserves special medical monitoring.

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