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Nuclear Abnormalities in Aspirated Thyroid Cells and Chromosome Aberrations in Lymphocytes of Residents Near the Semipalatinsk Nuclear Test Site

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Semipalatinsk nuclear test site (SNTS)/Thyroid cells/Apparent nuclear abnormalities (ANA)/Chromosome aberrations/Radiation effect.

Chromosomal studies in peripheral lymphocytes from 63 residents near the Semipalatinsk nuclear test site, at ages of 52–63 years old, were performed in 2001–2002. A higher rate of chromosome aberrations was observed in the two contaminated villages, Dolon and Sarjal, compared with the control village, Kokpekti. Moreover, a relationship of frequency of cells with radiation induced chromosome aberrations and the previously estimated exposure dose was observed. Furthermore, apparent nuclear abnormalities (ANA) of thyroid follicular cells were studied in 30 out of 63 residents, who were examined for chromosome aberrations. A higher rate of ANA was also found in the residents in the exposed villages compared with those in the control village. These results suggest radiation effects both on the chromosomes in peripheral lymphocytes and on the follicular cells in the thyroid.

INTRODUCTION

In-depth investigation and publication has established that thyroid diseases, especially thyroid cancer, following external radiation were frequently seen among atomic bomb survivors in Hiroshima and Nagasaki,[1)] and in children after the Chernobyl nuclear power plant accident.[2,3)] The incidence of thyroid cancer development showed a dose-response relationship among the atomic bomb survivors in Hiroshima and Nagasaki.[4)] Furthermore, combined studies of thyroid cancer after external irradiation showed that linearity best described the dose response for persons exposed to radiation before the age of 15 years.[5)]

The former Soviet Union's first nuclear bomb test was conducted at the Semipalatinsk Nuclear Testing Site (SNTS), located in the northern part of the Republic of Kazakhstan, on 29 August 1949. During the following 40 years, there were 456 nuclear explosions including 111 atmospheric events between 1949 and 1963.[6)] As a result, it is suspected that several hundreds of thousand residents near the SNTS in Kazakhstan were exposed to radiation. We performed a retrospective study of thyroid diseases in northeastern regions of Kazakhstan from 1966 to 1996, and reported that a noticeable increase in the number of cases with thyroid cancer was seen in the period of 1982–1996, especially among residents aged under 40.[7)] Therefore, since 1999, we have been sending a medical team for studying blood and thyroid health of the residents near the SNTS, and performing thyroid health screening and peripheral blood sampling.

Here, we report the results of studies performed in 2001–2002 for cytohistological analysis of aspirated thyroid follicular cells and chromosome analysis of peripheral lymphocytes. Except for studies in atomic bomb survivors, few studies have been published on the late effects of radiation on thyroid follicular cells with their relationship to the exposure dose or chromosome aberration rates. We found that high incidence of chromosome aberrations in peripheral lymphocytes and nuclear aberrations of thyroid follicular cells among the subjects who had ages ranging from 0 to 10

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Abbreviations, SNTS: Semipalatinsk nuclear test site, ANA: apparent nuclear abnormalities

at the first nuclear bomb test. These findings indicate that these abnormalities are suspected to relate to radiation exposure in the residents near the SNTS.

MATERIALS AND METHODS

In 2001–2002, chromosome analysis in peripheral lymphocytes and thyroid health examinations in the residents near the SNTS were performed. Three villages were selected to represent the area included this study, the two “contaminated” villages of Dolon and Sarjal, and one “control” village, Kokpekti. Residents in the two villages of Dolon and Sarjal, which are about 100km away from the center of SNTS, respectively, are suspected to have been exposed to 1.30 Sv in Dolon and 1.51 Sv in Sarjal.[8] The radiation dose of 1.5 Sv is comparable to the free-in-air (FIA) dose from the atomic bomb (A-bomb) radiation at 1.25 km ground range in Hiroshima. Kokpekti, which is located about 700 km east from the SNTS, was selected as a control village. The exposure level in Kokpekti is estimated to be almost 0 Sv because radiation contaminated clouds did not pass through this village.

Residents in these villages who were born in 1939–1949 (0–10 years old at the time of the first nuclear explosion test in 1949) and 52–63 years old at the time of sampling in 2001–2002 were selected for the present study. Cases with chronic thyroiditis who showed high anti-thyroglobulin antibody values (TgAb ≥ 0.4 U/ml) were excluded from this study, because many abnormal findings (such as degeneration and destruction of follicular cells and nuclei, oxyphilic cells, atypical nuclei, lymphocytic infiltration, stretched lymphocytes and fibrosis) in the cases of chronic thyroiditis are hard to distinguish from those abnormalities induced by radiation. Informed consent had been taken prior to all sampling. The blood of a total of 63 persons was analyzed for chromosomal aberrations in peripheral lymphocytes, and in 30 of the subjects there was additional analysis for abnormalities of thyroid follicular cells.

Chromosome analysis

A 10 ml sample of peripheral venous blood was drawn in a heparinized tube and stored in a container at 4°C. Chromosome analysis was performed according to the method described previously.[9,10] Briefly, whole blood was cultured with phytohemagglutinin for 48 hours at 37°C, then colcemid was added and cultured for another 2 hours. Cells were treated with a hypotonic solution, and then fixed with a methanol/acetic acid mixture. Slides were prepared by an air-drying method and stained with Giemsa. More than 100 well-spread metaphases were analyzed from each subject. Chromosome aberrations were scored under the microscope, and were photographed. Radiation-induced chromosome aberrations were as follows: stable (Cs type) aberrations including translocations (t), inversions (inv) and deletions (del), unstable (Cu type) aberrations including dicentrics (dic) and rings (r). Abnormalities were confirmed on the printed photographs.

Thyroid examination

Thyroid cells from non-nodular lesions that seemed to be normal were obtained by a needle aspiration biopsy under ultrasonography. Cells were aspirated by a 23G needle with a 20 ml syringe fixed in a pistol type apparatus. Aspirated cells were splashed onto the glass slides, dried with an air blower and stained with May-Gruenwald Giemsa.

These slides were analyzed under the microscope for abnormal thyroid follicular cells. In this study, nuclei showing apparent irregular surface, irregular rim, irregular shape and irregular size were classified as apparent nuclear abnormalities (ANA). These ANA are almost the same as atypical nuclear abnormalities of thyroid follicular cells.

RESULTS

Frequencies of chromosome aberrations in peripheral lymphocytes

Chromosome analysis was performed on a total of 63 residents near the SNTS. The distribution of age (mean ± 2 standard deviations) and sex (male : female) of the subjects in each area were as follows: 28 subjects in Dolon (age 58.0 ± 3.7 years, sex 8:20), 17 subjects in Sarjal (age 57.7 ± 3.8 years, sex 5:12), and 18 subjects in Kokpekti (age 53.7 ± 1.5 years, sex 4:14). Analyzed cell number ranged from 100 to 500 cells from each subject, and the total number was 9,000 cells (average: 321.4 ± 63.0 cells per subject) in Dolon, 5,150 cells (302.9 ± 156.6 cells) in Sarjal, and 6,600 cells (366.7 ± 118.8 cells) in Kokpekti. The types and frequencies of chromosome aberrations in lymphocytes are presented in Table 1 and the statistics of cells containing those aberrations are summarized in Table 2. The frequencies of aberrations in Dolon and Sarjal were compared with those in Kokpekti and the significance of difference was evaluated by the χ^2-test, in which $p < 0.05$ was regarded as significant and $p < 0.01$ as highly significant.

As shown in Table 1, chromosome aberrations were frequently found in the subjects living in the contaminated areas. The number of stable-type aberrations in Dolon and Sarjal were 1.2 and 1.0 per 1,000 cells, respectively, and they were higher than the 0.2 per 1000 cells in Kokpekti. The same trends were seen in the unstable-type aberrations. The number of these aberrations was 2.0 and 0.8 per 1,000 cells in Dolon and Sarjal respectively, and 0.2 per 1,000 cells in Kokpekti. Fragments, which are not classified among the radiation induced chromosome aberrations, were also found more frequently in the contaminated populations. The number of fragments was 1.1 per 1,000 cells in Kokpekti, whereas 4.1 and 1.9 per 1,000 cells were found in samples from Dolon and Sarjal, respectively.

Table 1. Chromosome aberrations in peripheral lymphocytes from 63 residents of the area near the SNTS.

	Contaminated		Control
	Dolon	Sarjal	Kokpekti
Total cell number	9,000	5,150	6,600
Stable aberrations (per 1,000 cells)			
translocation (t)	5 (0.6)	2 (0.4)	0 (0)
inversion (inv)	2 (0.2)	1 (0.2)	0 (0)
deletion (del)	4 (0.4)	2 (0.4)	1 (0.2)
total (t + inv + del)	11 (1.2)	5 (1.0)	1 (0.2)
Unstable aberrations (per 1,000 cells)			
dicentrics (dic)	16 (2.0)	4 (0.8)	1 (0.2)
rings (r)	2 (0.2)	0	0
total (dic + r)	18 (2.0)	4 (0.8)	1 (0.2)
fragments (f)	37 (4.1)	10 (1.9)	7 (1.1)

Table 2. Cells with chromosome aberrations in peripheral lymphocytes from 63 residents of the area near the SNTS.

	Contaminated			Control
	Dolon	Sarjal	Total	Kokpekti
Number of cells, total	9,000	5,150	14,150	6,600
Cs (t + inv + del)	9*	4	13*	1
Cu (dic + r)	13**	2	15*	1
Cs cells and Cu cells	22** (0.24%)	6 (0.12%)	28** (0.20%)	2 (0.03%)
Fragments only	29**	6	35**	5
Multiple complex aberrations ("rogue")	24**	8**	32**	0
Endoreduplication	3	0	3	0
Total cells with chromosome aberrations	78** (0.87%)	20** (0.39%)	98** (0.69%)	7 (0.11%)
Total subject number	28	17	45	18
Number of cases				
with Cs + Cu cells	16** (57%)	6 (35%)	22** (49%)	2 (11%)
with cells with aberrations	26** (93%)	9 (53%)	35** (78%)	6 (34%)

The significance of the differences was evaluated by the χ^2-test: **p* < 0.05, ***p* <0. 01.

The number of cells with these aberrations is shown in Table 2. The incidence of cells with radiation-induced chromosome aberrations (Cs cells and Cu cells) was 0.24% in Dolon (p = 0.0007; highly significantly different), and 0.12% in Sarjal (p = 0.0755; not significantly different; Fig. 2) compared with 0.03% in Kokpekti. It was also highly significant different for the total contaminated area (0.20%, p = 0.0031). Figure 1 shows the relationship between the

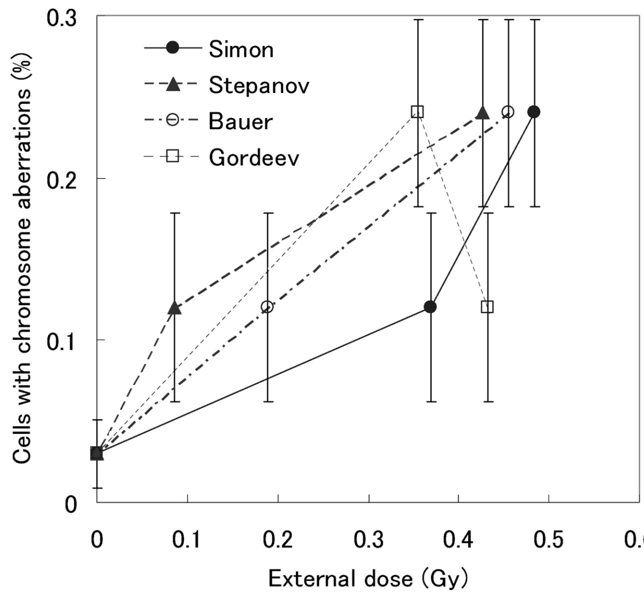


Fig. 1. The dose response of the cells with radiation-induced chromosome aberrations (Cs and Cu cells) for people living near SNTS area. The errors of frequency of aberrant cells are estimated according to Poisson statistics. The external dose are estimated using previous results[8,11–13] with correction factor: 0.306, which is obtained from the recent average result of external dose: 0.484 ± 0.075 Gy[23–25] and the previous result: 1.7 by Simon *et al.*[11] The uncertainty of the external dose to residents was discussed and it was stated that we were "lacking .. knowledge about the number of hours spend outdoors each day among different age groups" in reference by Gordeev *et al.*[8]

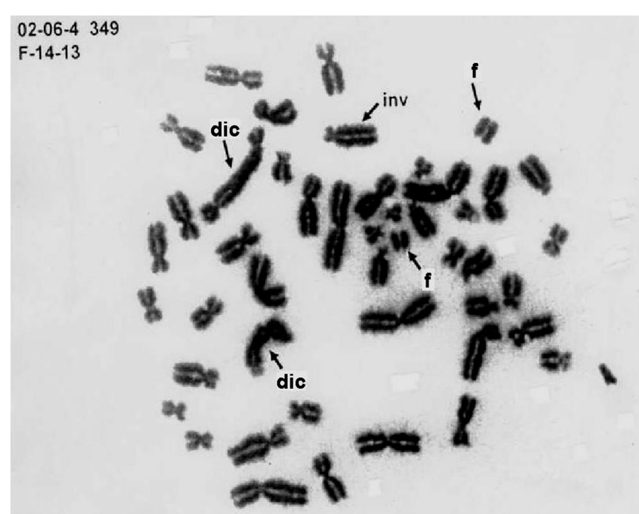
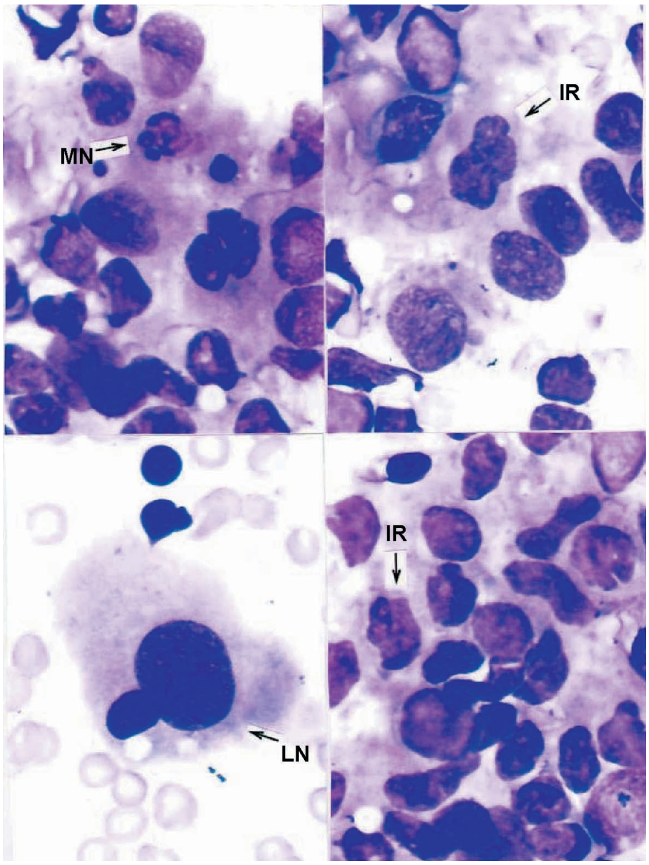


Fig. 2. A cell with chromosome aberrations from 59 year-old female in Sarjal. Arrows indicate 1 inversion (inv), 2 dicentrics (dic) and 2 fragments (f).



external dose estimated using the previous results[8,11–13] and the frequency of the cells with chromosome aberrations for people living near the SNTS. A possible dose-response relationship is statistically significant at the p = 0.05 level and the slope is 0.48% cells/Gy. Besides Cs and Cu cells, cells with chromosome aberrations that are not classified in the radiation induced types were seen (Table 2). These cells with fragments, multiple complex aberrations (defined as "rogue" cells [14]), and endoreduplication were found more frequently in the contaminated areas than the control. The frequency of total cells with all chromosome aberrations in Kokpekti was 0.11%, whereas they were 0.39% in Sarjal and 0.87% in Dolon, and they were 3.5 times ($p < 0.0001$) and 7.9 times ($p = 0.0015$) higher than that of Kokpekti, respectively.

As shown in Table 2, the cases with radiation induced chromosome aberrations were 57% in the 28 studied subjects ($p = 0.0018$) in Dolon and 35% in the 17 cases ($p = 0.0886$) from Sarjal, both of which were higher than the 11% in the 18 cases in Kokpekti. The percentage of the total cases who had any chromosome aberrations in Kokpekti was 34%.

Fig. 3. Typical apparent nuclear abnormalities (ANA) in thyroid follicular cells from 53 year-old female in Sarjal (MGG stains, × 600 magnifications). Arrows indicate micro nucleus (MN), large nucleus (LN), and nuclei showing irregular rim, irregular surface and irregular shape (IR). Many other atypical nuclei are also seen in these photos.

Table 3. Incidence of apparent nuclear abnormalities (ANA) in thyroid follicular cells and chromosome aberrations in peripheral lymphocytes from 30 residents of the area near SNTS.

		Contaminated Dolon & Sarjal	Control Kokpekti	Total
Total case number		19	11	30
Number of cases				
with ANA		12 (63%)*	2 (18%)	14 (47%)
with chromosome aberrations (Cs + Cu)		9 (47%)*	1 (9%)	10 (33%)
Relationship between ANA and Chromosome aberrations				
ANA	Chromosome aberrations	Contaminated Dolon & Sarjal	Control Kokpekti	Total
+	+	8	1	9
+	–	4	1	5
–	+	1	0	1
–	–	6	9	15

*

The significance of difference was evaluated by the χ^2-test: $*p < 0.05$.

On the other hand, it was 93% in Dolon and 53% in Sarjal, and they were 2.8 times ($p < 0.0001$) and 1.6 times (not significant) higher than that in Kokpekti, respectively.

Relationship between chromosome aberration rates in peripheral lymphocytes and apparent nuclear abnormalities (ANA) of thyroid follicular cells

Among 63 subjects examined for chromosome aberrations, 30 subjects contributed aspirated thyroid cells which were examined for abnormality, and nuclei showing apparent irregular surface, irregular rim, irregular shape and irregular size were classified as ANA. Figure 3 showed a case with ANA. The distribution of age (mean ± 2 standard deviations) and sex (male : female) of the cases in each area were as follows: 19 cases in contaminated area (Dolon and Sarjal) (age 57.6 ± 3.2 years, sex 3:18) and 11 cases in control area (Kokpekti) (age 53.8 ± 1.7 years, sex 4:7). The analyzed lymphocyte number in total was 6,700 cells (average: 352.6 ± 112.4 cells per subject) in the contaminated areas and 4,500 cells (409.1 ± 104.4 cells) in the control area. Results are shown in Table 3. The significance of differences was evaluated by the χ^2-test.

The number of cases with ANA was 12 (63%) in the contaminated area and 2 cases (18%) in control area. On the other hand, number of cases with radiation induced chromosome aberrations was 9 (47%) in contaminated populations and 1 (9%) in controls. Thus, both of these abnormalities were significantly higher in contaminated areas than those in the control area (p = 0.0321 and p = 0.0173, respectively). The relation between ANA and chromosome aberrations is shown in Table 3. Among 14 cases with ANA, 9 (64%) had chromosome aberrations, whereas 15 (94%) of 16 ANA negative cases had no chromosome aberrations, resulting in a highly significant relation between these abnormalities (p = 0.0008).

DISCUSSION

In this paper, we showed that a higher rate of chromosome aberrations in peripheral lymphocytes and ANA in thyroid follicular cells in the highly contaminated villages of Dolon and Sarjal was observed compared with that of the control village. The results of these studies clearly show a significant radiation effects in the residents near the SNTS.

A clear relationship of chromosome aberration rate and exposure dose has been observed in atomic bomb survivors in Hiroshima and Nagasaki.[10] However, a dose response of chromosome aberrations[15] or micronuclei[16] in lymphocytes from the residents near the SNTS has not been shown. Unlike Hiroshima and Nagasaki, this region near the SNTS did not receive direct radiation exposure from the explosion. The hazard studied in this area stemmed from local fallout that entered the body to give radiation exposure. The residents seem to have been exposed to both internal and external radiation. Consequently, we have to consider the effects of exposure to long-term low-dose radiation (low-dose rate exposure) to analyze the people living near the SNTS.

In this report, we analyzed radiation-induced chromosome aberrations in peripheral lymphocytes from the residents in both contaminated and non-contaminated area near the SNTS, and found that these aberrations were seen in the contaminated area with high significant increased frequency. Moreover, we gave the first report about a significant dose response for these chromosome aberrations, although the doses were estimated using some previous reports. Thus, the analysis of chromosome aberrations we used in this study may be able to be one of the methods of biological dosimetry in this area. Furthermore, chromosome aberrations such as fragments, multiple complex aberrations and endoreduplications were also found in the contaminated area with significantly higher frequency than those in the control area, although these aberrations have not been usually classified in the radiation induced types and have been suspected to be caused by a virus infection to explain their area specificity,[17,18] or an effect of biochemically active reagents the subject took.[19] Now we are trying to clarify the relationship between low radiation dose and chromosome aberrations in other residents with various age and areas near the SNTS.

The thyroid gland is well known as an organ sensitive to radiation,[5] and many reports have shown that patients with thyroid cancer increased after the atomic bomb in Hiroshima and Nagasaki[1] and the Chernobyl nuclear power plant accident.[20,21] Almost of all of the thyroid cancers developed in atomic bomb survivors in Hiroshima and Nagasaki were histopathologically papillary cancers.[22] However, a few papers reported nuclear abnormalities in the non-nodular normal lesions of the thyroid at a late stage following radiation exposure. From the present study on non-nodular lesions of residents near the SNTS, a late radiation effect was suggested to be induced in thyroid follicular cells because higher rate of ANA in the thyroid was found among the residents in Dolon and Sarjal villages, and significantly higher than that in the control village of Kokpekti. Similar types of nuclear anomalies are frequently observed in the struma (goiter) of chronic thyroiditis, however, they seem to be less severe than our findings of ANA in thyroid cells from the exposed peoples near the SNTS. The difference may be caused by the difference of atypism. In this study, we excluded the cases with chronic thyroiditis (TgAb ≥ 0.4) although we are expecting to be able to differentiate in the near future whether the ANA in the thyroid is radiation-induced or chronic thyroiditis.

The higher rate of ANA in thyroid cells in parallel with the higher rate of chromosome aberrations in peripheral lymphocytes among the same subjects in Dolon and Sarjal, may suggest that some late radiation effects were induced in the residents near the SNTS after the nuclear explosion tests. So far as we know, the present study may be the first to report the late radiation effects on thyroid follicular cells based on the information on lymphocyte chromosome aberrations in the area near the SNTS. The higher frequencies of lymphocyte chromosome aberrations in Dolon and Sarjal indicate a significant radiation exposure and at the same time late radiation effects were induced in the thyroid follicular cells in the residents near the SNTS. Furthermore, it is notable that these abnormalities must have been induced in the last part of the 52–53 years after the first nuclear explosion test in SNTS.

The analysis of ANA in thyroid cells may also be able to be one of the methods of biological dosimetry in this area. However, it has to be also considered that the classification of ANA is somewhat different among researchers. Obviously, further analysis has to be made after adding to the number of subjects. The same kind of studies are also expected to be done in other radiation exposed populations.

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