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Chromosome Aberration Analysis in Persons Exposed to Low-level Radiation from the JCO Criticality Accident in Tokai-mura

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Chromosome aberrations were studied in peripheral blood lymphocytes of 43 persons who were exposed to low-level radiation of mixed neutrons and γ-rays resulting from the JCO criticality accident. When the age-adjusted frequencies of dicentric and ring chromosomes were compared with the dose calibration curve established *in vitro* for ^{60}Co γ-rays as a reference radiation, a significant correlation was observed between the chromosomally estimated doses and the documented doses evaluated by physical means. The regression coefficient of the chromosomal doses against the documented doses, 1.47 ± 0.33, indicates that the relative biological effectiveness of fission neutrons at low doses is considerably higher than that currently adopted in the radiation protection standard.

INTRODUCTION

The criticality accident that occurred on October 30, 1999, in the JCO uranium processing facility in Tokai-mura had a strong impact on the evaluation of the biological effectiveness of neutron exposure. In this accident, neutrons and γ-rays were emitted from the uranium precipitation tank in the conversion building for about 20 hours, in which approximately 11% of all doses were due to the burst in the initial 25 min[1)]. The nuclear reaction resulted in severe radiation exposures to three workers in the conversion building and low-level overexposures to other JCO employees in the facility, emergency personnel and local residents near the facility.

This accident has received particular attention in the context of being the first case in which

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a considerably large number of people were exposed to neutrons. Previously, atomic-bomb radiation in Hiroshima had provided the only basis for evaluating the health consequences of neutron exposure to human populations. However, this biological basis was banished as a consequence of a reassessment of the atomic-bomb radiation in Hiroshima and Nagasaki, a new dosimetry system DS86, where the neutron dose was evaluated to be negligibly small in both cities[2]. The paucity of reference data on the biological effectiveness of neutrons, particularly at low doses, has been a serious concern in setting the radiation protection standard. Based on compiled experimental data on the relationship between the relative biological effectiveness (RBE) and linear energy transfer (LET) for various charged particles[3], the International Commission on Radiation Protection (ICRP) proposed the energy-dependent radiation quality factor of neutrons by extrapolating from the LET-RBE relationship of charged particles to that of recoil protons at the site of interest[4–6]. Although the quality factor, or radiation weighting factor, is an operational quantity for radiation protection, there is growing experimental evidence indicating that the RBE of neutrons at low doses, or a maximum RBE (RBE_{max}), is considerably larger than the conventional value[7–10].

Chromosome aberrations in peripheral blood lymphocytes provide a sensitive measure of the quality and quantity of radiation, and have been used for biological dosimetry in the human exposure to radiation[11]. The advantages of chromosome-based biological dosimetry are twofold: it not only supplements the dose evaluation on a physical or calculation basis in the effective dose equivalent, it but also offers direct evidence concerning the magnitude of biological effects of human radiation exposure. In this context, an interlaboratory cooperative study was performed immediately after the accident for a lymphocyte chromosome aberration analysis in persons who were assumed to be exposed to low-level radiation. The significantly elevated chromosome aberration frequency in those persons with documented doses as low as several to tens of mSv was consistent with the remarkably high RBE_{max} values of the fission neutrons.

MATERIAL AND METHODS

Study populations

The groups of persons included in the present study and their exposure conditions are summarized in Table 1. Peripheral blood samples were obtained from 43 persons who agreed with informed consent. They included local residents who were located at a remote distance from the site, but were diagnosed to have severely reduced lymphocyte counts in a hematological examination carried out 2–4 days after the accident (category A); local residents exposed outside the JCO facility, but located approximately 80 m from the site (category B); JCO employees whose exposure levels were evaluated by whole-body counting and/or personal monitors (category C); JCO employees who were engaged in the drainage of cooling water from the jacket of the precipitation tank (category D); and firemen engaged in the rescue of severely exposed workers (category E).

Table 1. Summary of the exposure conditions and blood sampling of persons studied for chromosome aberration analysis.

Exposure categories	Exposure conditions	No. of persons involved	Documented dose (mSv)[a]	No. of persons examined	and date of sampling
(A) Local residents (I)	Remote residents diagnosed to have severely depressed lymphocyte counts	8	ND	7	99.10.18
(B) Local residents (II)	Residents exposed at the vicinity of the site (~80m)	7	6.7–16	7	99.10.21 99.10.22
(C) JCO employees (I)	JCO employees in the facility[b]	49	0.6–48	18	99.10.21 99.10.22
(D) JCO employees (II)	Workers engaged in water drainage	18	3.8–48	8	99.10.21 99.10.22
(E) Emergency personnel	Firemen engaged in the rescue of severely exposed persons	3	4.6–9.4	3	99.10.21
Total number of persons examined for chromosome aberration analysis				43	

[a] Documented dose in effective dose equivalent estimated based on the whole-body counting of the activated ^{24}Na, reading of personal monitor and/or behavior after the accident in combination with the calculated neutron and γ-ray doses in the environment[12].

[b] JCO employees whose exposure levels were evaluated by whole-body counting of activated ^{24}Na and/or personal monitors. Those in category D are not included.

Lymphocyte culture and chromosome preparation

Approximately 3 ml of peripheral blood was obtained from each person at the Mito National Hospital in Mito, Ibaraki. The blood-sampling and cell-culture procedures were essentially the same as previously described[13,14]. Briefly, heparinized blood was immediately mixed with a 1 ml RPMI-1640 culture medium supplemented with 20% fetal bovine serum and 240 μg kanamycin in a VACUTAINER CPT tube (Becton Dickinson Co., Ltd.), and brought to the National Institute of Radiological Sciences, Chiba, for a lymphocyte culture and chromosome preparation. Lymphocyte-rich mononuclear cells were collected by centrifuging the blood sample in a VACUTAINER tube at 3,300 rpm for 15 mins, washed in Hanks' balanced salt solution supplemented with 2% fetal bovine serum, and cultured for 48 hours at 37°C under the aeration of 5% CO_2 in a 15 ml centrifuge tube containing a 6 ml RPMI-1640 culture medium supplemented with 20% fetal bovine serum, 120 μg phytohemagglutinin, 360 μg kanamycin and 0.3 μg colcemid. The cultured cells were harvested, subjected to 75 mM KCl for 20 min and fixed in a 1:3 mixture of acetic acid and methanol. Air-dried chromosome preparations were made under a warm and humidified atmosphere, as previously described[13].

Scoring of chromosome aberrations

In order to obtain analysis results in a limited time, and to minimize the scoring biases, an interlaboratory collaborative study was performed, which included National Institute of Radiological Sciences, Institute of Radiation Biology and Medicine of Hiroshima University, Radiation Effects Research Foundation, Nagasaki University School of Pharmaceutical Sciences and Radiation Biology Center of Kyoto University. Chromosome preparations were distributed to

each laboratory, where all chromosome-type aberrations were scored and photographed. The chromosome aberrations were confirmed by the scorers on the photoprints in a coordination meeting.

Chromosomal dose assessment

A chromosomal dose assessment was made based on the frequencies of dicentrics and rings, where any dicentrics and centric rings not associated with acentric fragments were excluded. The method of the dose assessment was essentially the same as that described in the IAEA Technical Report Series No. 260 (Ref. 11). Namely, assuming a linear-quadratic relation between the aberration frequency (Y) and the dose (D in Gy), $(Y\text{-}C) \pm \varepsilon = (\alpha \pm \sigma_1)D + (\beta \pm \sigma_2)D^2$, the dose (in Gy equivalent chromosomal) was estimated by a nonlinear iteration method for the maximum likelihood, where C was the control aberration frequency, and ε and σ were standard errors. For the reference dose-response of the dicentrics and rings in human peripheral blood lymphocytes, we used dose-response parameters obtained from *in vitro* irradiation with ^{60}Co γ-rays at 37 dose points in a dose range between 0.01 and 5 Gy (Sasaki, previously unpublished). They are, on a per-cell basis, $C = (8.50 \pm 1.85) \times 10^{-4}$, $\alpha = (2.31 \pm 0.88) \times 10^{-2}$ and $\beta = (6.33 \pm 0.25) \times 10^{-2}$. The control aberration frequency has been documented to be age dependent. In the present study population, the control values were not known *a priori* and, moreover, the age was widely distributed from 19 to 86 years old. Therefore, instead of using the control value obtained in the experiments, the age-dependent control values in Japanese general populations were adopted from Tonomura *et al.*[15], which were expressed by a linear approximation of $C_t = aX$, where X was age in year and $a = (2.92 \pm 0.52) \times 10^{-5}$ dicentrics and rings per cell. For persons who were diagnosed to have severely depressed lymphocyte counts, the base level of the aberration frequency was further modified, because such lymphocyte insufficiency was not likely to be a consequence of radiation exposure, as deduced from the calculated radiation doses (<1.2 mSv) in their environment. It could be irrelevant to such small doses, but might affect the spontaneous aberration frequency, and hence would interfere with the chromosome-based dosimetry. In a separate study on the spontaneous aberration frequencies in 44 patients (average age 5.3 yeas old) with aplastic anemia of unknown etiology, 8 dicentrics were identified in 4,507 cells (Sasaki, unpublished data). The frequency is expressed by $\Gamma = (1.78 \pm 0.63) \times 10^{-3}$. Thus, $C = \Gamma + aX$ was applied for the control value of each person, where $\Gamma = 0$ was used for otherwise healthy individuals.

RESULTS

Table 2 summarizes the results of a chromosome aberration analysis. A total of 67,879 cells, or on average about 1,600 cells per person, were analyzed in 43 persons. Out of 107 dicentrics and rings (1.58 per 1,000 cells) , 87 (1.28 per 1,000 cells) were associated with acentric fragments (acentric rings inclusive), which provided the basis of the dose assessment. An example of chromosome aberrations observed in an exposed person is shown in Fig. 1. Fig. 2 plots the observed frequencies of dicentrics and rings against age. The correlation coefficient was $R = 0.298 \pm 0.149$ and the probability of uncorrelatedness was $p = 0.112$, suggesting a weak correlation

Table 2. Summary of a chromosome aberration analysis in persons involved in low-level exposure.

No.	Subjects	Dose (mSv)[a]	No. of cells	DR-1[b] No.	DR-2[c] No.	DR-2[c] (0/00)	Estimated dose (mGy-Eq)[d] D_m	D_L	D_U
1	A018181	0	1,391	4	3	2.16	0	0	27.6
2	A023181	0	1,600	2	2	1.25	0	0	24.3
3	A035186	1.4	1,355	4	3	2.21	0	0	28.2
4	A046183	0	1,227	3	2	1.63	0	0	30.9
5	A058186	0	1,083	1	1	0.92	0	0	34.5
6	A063183	0	1,600	4	3	1.88	0	0	24.3
7	A072186	0	1,600	2	1	0.63	0	0	24.3
8	B014219	6.9	1,765	0	0	0	0	0	22.2
9	B027214	9.7	1,015	3	3	2.96	31.7	0	117.1
10	B035210	12.0	1,600	2	1	0.63	0	0	24.3
11	B042218	15.0	1,800	1	1	0.56	0	0	21.8
12	B054228	6.7	1,600	3	3	1.88	19.7	0	81.3
13	B062225	14.0	1,600	0	0	0	0	0	24.3
14	B072229	16.0	1,600	5	5	3.13	80.9	26.3	155.2
15	C013216	1.5	1,700	5	3	1.76	28.5	0	87.9
16	C023216	23.0	1,341	5	5	3.73	92.5	29.9	174.6
17	C033214	30.0	1,700	3	3	1.76	30.6	0	90.3
18	C042214	23.0	1,600	1	0	0	0	0	24.3
19	C053216	47.0	1,700	4	3	1.76	28.5	0	87.9
20	C064219	5.9	1,600	3	3	1.88	18.5	0	80.1
21	C074212	11.0	1,600	2	1	0.63	0	0	24.3
22	C084211	7.0	1,600	1	1	0.63	0	0	24.3
23	C093211	8.5	1,578	0	0	0	0	0	24.6
24	C103219	13.0	1,600	5	4	2.50	51.6	3.5	120.8
25	C111219	32.0	1,700	2	1	0.59	1.5	0	37.7
26	C125222	18.0	1,600	4	4	2.50	38.5	0	107.3
27	C133228	0.6	1,600	1	1	0.63	0	0	24.3
28	C144224	6.1	1,600	2	2	1.25	0	0	24.3
29	C153227	4.9	1,600	1	1	0.63	0	0	24.3
30	C163226	2.0	1,630	1	1	0.61	0	0	23.9
31	C173221	1.9	1,600	1	0	0	0	0	24.3
32	C183227	2.0	1,374	0	0	0	0	0	27.9
33	D015213	13.0	1,700	2	2	1.18	0	0	23.0
34	D023218	14.0	1,700	4	3	1.76	26.3	0	85.6
35	D033216	13.0	1,700	2	2	1.18	5.5	0	54.6
36	D043217	19.0	1,700	4	4	2.35	48.5	2.9	115.0
37	D053218	9.4	1,600	4	3	1.88	30.8	0	93.0
38	D063215	19.0	1,600	4	1	0.63	0	0	24.3
39	D073225	9.8	1,600	2	2	1.25	9.6	0	61.7
40	D083227	14.0	1,600	4	3	1.88	31.8	0	94.1
41	E014213	9.4	1,600	2	2	1.25	0	0	24.3
42	E022217	4.6	1,800	2	2	1.11	13.4	0	61.4
43	E034214	8.6	1,720	2	2	1.16	0	0	22.7
	Total[e]	(10.53)	67,879	107	87	(1.28)	(13.7)	(1.5)	(54.3)

[a] Documented dose (combined neutron and γ-ray doses).
[b] Number of dicentrics and rings (DR).
[c] Number of dicentrics and rings (DR) associated with acentric fragments (acentric rings inclusive). Frequencies in number per 1,000 cells.
[d] Chromosomally estimated dose (D_m) with lower (D_L) and upper limit (D_U) in mGy equivalent chromosomal.
[e] Figures in parentheses are averages of 43 persons.

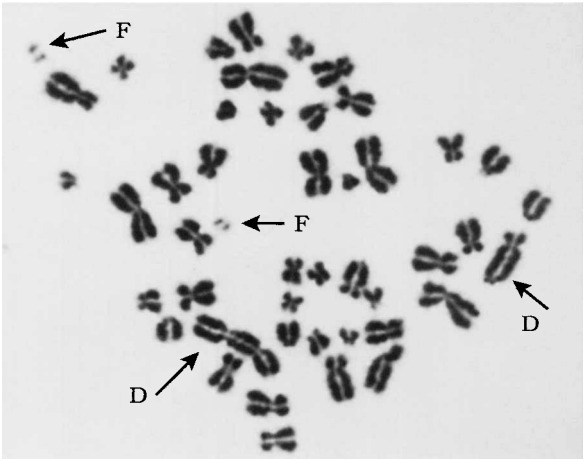

Fig. 1. Metaphase spread with chromosome aberrations observed in an exposed person (D053218). Dicentrics (D) and associated acentric fragments (F) are indicated by the arrows.

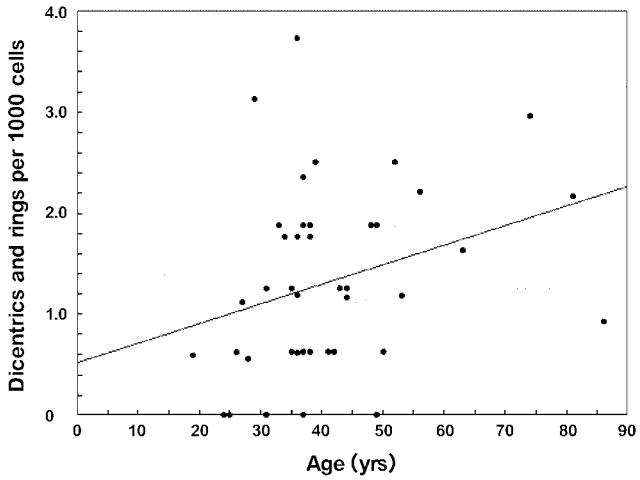

Fig. 2. Frequencies of the dicentrics and rings against the age of the donors (before adjustment by age). The curves show a regression curve and its 95% confidence limits.

with age, probably in part due to the distortion of the age-effect due to the contribution of radiation exposure in some persons.

Then, the observed frequencies of dicentrics and rings were adjusted by age and disease condition (aplastic anemia) to obtain the net-induced aberrations. For a dose assessment, the net-induced aberration frequency with its standard errors was used to calculate the dose by the Newton-Raphson nonlinear iteration method. According to the chromosomal dose assessment, overexposure was suggested in 18 persons, the estimated doses being in a range from 1.5 to 92.5 mGy equivalent chromosomal. However, the overall standard errors were considerably large,

and the lower limit of the estimated dose, D_L, reached to zero dose in 14 of them. Since the present study was not a case-control study, the validity of the chromosome aberration analysis was evaluated by an internal comparison to determine any relevance to the documented doses, which were estimated by physical means. Fig. 3 plots the chromosomally estimated doses against the physically estimated documented doses. As can be seen in Fig. 3a, where the two doses were compared at an individual level, a significant correlation was found between the two doses (correlation coefficient $R = 0.405 \pm 0.143$ with the probability of uncorrelatedness of $p = 0.019$). When the two doses were compared as averages of the exposure categories (Fig. 3b), the correla-

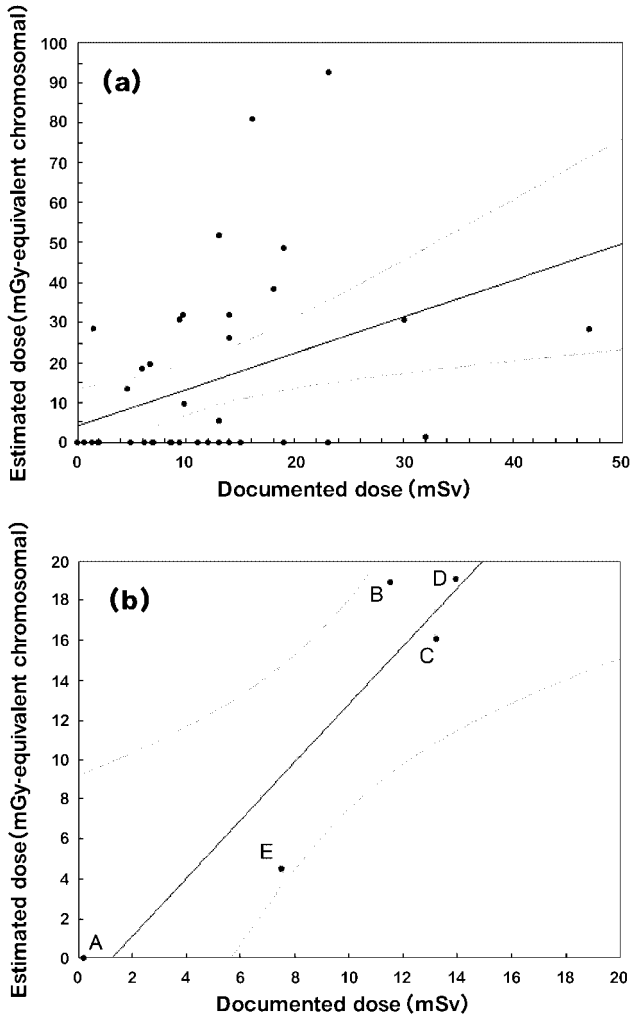

Fig. 3. Comparison between the chromosomally estimated doses and the documented doses. (**a**) comparison at individual level. (**b**) comparison at group average. For the group categories, see Materials and Methods and the first letter of subject numbers in Table 2. The curves represent regression curves and the 95% confidence limits.

tion was highly significant ($R = 0.932 \pm 0.210$, $p = 0.013$). In this case, the regression coefficient was 1.47 ± 0.33, indicating that the chromosomally estimated doses were approximately 1.5-times higher than the documented doses.

DISCUSSION

The JCO criticality accident provided a unique opportunity to evaluate the biological effects of neutron exposure to human populations. In this accident, except for three severely exposed workers, overexposure (5–48 mSv) has been identified in 80 persons[1]. The dose assessment in the overexposure to low-level radiations usually meets several difficulties, such as previous history of occupational and medical exposures, exposure-unrelated base level of aberration frequency with its modulation by health conditions, exposures to other environmental factors, including smoking, and the confidence level of the dose-response relationship in the low-dose range. In the compilation of data in the literature, the spontaneous frequency of dicentrics in peripheral blood lymphocytes of healthy adult controls has been estimated to be 7.8×10^{-4} per cell[16]. The age factors adopted in the present study as a base level corresponds to 8.8×10^{-4} dicentrics and rings per cell for a 30 year old person, which is comparable to that in the literature since ring chromosomes are a minor fraction in spontaneous aberrations constituting no more than 10% of the dicentrics+rings. Here, no data were available for the past radiation dose due to occupational and medical exposures. Therefore, it should be noted that the chromosomally estimated doses may also include such pre-accidental doses, although the contribution of small doses received 2 or more years before may be negligible, because the dose from diagnostic X-rays before 2 years has been reported to have no significant influence on lymphocyte chromosome aberrations[17]. Another uncertainty is the base-level aberration in persons with severely depressed lymphocyte counts. In a hematological examination of 1,838 local residents, 193 persons were diagnosed to have lower lymphocyte counts, of which 8 persons were diagnosed to have severely depressed lymphocyte counts. Seven of those 8 persons were included in the present study. Considering the calculated doses in their environment, it is highly likely that the lymphocyte insufficiency is not a consequence of radiation exposure, but is a constitutive feature. Such an ill-health condition may raise the base level of the aberration frequency. Indeed, the spontaneous chromosome aberration frequency in children suffering aplastic anemia of unknown etiology is significantly elevated (see Material and Methods). The disease-related aberrations may mislead the chromosome-based biological dose assessment. The lymphocyte counts are often used as an indicator of deterministic effects of radiation exposure. However, it is obvious that radiation exposure is not the sole reason for such hematological insufficiency. In this context, the base level of chromosome aberrations and its age dependency in such hematological insufficiency are critical for a chromosome-based dose assessment in a radiation accident, particularly for exposures involving the public.

When the base levels of the aberration frequency were adjusted by age and hematological condition, significantly elevated chromosome aberrations were observed in the peripheral blood lymphocytes in some persons and made amenable to a dose assessment. Despite an imprecision

inherent in the dose evaluation by physical as well as biological means, particularly for low-dose accidental exposure, the correlation between the documented doses and the chromosomally estimated doses is noteworthy. In a comparison of the two doses, chromosomally estimated doses tended to be higher than the documented doses. This may evoke the currently discussed problem of the quality factor, Q, and radiation weighting factor, w_R, of fission neutrons. From the data compiled on the LET-RBE relationship for charged particles, ICRP suggested in its publication 60 that the radiation weighting factor increased with an increase of the neutron energy, reaching a maximum of about 20 at around 500 keV, followed by a decrease with a further increase of energy[4]. In the *in vitro* experiments on the RBE of neutrons, there is no fundamental discrepancy between proposed and experimental values in the high-energy range over 2 MeV. However, in contrast to the ICRP prediction, experimental evidence has been accumulated indicating much higher Q or w_R values for lower energy, even under carefully designed experimental conditions simulating 10 mm depth in the ICRU sphere[7–10]. Moreover, there is experimental evidence suggesting that the quality factor, or RBE_{max}, is refractory to the energy in an energy range below 1 MeV[8]. A scarcity of experimental data on the energy-dependent biological effectiveness of neutrons considerably weakens the biological basis for setting the radiation protection standard and risk assessment for neutron exposure. The experience with the criticality accident emphasizes the importance of the experimental delineation of the energy-dependent biological effectiveness of neutrons.

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