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Scientific Paper

CHROMOSOME ABERRATIONS IN PERIPHERAL BLOOD LYMPHOCYTES OF CROATIAN HOSPITAL STAFF OCCUPATIONALLY EXPOSED TO LOW LEVELS OF IONISING RADIATION

Vilena KAŠUBA[1], Ružica ROZGAJ[1], and Anamarija JAZBEC[2]

Institute for Medical Research and Occupational Health[1], Faculty of Forestry, University of Zagreb[2], Zagreb, Croatia

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Medical staff is an occupational group exposed to different agents suspected to induce genetic damage. Among them ionising radiation is the most studied. Cytogenetic analysis of human chromosomes in peripheral lymphocytes allows direct detection of mutation in somatic cells. This study investigated the cytogenetic effects of low-level ionising x-radiation in 48-hour peripheral blood lymphocyte cultures sampled from 765 hospital staff occupationally exposed to several agents known or suspected to induce chromosome damage and compared them with 200 control subjects. The exposed subjects were divided in eight (8) groups according to their specialities and job titles. The exposed groups manifested an increase in all types of chromosome aberrations. Acentric fragments were the most frequent chromosome-type aberration. Dicentric chromosomes were statistically significant only in urologists/gynaecologists. Age and smoking significantly influenced the incidence of dicentrics in the exposed groups. The frequency of ring chromosomes was low in all exposed groups (range: 0-2), and none were found in the control group. These findings indicate the importance of periodic medical checkups of hospital staff occupationally exposed to low doses of ionising radiation. The purpose is to create an individual cytogenetic register, where changes could evidence individual risks.

KEY WORDS: *cytogenetic analysis, dicentric chromosomes, individual risk, medical workers*

Hospital staff are an occupational group exposed to different agents suspected to induce genetic damage, such as ionising radiation (x- and gamma-rays), radionuclides, cytostatic drugs, and anaesthetic gases, all of which have been investigated for their cytogenetic effects. Ionising radiation has been the most studied among them. The late effect of low doses can aid in the formation of very active free radicals that can produce chromosomal aberrations related to complex chromosomal rearrangements (1). Although the doses are reduced nowadays, exposure to ionising radiation still is a potential hazard for hospital workers. However, because of the accumulation of aberrations with exposure time, chromosome analysis is a valuable method for screening working populations at risk with a common occupational radiation history (2).

The scoring of specific unstable chromosome-type aberrations such as acentric fragments, dicentrics, and ring chromosome in peripheral blood lymphocytes of exposed workers was established in the early 1960s as a reliable method to detect and possibly measure previous exposures to ionising radiation in humans (3). An advantage of using asymmetrical chromosome aberrations in routine monitoring of radiation exposure is that they can be scored with conventional staining methods.

For subjects exposed to zero or low doses, cytogenetic studies can provide useful information for physicians (4). Radiation protection limits do not define safe or unsafe levels of radiation exposure. Exceeding a limit does not mean that one will get cancer. For radiation protection purposes, it is assumed that risks are related to the size of the radiation dose. Occupational radiation exposure is normally less than a few cGy per year. The International Commission on Radiological Protection (ICRP) has set the following limits on exposure to ionising radiation: the general public shall not be exposed to more than 1 mSv per year (over and above natural background); occupational exposure shall not exceed 20 mSv per year. These limits exclude exposure due to background and medical radiation. The limit for normal occupational exposure is 0.05 Sv a year (5).

Cytogenetic analysis was performed within systematic examinations that were obligatory every five years for persons working in an ionising radiation zone in Croatia. The current whole-body dose limit is 50 mSv per person occupationally exposed to radiation. All workers exposed to ionising radiation were regularly monitored with film dosimeters.

The purpose of this study was to provide an assessment of the genotoxic risk associated with exposure to ionising radiation in different medical professions. We used a large database (including years 1991-2005) of our laboratory in Zagreb that performed routine surveillance of the occurrence of cytogenetic damage in hospital workers exposed to ionising radiation. The size of this group allowed evaluation of the extent of cytogenetic damage in hospital staff.

SUBJECTS AND METHODS

Study population

A total of 765 medical workers of different job titles were examined for the incidence of chromosome aberrations. Two hundred healthy volunteers who had not been occupationally exposed to ionising radiation served as control. The subjects were divided in groups according to their job title at the time of blood collection, as follows: anaesthesiologists (n=80), anaesthetic technicians (n=45), radiology technicians (n=250), operating room nurses (n=100), surgeons (n=100), nurses (n=50), radiologists (n=100), and urologists/gynaecologists (n=40). All subjects were interviewed and completed a questionnaire including demographic data, smoking habit, exposure to ionising radiation and anti-neoplastic drugs, and intake of antibiotic drugs. They signed an informed consent form prior to their inclusion in the study. The study was approved by the ethics committee of the Institute for Medical Research and Occupational Health in Zagreb, Croatia.

The groups did not completely match in age. The control group consisted of younger people who underwent pre-employment screening. Matching was also not possible for sex. Nurses and operating room nurses were all women, and women prevail in the anaesthetic technician group. In contrast, surgeons and urologists/gynaecologists were mostly men.

Smoking habit is presented as smokers and non-smokers, and as a smoking index, which is defined as the average number of cigarettes smoked per day multiplied by the average duration of smoking in years (6). The portion of smokers in the control group was smaller than in the exposed group (Table 1).

Cytogenetic method

Venous blood samples were collected into heparinised tubes. All samples were coded and culture was generally initiated within 24 hours. A standard procedure for chromosome aberration analysis from whole blood was applied (7), and the slides were screened for unstable chromosomal aberrations, including dicentric and ring chromosomes, acentric fragments, and tri- and tetra-radial exchanges. From each person, 200 metaphases were scored.

Statistical analysis

The Poisson regression analysis was performed to evaluate independent association between the acentric fragments and dicentric chromosomes, and potential confounders, i.e., age, sex, smoking habit, and duration of exposure. Logarithm of the number of cells scored was used as an offset variable to adjust for the differences in these numbers. Models were weighted for the number of cells scored, and 95 % confidence interval (95 % CI) was always reported. This statistical analysis was performed using SAS 8.0 statistical package (8). The differences between groups were determined by the two-sided chi-square test with Yates's correction.

RESULTS

Population profiles are shown in Table 1. The study subjects were divided in eight exposed groups

(anaesthesiologist, anaesthetic technician, radiology technician, operating room nurse, surgeon, nurse, radiologist, and urologist/gynaecologist) and the control group. A total of 193,000 cells were analysed. Table 2 shows the mean frequencies of various types of chromosome aberrations in each group. The most frequent type of aberrations in exposed subjects was acentric fragment (5.33 ac per 1000 cells), followed by dicentric chromosome (0.87 dic per 1000 cells), tri- and tetra-radial exchanges (0.12 exch per 1000 cells), and ring chromosome (0.07 R per 1000 cells).

The frequency of dicentric chromosome (dic per cell), which is considered the most important aberration type indicating exposure to ionising radiation, were as follows: control subjects $0.50x10^{-3}$; anaesthesiologists $1.44x10^{-3}$; anaesthetic technicians $0.89x10^{-3}$; radiology technicians $0.74x10^{-3}$; operating room nurses $1.00x10^{-3}$; surgeons $1.15x10^{-3}$; nurses $1.10x10^{-3}$; radiologists $6.00x10^{-3}$, and urologists/gynaecologists $2.13x10^{-3}$.

All analysed types of aberrations except ring chromosomes were higher in the exposed groups than in controls. Ring chromosomes were not found in nurses, operating room nurses, and anaesthetic technicians.

In the Poisson regression analysis the magnitude of the association between variables was expressed in terms of parameter estimate, p value, relative risk ratio (RR), and 95 % confidence interval (95 % CI). Table 3 shows the results of Poisson regression analysis of acentric fragments and dicentric chromosomes by job title, age, sex, smoking habit (smokers and non-smokers, and smoking index), and years of exposure.

There was a significant increase in acentric fragments in all exposed groups (Table 3). Age as a confounding factor was also statistically significant for acentric fragments between the exposed groups and controls (RR 1.033).

For the dicentric chromosomes there was a statistical difference only between the urologists/gynaecologists and controls (RR 2.290). Age and smoking index were statistically significant between the exposed groups and controls for dicentric chromosomes (RR_{age} 1.056; $RR_{smoking\ index}$ 1.001) (Table 3).

With the exception of urologists/gynaecologists, chromatid exchanges (tri- and tetrardial exchanges) were significantly higher in all exposed groups than in

Table 1 *General characteristics of the study population concerning sex, age, exposure time, and diagnostic irradiation*

	Control (n=200)	Anaesthesiologist (n=80)	Anaesthetic technician (n=45)	Radiology technician (n=250)	Operating room nurse (n=100)	Surgeon (n=100)	Nurse (n=50)	Radiologist (n=100)	Urologist and gynaecologist (n=40)
Sex									
F	90	55	31	137	100	8	50	42	6
M	110	25	14	113	-	92	-	58	34
Age / year									
Mean (SD)	28.3 (7.19)	41.51 (8.39)	37.8 (7.91)	37.06 (10.94)	34.62 (9.01)	44.40 (9.28)	38.14 (8.56)	44.11 (9.36)	42.95 (8.90)
Range	19-57	27-62	22-55	21-63	20-59	27-65	22-56	27-63	27-61
Smoking habit									
Smoker	62	33	20	122	54	42	27	46	22
Non-smoker	138	47	25	128	46	58	23	54	18
Diagnostic X - ray examinations									
Yes	67	63	10	90	25	37	12	37	6
No	133	27	35	160	75	63	38	63	34
Exposure time / year									
Mean (SD)	-	12.176 (8.90)	15.82 (9.79)	12.288 (10.63)	12.115 (9.082)	15.218 (9.995)	12.105 (8.40)	12.77 (9.67)	12.925 (9.78)

controls (results not shown). RR was very high because there were very few chromatid exchanges (range 0-1 per person; 24 exchanges in the exposed groups, and no exchanges in controls; they were very rare).

Ring chromosomes were very rare in all subjects (range 0-2 per person) (Table 2) and Poisson regression analysis was not applied to these results.

Differences between the groups were determined using the two-sided chi-square test. Differences in acentric fragments between all the exposed groups and controls were highly significant (Table 3). Anaesthesiologists too significantly differed from operating theatre nurses ($p=0.0003$), radiology technicians ($p=0.0001$), radiologists ($p=0.0010$), surgeons ($p=0.0012$), and nurses ($p=0.0036$), and comparing to urologists/gynecologists they are considered to be statistically significant ($p=0.0214$). Differences in dicentric chromosomes between controls and anaesthesiologists and urologists/gynecologists were highly significant ($p=0.0006$ and $p=0.0001$, respectively). The differences were also high between radiology technicians and urologists/gynaecologists ($p=0.0004$) and radiologists and urologists/gynaecologists ($p=0.0007$). Surgeons significantly differed from controls ($p=0.0083$). Anaesthesiologists significantly differed from radiologists and radiology technicians ($p=0.0182$ and $p=0.0166$, respectively), and operating theatre nurses from urologists/gynaecologists and controls ($p=0.0311$ and $p=0.0387$, respectively). Ring chromosome was the least frequent aberration type, both in the exposed and control population (Table 2). However, the only significant difference was found between urologists/gynaecologists and controls ($p=0.0269$). Although minor inter-group differences were observed; for example, anaesthesiologists had higher incidence of ring chromosomes than anaesthetic technicians, operating room nurses and nurses (Table 2), this difference was not statistically significant.

Differences in chromosomal exchanges (tri- and tetra-radials) were highly significant between controls and nurses and operating theatre nurses ($p=0.0061$ and $p=0.0024$, respectively).

DISCUSSION

Implications of delayed cumulative effects of occupational exposure to low-dose X-rays seem very important, especially with respect to the growing use of ionising radiation in medicine. Occupational exposure to ionising radiation has decreased over the past decades as a result of improved equipment, more rigorous protection measures, and greater awareness of radiation hazards by workers. In spite of these facts, the exposed population has manifested an increased rate of chromosome aberrations (1, 9-13). We used this rate to evaluate the extent of chromosome damage in metaphase preparations of peripheral lymphocytes in hospital staff.

Although limited by the routine technique used, this case-control study still shows interesting results that might contribute to our knowledge on the risk associated with ionising radiation sources. The other value of this study is the great number of

Table 2 *Frequencies of chromosomal aberrations by profession*

Group	Number of subjects	Number of cells analysed	Number of acentric fragments per 1000 cells	Number of dicentric chromosomes per 1000 cells	Number of ring chromosomes per 1000 cells	Number of exchanges (tri- and tetra-radials) per 1000 cells
Anaesthesiologist	80	16000	9.06	1.44	0.25	0.25
Anaesthetic technician	45	9000	6.78	0.89	0	0.11
Radiology technician	250	50000	5.50	0.74	0.08	0.08
Operating room nurse	100	20000	5.75	1.00	0	0.30
Surgeon	100	20000	6.15	1.15	0.05	0.15
Nurse	50	10000	5.70	1.10	0	0.30
Radiologist	100	20000	6.0	0.60	0.05	0.05
Urologist and gynaecologist	40	8000	6.13	2.13	0.13	0.25
Control	200	40000	2.10	0.50	0.05	0

subjects involved (765 exposed hospital workers, and 200 controls). The total of 193,000 lymphocyte metaphases that were microscopically screened to determine the frequencies of chromosome aberrations make a valid sample for statistical evaluation.

The pattern of chromosomal damage recorded in peripheral blood lymphocytes of the exposed population was acentric fragments > dicentric chromosomes > exchanges (tri- and tetra-radials) > ring chromosomes. As expected, in the control population ring chromosomes were extremely rare, exchanges were not recorded at all, while other aberration types occurred with significantly lower frequency than in the exposed subjects. The control values of dicentric chromosomes in this study lie within the range of other published data ($0.49x10^{-3}$ per cell) (14) and our earlier studies ($0.26x10^{-3}$ per cell) (15).

The results of this study indicate that the frequency of dicentric chromosomes, as one of the most important indicators of radiation exposure, strongly correlated with profession, possibly due to specific modes of exposure and radiation doses absorbed. This observation was also sustained by the results of statistical evaluation. The order of dicentric chromosome frequencies by profession was as follows: radiologists < radiology technicians < anaesthetic technicians < operating room nurses < nurses < surgeons < anaesthesiologists < urologists/ gynaecologists.

Certain job-related exposures were definitely associated with increased incidence of particular aberration types. For example, urologists and gynaecologists had the highest rates of dicentric chromosomes. Anaesthesiologists, on the other hand, showed the highest RR for acentric fragments. In this group, high aberration rates, evidently were the outcome of combined occupational exposure to ionising radiation and genotoxic chemicals.

Other authors also report higher rates of chromosome aberrations in subjects occupationally exposed to low levels of ionising radiation. In their meta-analysis of cytogenetic studies performed in four Italian laboratories in the period 1965-1993, Bonassi et al. (11) reported significantly higher frequencies of chromosome aberrations for various job titles in medical workers exposed to low doses of ionising radiation. Garaj-Vrhovac et al. also reported higher rates of chromosome aberrations in workers exposed to ionising radiation but differences between various job titles were not significant (16).

Some studies showed that aberration frequency increased with age (17-22). No significant age-related differences were observed in the study of Bender et al. (23). A FISH study by Ramsey et al. showed an increase in dicentrics with age (24). Ballardin et al. (25) observed a slight increase in total chromosome aberration frequency with age. They also showed that mean chromosome aberration frequency in exposed technicians was significantly higher than in other profession groups. In our study, age is a significant confounding factor for acentric fragments (Table 3). An increase of 3.3 % for each year of age was observed for the frequency of acentrics (RR=1.033).

Literature reports on variations in smoking habits are conflicting. Health et al. (26), Lazutka et al. (27), and Ballardin et al. (25) did not find any influence of smoking on the aberration level. Chung et al. (14) did not find any significant association between age or cigarette smoking and any type of chromosomal aberrations. On the other hand, some studies indicate greater aberration frequency in smokers than in nonsmokers (12, 28, 29). Data from a study of Au et al. (30) suggest that the lymphocytes of smokers made more errors in DNA repair than the cells of non-smokers. Recent literature shows that the effect of smoking is more pronounced in men than in women (31). Rowland and Harding (32) reported that the cells of cigarette smokers might have DNA repair problems. The major problem is a delay in repairing damaged DNA with respect to the cells of non-smokers. Bender et al. (23, 33) suggested that background aberration frequencies should be determined separately for smokers and nonsmokers in all studies where smoking is a confounding variable. Maffei et al. (34) showed that smoking significantly increased micronucleus frequency in exposed workers, but not in controls. Galloway et al. (17) found cigarette smoking a potential confounding variable for the frequency of chromosome aberrations. We found a significant correlation between dicentric frequency and smoking index (RR=1.00080; Table 3) as a parameter used to express cumulative smoking exposure quantitatively.

Literature data have not demonstrated significant differences in aberration frequency between the sexes over a wide age range. Bonassi et al. (35) expressed the differences between the sexes in terms of relative risk (RR) in women versus men after adjustment for age, smoking habit, and occupational exposure.

Our results showed that chromosome aberrations such as dicentrics were present in relatively low percentages and chromatid interchanges and rings

Table 3 *Parameters, relative risks (RR), and their 95 % confidence intervals (95 % CI) estimated using the Poisson regression analysis* for chromosomal aberrations as dependent variable*

Variable	Parameter estimate	p	RR	95 % CI
ACENTRIC FRAGMENTS				
Job title				
Anaesthesiologist	1.1095	<0.0001	3.03284	2.26687-4.05763
Anaesthetic technician	0.9077	<0.0001	2.47862	1.73395-3.54309
Radiology technician	0.9623	<0.0001	1.99831	1.52867-2.61222
Operating room nurse	0.8347	<0.0001	2.30412	1.68102-3.15788
Surgeon	0.5918	0.0002	1.80724	1.32950-2.45665
Nurse	0.6874	0.0002	1.98854	1.38625-2.85280
Radiologist	0.5896	<0.0001	1.80498	1.33069-2.44391
Urologist and gynaecologist	0.6286	0.0009	1.87498	1.29330-2.71801
Age	0.0320	<0.0001	1.03252	1.01990-1.04519
Sex (M)	-0.0374	0.6291	0.96329	0.82754-1.12120
Nonsmokers	-0.0156	0.8566	0.98452	0.83127-1.16602
Smokers	-0.0764	0.6591	0.92645	0.65968-1.30096
Smoking index	0.0002	0.2537	1.00020	0.99990-1.00050
Years of exposure	-0.0037	0.5419	0.99631	0.98442-1.00833
DICENTRIC CHROMOSOMES				
Job title				
Anaesthesiologist	0.4746	0.1648	1.60737	0.82275-3.14024
Anaesthetic technician	0.2344	0.6076	1.26415	0.51680-3.09225
Radiology technician	0.0449	0.8877	1.04592	0.56108-1.94975
Operating room nurse	0.4911	0.1779	1.63411	0.79979-3.33910
Surgeon	0.1139	0.7484	1.12064	0.55884-2.24723
Nurse	0.3470	0.3944	1.41482	0.63667-3.14401
Radiologist	-0.4311	0.2763	0.64979	0.29906-1.41199
Urologist and gynaecologist	0.8302	0.0236	2.29378	1.11795-4.70629
Age	0.0542	<0.0001	1.05570	1.02798-1.08405
Sex (M)	-0.1900	0.3379	0.82696	0.56063-1.21969
Nonsmokers	-0.3626	0.0942	0.69586	0.45507-1.06407
Smokers	-0.6801	0.1427	0.50657	0.20403-1.25772
Smoking index	**0.0008**	**0.0133**	**1.00080**	**1.00020-**1.00140
Years of exposure	-0.0135	0.3126	0.98659	0.96098-1.01278

* *Relative risks for the exposed groups were estimated relative to the control group. Bold indicates statistically significant values at P<0.05*

were very rare in the exposed groups. This may be because DNA repair mechanisms act better at low radiation doses and over a long period of time (1). Everyone bears their own radiation burden, consisting mainly of external exposure in the general and occupational environment and diagnostic x-ray doses. Furthermore, any biological effect and repair capacity vary individually (36, 37). This includes variability in DNA repair mechanism and capacity, and inherited mutations (38).

Our data show the importance of performing periodic controls of occupationally exposed populations. It is also very important to use cytogenetic analysis in pre-employment screening for such occupational profiles.

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Sažetak

KROMOSOMSKE ABERACIJE U LIMFOCITIMA IZ PERIFERNE KRVI BOLNIČKOG OSOBLJA U REPUBLICI HRVATSKOJ IZLOŽENOG NISKIM RAZINAMA IONIZIRAJUĆEG ZRAČENJA

Medicinsko osoblje u svom je radu izloženo različitim potencijalno genotoksičnim agensima. Zbog široke primjene u medicini ionizirajuće zračenje je jedan od najistraživanijih fizikalnih agensa. Citogenetička analiza kromosoma iz limfocita periferne krvi omogućuje izravno određivanje oštećenja genoma izazvanog kroničnom izloženošću zračenju. Ova je studija uključila 765 ispitanika različitih medicinskih profesija izloženih pretežno ionizirajućem zračenju, ali uz to i nekim od potencijalno genotoksičnih kemijskih agensa, kao i 200 kontrolnih ispitanika. Izložena skupina ispitanika podijeljena je u osam podskupina prema profesiji. U izloženoj skupini uočen je porast svih tipova kromosomskih aberacija. Najčešći tip kromosomskih aberacija je acentrični fragment. U usporedbi s kontrolnom skupinom statistički značajna razlika za dicentrične kromosome uočena je jedino kod podskupine urologa/ginekologa. Životna dob i pušenje značajno su utjecali na pojavu dicentričnih kromosoma u izloženim skupinama. Učestalost prstenastih kromosoma bila je niska u svim izloženim skupinama (raspon: 0-2), dok u kontrolnoj skupini prstenasti kromosomi nisu nađeni. Rezultati upućuju na važnost periodičkih kontrolnih medicinskih pregleda u zdravstvenih radnika profesionalno izloženih genotoksičnim agensima. Svrha takvih pregleda je i stvaranje baze podataka u kojoj su pohranjeni svi citogenetički nalazi pojedinačnih izloženih ispitanika, koji su iznimno važni za pravilnu procjenu njihova individualnog rizika proizašlog iz profesionalne izloženosti.

KLJUČNE RIJEČI: *citogenetičke analize, dicentrični kromosom, individualni rizik, medicinsko osoblje, profesionalna izloženost*

CORRESPONDING AUTHOR:

Vilena Kašuba, Ph.D.
Mutagenesis Unit
Institute for Medical Research and Occupational Health
P.O. Box 291, HR-10001 Zagreb, Croatia
E-mail: *vkasuba@imi.hr*