Risk of Cancer in an Occupationally Exposed Cohort with Increased Level of Chromosomal Aberrations

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We used cytogenetic analysis to carry out a cohort study in which the major objective was to test the association between frequency of chromosomal aberrations and subsequent risk of cancer. In spite of the extensive use of the cytogenetic analysis of human peripheral blood lymphocytes in biomonitoring of exposure to various mutagens and carcinogens on an ecologic level, the long-term effects of an increased frequency of chromosomal aberrations in individuals are still uncertain. Few epidemiologic studies have addressed this issue, and a moderate risk of cancer in individuals with an elevated frequency of chromosomal aberrations has been observed. In the present study, we analyzed data on 8,962 cytogenetic tests and 3,973 subjects. We found a significant and strong association between the frequency of chromosomal aberrations and cancer incidence in a group of miners exposed to radon, where a 1% increase in frequency of chromosomal aberrations was followed by a 64% increase in risk of cancer ($p < 0.000$). In contrast, the collected data are inadequate for a critical evaluation of the association with exposure to other chemicals. *Key words*: cancer incidence, chemical mutagens, chromosome aberrations, radon, risk. *Environ Health Perspect* 109:41–45 (2001). [Online 12 December 2000]
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Cytogenetic analysis of peripheral blood lymphocytes (PBLs), a sensitive assay to detect exposures to mutagens and carcinogens in occupational settings, has been used in the Czech Republic since 1975. Its validity at an ecologic level has been confirmed by numerous biomonitoring studies (*1–10*). Cytogenetic analysis is a valuable tool widely applied in the field of occupational health in the Czech Republic. Since 1975, several thousand employees exposed to carcinogens, mostly in chemical industries, have been assayed, many of them repeatedly. This has made it possible to assemble a retrospective cohort large enough to carry out an epidemiologic study in which the major objective is to test for an association between the frequency of chromosomal aberrations (CAs) and a subsequent risk of cancer. In spite of the extensive use of the cytogenetic analysis in biomonitoring of exposure on an ecologic level, the long-term effects of an increased frequency of CAs in individuals are still uncertain.

Only a few epidemiologic studies have attempted to address the problem of the predictive value of the CA assay in PBLs. A modest increase in total cancer incidence rate [incidence ratio = 2.08; 95% confidence interval (CI), 1.26–3.40] was observed in individuals assigned to the high CA frequency category in the Nordic cohort (*11–14*). The results of the Italian cohort (*14–16*) suggest an association between the frequency of PBL CAs and cancer mortality rates. In that case, the mortality ratio for individuals with a high frequency of CAs in PBLs was estimated to be 2.56 (95% CI, 1.35–4.86) for total cancer, 4.2 (95% CI, 1.14–4.38) for lung cancer, and 4.36 (95% CI, 1.18–11.1) for cancers of lymphatic and hematopoietic tissues (*14–16*). Also, in a nested case–control study carried out in a blackfoot endemic area, Liou et al. (*17*) found a statistically significant association between chromosome type-aberrations and cancer. Kleinerman et al. (*18*) noted a correlation between the CA frequency in PBLs and cancer risk in women who received different therapeutic doses of ionizing radiation. Recently published outcomes of the case–control study nested within the Nordic and Italian cohorts confirmed previous outcomes; furthermore, Bonassi et al. (*19*) found that the association between the CA frequency and cancer did not appear to be modified by sex, age, or time since the CA assay.

Because better understanding of the nature of the relationship of CA frequency in PBLs to cancer risk is not only a scientific issue but also a matter of public health concern, we chose to discuss the results of ongoing epidemiologic research in the Czech Republic. Contrary to previously published studies, in the Czech cohort, we could treat the frequency of CAs as a continuous variable. Furthermore, in addition to the variables such as age at cytogenetic analysis, time since testing, and sex, we could control for the type of occupational exposure. Finally, as far as power considerations are of interest, the present study is based on the largest study population hitherto studied.

Methods

Study Population

The study base consists of individuals examined between May 1975 and October 1998 for the frequency of CAs in PBLs in four cytogenetic laboratories (the Cytogenetic Laboratory of the South Moravian Regional Institute of Hygiene, the Cytogenetic Laboratory of the North Bohemian Regional Institute of Hygiene, the Cytogenetic Laboratory of the Municipal Institute of Hygiene at Brno, and the Cytogenetic Laboratory of Institute of Hygiene of the Capital, Prague). The subjects were selected for cytogenetic analysis because of their exposures to various occupational mutagens and carcinogens.

Radon. The radon group consists of underground miners exposed to radon gas in one ore mine. Participants were examined for the CA frequency in PBL in May 1975–December 1990.

Radiation. The radiography ward group consists of staff of the X-ray and radiotherapeutic wards. Subjects were examined in February 1989–August 1998.

Cytostatic drugs. The cytostatic drug group consists of personnel exposed during cytostatic drug production and medical personnel who handled cytostatics. They were examined in October 1981–October 1998.

Bis(chloromethyl) ether. The bis(chloromethyl) ether (BCME) group includes workers exposed to BCME in one chemical plant. Subjects were examined November 1975–November 1987.

Coal gasification. The coal gasificication group is composed of workers who were exposed to by-products of hard pressure coal

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gasification in one gasworks. They were examined January 1980–May 1992.

Polyaromatic hydrocarbons. Members of the polyaromatic hydrocarbon (PAH) group were workers who had been exposed to different PAHs generated mostly by burning processes. They were examined April 1983–October 1990.

Nonexposed. The nonexposed matched referent group is made up of a small group of subjects who were examined January 1981–October 1998.

Other chemicals. The other chemicals group includes individuals exposed to miscellaneous chemicals or mixtures of chemicals for whom the numbers of participants were too small to create meaningful strata. These subjects were examined from July 1978 to October 1998.

We retrieved data on 4,288 individuals from laboratory records. Because of insufficient personal identification, 231 (5.39%) were excluded. Furthermore, we did not include 28 (0.65%) subjects with cancer onset before the date of cytogenetic analysis and 56 (1.31%) subjects with < 100 metaphases scored, leaving 3,973 (92.66%) subjects in the study. All subjects were at least 17 years of age at the date of cytogenetic analysis. Because many of the subjects included in the study were repeatedly examined for the frequency of CAs, altogether 8,962 cytogenetic tests were available for the epidemiologic analysis. Basic descriptive characteristics of the cohort are presented in Tables 1–3.

Cytogenetic Analysis

The cytogenetic analysis of human PBLs followed the same protocol in all participating cytogenetic laboratories. We used the conventional modified Hungerford method on short-term cultures for 52 hr, with all cells being in the first division. The peripheral blood was collected by venipuncture in heparinized tubes, and whole-blood cultures were established from the collected blood within 24 hr. Before culturing, we stored the tubes containing heparinized blood at 4–8°C. The cultures were set up in RPMI 1640 medium supplemented with 20% calf serum and 1% phytohemagglutinin. We added colchicin 2 hr before harvesting. The cells were collected by centrifugation, resuspended in a prewarmed hypotonic solution (0.075 M KCl) for 20 min, and fixed in acetic acid:methanol (1:3, v:v). The slides were prepared by air drying and stained with a 5% Giemsa solution (pH 6.8). Slides from each culture were randomly numbered and scored "blind" in numerical order. We examined at least 100 well-spread metaphases with 46 ± 1 centromeres per donor on coded slides (*10,20*).

The National Reference Laboratory of Genetic Toxicology of the National Institute of Public Health, Prague, coordinated the effort of all participating cytogenetic laboratories. The National Reference Laboratory has been responsible for the standardization (development of standard methods, supply media, and training of new personnel) and control (quality control of field laboratory workers by assessing the cytogenetic analysis results on coded slides, blood sampling and handling, and preparation of cell cultures, etc.). This method ensured the comparability of cytogenetic analysis results of all laboratories (*10*).

We evaluated the four categories of CAs: chromatid and chromosome breaks and chromatid and chromosome exchanges. Gaps were not scored as aberrations. Cells bearing breaks or exchanges were considered as aberrant cells. We treated the frequency of CAs enumerated as a percentage of aberrant lymphocytes as continuous variable. To account for possible differences in mechanisms of inducing CAs in relation to the type of exposure and for the sake of some statistical procedures as well as comparability of the results with previously published studies, the subjects were also categorized into the terciles and/or quartiles. Cutoff points are presented in Table 4 and may differ for specific occupational exposure subgroups as well as for the whole cohort.

For subjects who had been examined for CAs more than once, we used mean scores for all computations.

Cancer Incidence and Total Mortality

We obtained the information on the incidence of cancer and the specific mortality in the cohort up to 31 March 1999 (the end of the overall follow-up period) from the National Oncological Registry maintained by the Institute of Health Information and Statistics of the Czech Republic.

The critical point in the identification of the cancer cases in the Oncological Registry is the knowledge of a birth number, which is the unique personal identification in the

Table 1. Distribution of the chromosomal aberrations.

Exposure	No. of subjects	Percentiles of CA 10th	50th	90th
Radon	236	1.50	2.38	4.00
Radiography wards	73	1.00	2.00	5.00
BCME	244	1.23	2.66	4.67
Cytostatic drugs	1,297	0.67	2.00	4.00
Coal gasification	217	1.00	2.00	4.00
PAHs	365	1.00	2.00	5.00
Referents	336	0.00	2.00	4.00
Other chemical substances	1,205	0.00	2.00	5.00
Total	3,973	1.00	2.00	4.25

Table 2. Distribution of sex, cases, and deaths.

Exposure	No. of subjects	Percent of total	Percent male	Cases No.	Cases Percent	Deaths[a] No.	Deaths[a] Percent
Radon	236	5.9	97.0	33	14.0	27	11.4
Radiography wards	73	1.8	30.1	3	4.1	0	0.0
BCME	244	6.1	87.7	12	4.9	9	3.7
Cytostatic drugs	1,297	32.6	16.6	13	1.0	3	0.2
Coal gasification	217	5.5	87.6	16	7.4	10	4.6
PAHs	365	9.2	91.8	7	1.9	15	4.1
Referents	336	8.5	45.2	15	4.5	6	1.8
Other chemical substances	1,205	30.3	63.6	45	3.7	24	2.0
Total	3,973	100.0	53.4	144	3.6	94	2.4

[a]Deaths from causes other than cancer.

Table 3. Distribution of age at testing and the length of follow-up.

Exposure	No. of subjects	Age at testing (years) 10th	50th	90th	Follow-up (person-years) 10th	50th	90th	Total follow-up
Radon	236	29	38	54	9	17	22	3,792
Radiography wards	73	24	40	52	3	9	10	592
BCME	244	22	31	47	13	18	22	4,344
Cytostatic drugs	1,297	21	33	51	1	4	11	6,771
Coal gasification	217	27	39	52	8	13	17	2,948
PAHs	365	24	38	50	9	12	15	4,267
Referents	336	22	36	51	1	10	15	2,960
Other chemical substances	1,205	25	38	53	2	10	16	12,101
Total	3,973	22	36	52	1	9	17	37,775

Czech Republic. In cases of uncertainty, we checked the accuracy of the birth numbers in records maintained by employers and crosschecked the numbers in the Central Registry of Inhabitants of the Czech Police. The Central Registry of Inhabitants also confirmed the accuracy of mortality data.

Statistical Methods

We calculated the expected numbers of cancer cases, the standardized incidence ratios (SIRs), and the 95% confidence intervals for SIRs on basis of the distribution of age- and sex-specific rates within the cohort. We used the Kaplan-Meier survival analysis to describe the differences in total cancer incidence during the follow-up period and plotted Kaplan-Meier survival curves. We used Cox regression (*21*) to model the associations between cancer incidence, the CA frequency, age at first testing, and sex. For a dependent time variable, we used either *a*) the time from the first test until the diagnosis of malignant neoplasm or death for causes other than cancer or *b*) the end of the follow-up period. The stratification on the types of occupational exposure allowed for different shapes of baseline hazard function in each occupational exposure subgroup. Routine diagnostic tests did not detect any substantial violation of underlying assumptions of Cox regression.

Results

At time of the analyses, there were data on 3,973 subjects, who contributed with 37,775 person-years to the total follow-up time. All subjects were divided into eight occupational groups by type of occupational exposure. In the cohort, there were 144 cases of cancer, shown in Table 5; 94 subjects were censored because their deaths were not caused by cancer. Of the participants, 53.4% were male; however, the sex distribution was not proportional. Males were overrepresented in several occupational groups (exposure to radon and PAHs), but females represented a larger portion of the group exposed to cytostatic drugs. The age distribution at the time of cytogenetic analysis and at follow-up are presented in Table 3. In spite of the fact that the subjects' ages were similar when the follow-up began (overall median 36 years of age), the length of the follow-up was significantly different. For example, the medians of follow-up periods in the radon and BCME groups were 17 and 18 years, respectively; in contrast, the median follow-up period was only 4 years in the cytostatic drug group. The distribution of CA frequencies and cutoff points used to classify study subjects into the specific CA frequency groups are shown in Tables 1 and 4. The overall median CA frequency (2%) was found in the cohort (10th percentile = < 1.00%, 90th percentile = < 4.25%). Descriptive characteristics of the cohort are presented in Tables 1–3.

Differences in SIRs and in Kaplan-Meier survival analyses did not indicate an association between CA frequency and cancer incidence in pooled data. Although the SIR was elevated for high CA frequency (1.20; 95% CI, 0.94–1.52), the difference was not statistically significant ($p > 0.1$). We found no increase in the SIR (0.94; 95% CI, 0.67–1.28) in the medium CA frequency group. There were also no statistically significant trends in SIR ($p > 0.05$). This is consistent with the result of the Kaplan-Meier survival analysis shown in Figure 1. However, the more sophisticated Cox regression model, which accounted for the age at the time of the test, sex, and the type of occupational exposure, showed a statistically significant increase in the hazard ratio (HR) in the high CA frequency group (1.6; 95% CI, 1.01–2.37; Table 6).

Table 4. Categorization of subjects according to chromosomal aberration frequency (%).

	Tercile			Quartile			
Exposure	1st (low)	2nd (medium)	3rd (high)	1st (low)	2nd (lower intermediate)	3rd (upper intermediate)	4th (high)
Radon	< 2.00	2.00– < 2.88	≥ 2.88	< 1.87	1.87– < 2.38	2.38– < 3.00	≥ 3.00
Radiography wards	< 2.00	2.00– < 3.00	≥ 3.00	–	–	–	–
BCME	< 2.10	2.10– < 3.11	≥ 3.11	–	–	–	–
Cytostatic drugs	< 1.50	1.50– < 2.50	≥ 2.50	–	–	–	–
Coal gasification	< 1.78	1.78– < 2.57	≥ 2.57	–	–	–	–
PAHs	< 2.00	2.00– < 3.00	≥ 3.00	–	–	–	–
Referents	< 1.00	1.00– < 3.00	≥ 3.00	–	–	–	–
Other chemical substances	< 2.00	2.00– < 3.00	≥ 3.00	–	–	–	–
Chemicals	–	–	–	< 1.00	1.00– < 2.00	2.00– < 3.00	≥ 3.00
Total	< 1.89	1.89– < 2.99	≥ 3.00	–	–	–	–

Table 5. Classification of neoplasms according to *International Classification of Diseases, Revision 10* (ICD-10).

	Occupational exposure								
ICD-10 code	Radon	Radiography wards	BCME	Cytostatic drugs	Coal gasification	PAHs	Referents	Other chemicals	Total
00–14 Lip, oral cavity, and pharynx	1	–	–	1	–	2	1	–	5
15–26 Digestive organs	6	–	4	1	3	1	2	8	25
30–39 Respiratory and intrathoracic organs	18	–	1	–	5	1	3	7	35
40–43 Skin	3	1	2	2	3	1	3	11	26
45–49 Mesothelium and soft tissue	–	–	1	1	–	–	–	–	2
50 Breast	–	1	–	2	–	–	–	2	5
51–58 Female genital organs	–	–	–	4	1	1	3	4	13
60–63 Male genital organs	1	–	2	–	–	–	–	4	7
64–68 Urinary tract	2	1	2	1	3	1	1	3	14
69–72 Eye, brain, and other parts of CNS	1	–	–	–	–	–	1	1	3
73–75 Thyroid and other endocrine glands	–	–	–	–	–	–	–	2	2
76–80 Malignant neoplasms of ill-defined, secondary, and unspecified sites	–	–	–	–	1	–	–	–	1
91–96 Lymphoid, hematopoietic, and related tissue	1	–	–	1	–	–	1	3	6
Total	33	3	12	13	16	7	15	45	144

CNS, central nervous system.

The stratification of the data on occupational exposures brought more insight into the nature of the association between CA frequency and cancer incidence. We constructed Kaplan-Meier survival curves for each occupational group; there was an apparent association between CA frequency and total cancer incidence in the group of miners exposed to radon (Figure 2). In the other occupational groups, we found no similar pattern of an association between CA in PBL and cancer. Therefore, only the results of the Kaplan-Meier survival analysis of combined groups that included only subjects with a history of chemical exposure and referents is shown in Figure 3.

This finding was confirmed in models with several explanatory variables. Two Cox regression models of the association between CA frequency and total cancer incidence in the radon-exposed group are presented in Table 7. When we allocated the radon-exposed subjects into the CA frequency groups according to quartiles, there was a statistically significant excess in HR in the high CA frequency group (8.0; 95% CI, 2.42–26.13). Moreover, an increase in CA frequency was followed by an increase in the HR. If the model was simplified using a continuous term describing CA frequency instead of the dummy variables, the association between CA frequency and total cancer incidence remained statistically significant.

No statistically significant differences were detected in HR in the other occupational groups. Table 8 shows the results of Cox regression analysis performed on the combined group of subjects exposed to chemicals or chemical mixtures and referents. Attempts to detect an association between CA frequency and a specific group of cancers failed.

Discussion

Cytogenetic analysis has been successfully used in occupational medicine for decades. On many occasions, it has been shown to be an effective tool to identify occupational exposures to mutagens and carcinogens. Nevertheless, at a time when the PBL CAs and other cytogenetic end points were conceptualized as biomarkers of early effects in the process of carcinogenesis, there was no empirical evidence of an association between cancer incidence and CAs. Until recently, few epidemiologic studies addressed that issue. The present study was designed to test the validity of CAs as the biomarker of early effect and as a predictive value for a subsequent risk of cancer.

In the present study, there has been improvement over previous methods. First of all, in spite of the fact that the study includes subjects examined for CAs in four laboratories, the interlaboratory differences in the scoring of CAs have not been significant. The quality of performance of the cytogenetic laboratories was under the quality control program of the National Institute of Public Health in Prague since their establishment; this originally included a uniform laboratory protocol and classification and scorers' training. In the early 1980s, the quality control program gradually developed into a quality assurance/quality control system, which includes regular testing of reference samples (*10*). Second, the information on the occupational exposures of all subjects in the study was available. Finally, the study is based on the largest population examined systematically for CAs (3,973 subjects who underwent 8,962 cytogenetic analyses).

The data analysis revealed strong associations between CA frequency and total cancer incidence in the group of underground miners exposed to radon. The validity of this finding is supported by the fact that, in that particular case, all subjects were examined for CA frequency in the same laboratory by the same personnel; therefore, interlaboratory bias could not affect this result. Also, the potential for other bias, such as selection or information bias, is very limited. All eligible workers were included in the study, and cytogenetic assays had been performed repeatedly in all miners. (It is important to note that all subjects in this subgroup worked in the same ore mine.)

In contrast, we could not demonstrate any association between CAs and cancer in cases of other occupational exposures. If we exclude interlaboratory bias as an explanation for this finding, there are still other alternatives. The most probable explanation is that the most numerous subgroups in the study were relatively young and the length of follow-up has been too short to experience a sufficient number of cases. In contrast, in the occupational subgroups where the follow-up period is sufficiently long, there are few participants. Also, confounding bias could have masked the association. Heterogeneity caused by random factors is very likely to be substantial, decreasing the study power. In the Cox regression model, we have been able to account only for age at testing, sex, and the type of occupational exposure. Data on

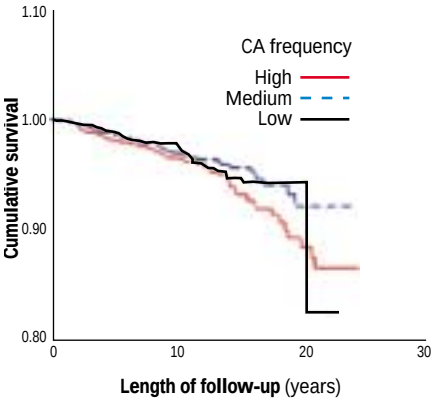

Figure 1. Kaplan-Meier survival analysis for the whole cohort ($p = 0.177$).

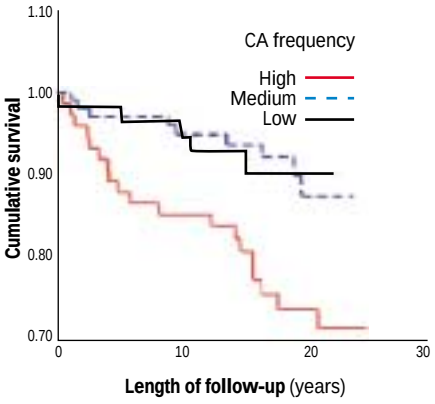

Figure 2. Kaplan-Meier survival analysis for the radon exposed group ($p = 0.011$).

Table 6. Cox regression analyses for the whole cohort.

Variable	HR	Significance	95% CI for HR	
			Lower	Upper
CA frequency		0.079		
Low	1.0	–	–	–
Medium	1.1	0.679	0.69	1.76
High	1.6	0.044	1.01	2.37
Age at testing (years)	1.1	0.000	1.07	1.10
Sex (1 for female)	0.8	0.321	0.50	1.25
Overall significance		0.000		

The model was adjusted for the type of occupational exposure.

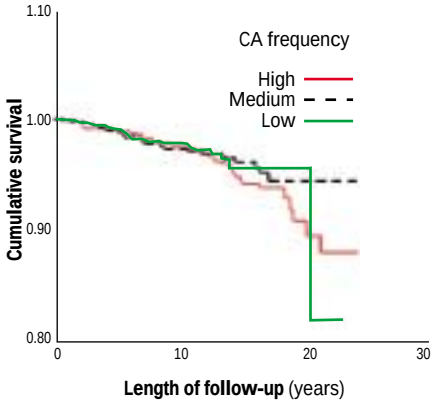

Figure 3. Kaplan-Meier survival analysis for the workers exposed to chemicals ($p = 0.60$).

Table 7. Cox regression analyses for radon-exposed miners.

Model	Variable	HR	Significance	95% CI for HR Lower	95% CI for HR Upper
Categorized CA frequency	Frequency of CA (%)		0.027		
	Low	1.0	–	–	–
	Lower intermediate	2.8	0.125	0.75	10.23
	Upper intermediate	3.0	0.090	0.84	10.95
	High	8.0	0.001	2.42	26.13
	Age at testing (years)	1.1	0.000	1.07	1.15
	Overall significance		0.000		
Continuous CA frequency	Frequency of CA (%)	1.64	0.000	1.38	1.94
	Age at testing (years)	1.10	0.000	1.07	1.14
	Overall significance		0.000		

Table 8. Cox regression analyses for individuals exposed to chemical substances and referents.

Model	Variable	HR	Significance	95% CI for HR Lower	95% CI for HR Upper
Categorized CA frequency	Frequency of CA (%)		0.852		
	Low	1.0	–	–	–
	Lower intermediate	1.0	0.992	0.53	1.92
	Upper intermediate	0.8	0.566	0.41	1.62
	High	1.0	0.905	0.53	2.04
	Age at testing (years)	1.1	0.000	1.06	1.10
	Sex (1 for female)	0.9	0.835	0.54	1.65
	Overall significance		0.000		
Continuous CA frequency					
	Frequency of CA (%)	0.96	0.602	0.84	1.11
	Age at testing (years)	1.08	0.000	1.06	1.10
	Sex (1 for female)	0.94	0.815	0.54	1.63
	Overall significance		0.000		

Models were adjusted for the type of occupational exposure.

other potential confounders or modifying factors, such as the length and intensity of occupational exposures, diet or smoking, was not available at the time of analyses.

The predictive value of a spot test on CAs is low. When we used predictor spot tests (the outcome of the first CA assay or the outcome of the highest CA assay observed in participant) in Cox regression models, the association between CA frequency and cancer incidence vanished even in the radon-exposed group. This is consistent with the early findings of high intraindividual variability in CA frequencies. Consequently, because the subgroups exposed to chemicals were not systematically examined and because the frequency of CAs per capita is much lower than in the radon-exposed group, it may be difficult to detect an association between CA frequency and cancer.

The frequency of CAs in PBLs is a surrogate measure of events, which may occur in other tissues. It is plausible to expect that changes in specific tissues are reflected in PBLs with a different intensity. Consequently, the association between CA frequency and specific cancers may be assumed to vary (*11,12*). However, we failed to demonstrate such specific association, probably because of the low number of different types of malignancies under scrutiny (Table 5).

In conclusion, the present study has been, to a certain degree, consistent with previous observations. Also, this study has shown evidence that supports the association between CA frequency in PBLs and cancer incidence. However, more subjects are needed before analyses and conclusions can be completed. The study should be able to provide more information on the relationship between CAs and cancer after a substantial increase in the number of individuals in the study and a somewhat longer follow-up time. Furthermore, we have made an effort to collect additional data on potentially modifying factors and confounders such as smoking and the length of occupational exposures. We are interested in testing the independence of predictivity of CAs on radiation dose and cigarette smoking in the group of miners exposed to radon.

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