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Chromosome Aberrations as a Biological Dose–Response Indicator of Radiation Exposure in Uranium Miners

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Cultured peripheral blood lymphocytes of controls and uranium miners were analyzed for the prevalence of structural chromosomal aberrations. The frequency data are compared between controls and five groups of miners with exposures expressed in working level months (WLM). The results demonstrate: (i) the prevalence of dicentrics + rings is not a good biological dose–response indicator; (ii) there is a marked decrease in the prevalence of deletions or dicentrics + rings + deletions in the most highly exposed individuals (Group V; >3000 WLM); (iii) apart from the Group V results, all aberration categories except dicentrics + rings demonstrate a significant and monotonic biological response increasing uniformly with estimated radiation dose through Group IV (1740–2890 WLM); (iv) including Group V individuals, the aberration category which shows the most consistent pattern of increase with dose is the pericentric inversions + translocations grouping (Spearman's $r_s = 0.943$; $P = 0.01$); (v) excepting dicentrics + rings, the prevalence of chromosome aberrations is a sensitive biological indicator of low-level uranium miner irradiation; (vi) significant ($P = 0.01$) differences in the prevalence of chromosome aberrations are observed between miners with regular to mildly atypical bronchial cell cytology and those with markedly atypical cells to carcinoma *in situ*. A marked increase in the prevalence of chromosome aberrations is probably a valid indicator of health risk in the miner groups. The relevance of the chromosome aberrations test for individual miners is more difficult to assess, but the absence of a high frequency of aberrations in an individual cannot be construed as a lack of risk. The application of radiation cytogenetic monitoring to other populations potentially exposed to high doses of radon daughters is discussed.

INTRODUCTION

Few occupational medical experiences have been as thoroughly studied and documented as the lung cancer problem in underground uranium miners.

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The epidemic of pulmonary cancer in uranium miners has not abated (*1*, *2*), notwithstanding the increasingly restricted permissible exposure to radiation in the ambient mine air. A recent epidemiological study of Czechoslovakian miners reports statistically significant increases in lung cancer risk at exposures approaching U.S. permissible limits (*2*). In addition, nonmalignant respiratory disease among white American uranium miners is approaching cancer in importance as a cause of death, probably as a result of diffuse parenchymal radiation damage (*3*). An increased prevalence of small-cell, undifferentiated carcinomas is observed with increasing uranium miner radiation exposure (*4*), and American miners are retrospectively and prospectively monitored cytopathologically by periodic examination of exfoliated bronchial cells (*5*). However, no biological response related to estimated radiation dose has been observed in nonpulmonary cells of uranium miners. Consideration of the high radiosensitivity of lymphocytes, and the transport of high-energy α-emitter nuclides (^{210}Pb and ^{210}Po) from lung to lymph nodes, liver, bone, and blood (*6*), prompted a small study of the prevalence of chromosome aberrations in peripheral blood lymphocytes of uranium miners (*7*). These results showed that the frequency of structural chromosomal aberrations was significantly greater in the uranium miners' cells than in the cells of control individuals, but the sample was insufficient to reveal intraminer differences that could be related to estimated mine air exposure. Other studies of lymphocyte chromosomes of humans exposed to ^{222}Rn or ^{220}Rn and their radioactive daughters demonstrated either no effect compared to control levels (*8*), increased prevalence of chromosome aberrations (*9*, *10*), or a dose dependence (*11*). The present paper reports on lymphocyte chromosome aberrations in an additional 100 uranium miners and controls, and demonstrates a dose response in aberration frequencies across exposure groups.

MATERIALS AND METHODS

Eighty underground uranium miners were studied from those among the outpatients at St. Mary's Hospital, Grand Junction, Colo., and from miners changing shifts at mine sites in the region. Twenty males from the Colorado Plateau, balanced with the miners for age and smoking habits, served as controls. All potential subjects were screened by questionnaire and excluded from the study if one or more of the following conditions was present: recent viral or bacterial infection, diagnostic radiation or severe sunburn, therapeutic radiation or drugs, exposure to toxic substances, familial congenital defects, or habitation in dwellings built over radioactive mill tailings. Procedures for cell procurement, cell culture, slide preparation, and analysis were identical for miners and controls excepting the transport of a portion of the heparinized blood samples from the mine sites to Grand Junction, a procedure that does not affect aberration yields (*7*, *12*).

Microcultures were initiated with 0.3 ml of whole blood in 5 ml of McCoy's 5a Medium containing phytohemagglutinin-*M* (Modified, GIBCO Chromosome Medium 167-SP, 15% fetal calf serum). Cells were cultured for 68 to 72 hr

at 36.0 to 36.5°C, the last 2 hr of culture with 0.2 μg/ml of Colcemid (CIBA). Cells were treated with 0.075 *M* KCl, fixed three times in fresh 3:1 absolute methanol:glacial acetic acid, affixed to cold wet slides, dried on a warming plate, and stained with buffered Giemsa blood stain. Trypsin G-banding and C-banding methods were applied to cells of individuals with suspected chromosomal mosaicisms or variants. The very sensitive sister chromatid exchange test for chemical mutagens is not indicated for the uranium miners because it is not as effective for measuring radiation effects as are chromosomal aberrations (*13*).

All chromosome analyses were done on coded slides without knowledge of radiation-exposure estimates. Approximately 100 cells were analyzed from each of the 100 subjects (9849 cells). Metaphase plates were screened at 125X for optimal dispersion and chromosome morphology. The entire chromosome complement for each cell was analyzed at 1260X (Zeiss optics) for heteroploidy, chromatid breaks and exchanges, and any of the following chromosomal aberrations: dicentrics, rings (centric and acentric), pericentric inversions, translocations, isochromatid breaks, and terminal and interstitial deletions (acentric fragments and doublet minutes). All cells with 45 or more centromeres were included in order to avoid the rejection of centric fusion translocations. All cells with suspected exchange aberrations were photographed and karyotypes were made to ensure accurate analysis. Numerical and chromatid aberrations were excluded from the final data but dicentric and ring chromosomes without accompanying deletions were included.

The data were decoded after cytogenetic analysis of all the 100 miners and controls was completed, and the subjects were assigned to radiation-exposure groups. Exposure estimates are based on mine air measurements and underground work time. One working level (WL) is defined as any combination of radon and radon daughters in 1 liter of mine air which will result in the emission of 1.3×10^5 MeV of α energy. One working level month (WLM) is 1 WL times 170 working hr. Alpha particles from short-lived ^{218}Po and ^{214}Po deliver the main radiation dose to the tracheobronchial epithelium (*14*). Excess long-lived ^{210}Pb in bone (*15*) and blood (*16*) is reported to be related to WLM estimates. The term "dose" used in this paper is an abbreviated expression for WLM exposure estimates. The exposure groups (I–V, Fig. 1) were selected to approximate epidemiological study groupings (*17*) and to obtain discrete exposure subsets in the population.

The chromosome aberration categories were selected with concern for comparison with other mammalian radiation cytogenetic studies and are arbitrarily arranged in the order of increasing prevalence of aberrations (Fig. 1).

Both parametric and nonparametric statistical methods were used in the analysis. Specifically, Spearman's rank correlation coefficient was used to both measure and test for dose response, since it is particularly sensitive to an alternate hypothesis of monotonicity (*18*) and not just to linearity. Furthermore, its use is conservative with these data in the sense that if the rank correlation is significantly different from zero, one can be fairly confident that an appropriate parametric procedure would also have been significant at a comparable or lower probability level.

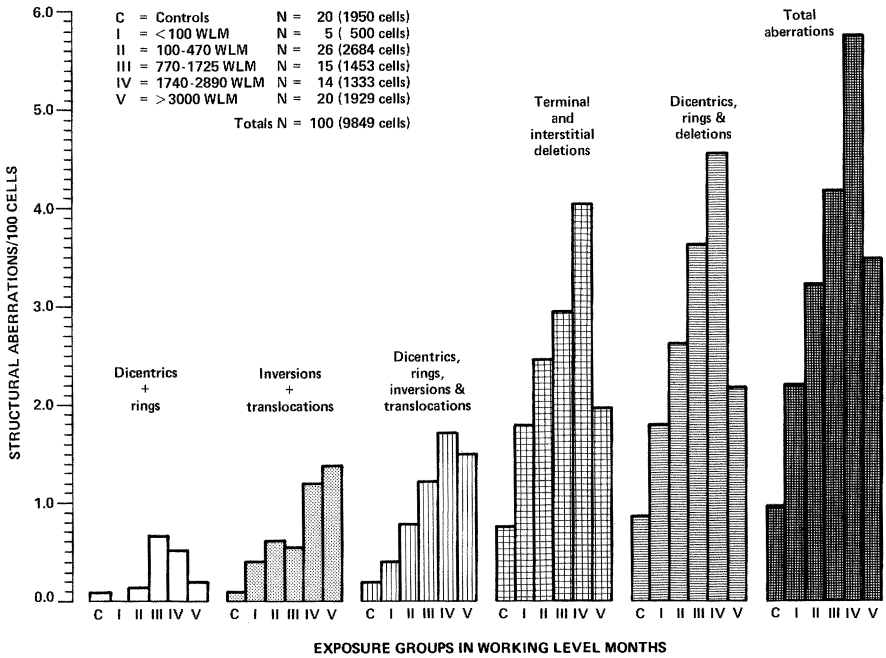

FIG. 1. Histograms of the mean prevalence of structural chromosomal aberrations in lymphocytes of controls and subset exposure groups of uranium miners.

Other statistical procedures that were used where necessary and appropriate were the Kolmogorov–Smirnov two-sample test, the χ^2 test for contingency tables, the normal approximation for the comparison of two binomial frequencies, and standard regression techniques.

Demographic, medical, and work-history data were obtained by questionnaire or from the uranium miner records at the NIOSH facility in Salt Lake City and include: estimated exposure, age, age started mining, years mined, years since mined, age at receipt of half-dose, year of receipt of half-dose, and smoking history. Some of our subjects (64 of 100) were also participants in an extensive sputum-cell cytology (SCC) study of uranium miners, and SCC classifications were provided by St. Mary's Hospital personnel. Selection of participants in the chromosome study was not based on SCC classifications and analyses were done without knowledge of the SCC status.

RESULTS

The demographic data on the 20 controls and 80 uranium miners revealed that the age distribution and smoking histories were comparable between all miners and all controls ($P > 0.3$) and that, although the ages tend to increase with increasing WLM, the average ages in the three highest WLM groups were not significantly different.

Sputum-cell cytology classifications were available for 64 of the miners.

TABLE I

Sputum Cell Cytology (SCC) Categories and Chromosome Aberrations

SCC Classes[a]	*Number of subjects*	*Range of WLM (average)*	*Number of cells*	*Number of complex aberrations (%)*[b]	*Number of all aberrations (%)*[c]
I, II_1, II_2	53	1–17,047 (1,931)	5,284	50 (0.95)	187 (3.54)
II_3, IV, V	11	135–5,700 (2,216)	1,046	18 (1.72)	55 (5.26)

[a] I = regular exfoliated cell cytology; II_1 = mildly atypical; II_2 = moderately atypical; II_3 = markedly atypical; III = suspicion of carcinoma; IV = positive carcinoma; V = carcinoma *in situ*.

[b] Complex aberrations = dicentrics, rings, inversions, or translocations.

[c] Complex aberrations plus deletions.

The proportion of lymphocytes with any chromosomal aberration as well as the proportion with two-hit aberrations was higher in those miners who were classed as having the more atypical cells than in those with normal or mild to moderately atypical cells (Table I). In both cases, the difference in chromosomal aberration frequencies is significant ($P < 0.02$), even though the radiation exposure is comparable for the two groups.

The cytogenetic dose–response data are summarized by the histograms in Fig. 1. The difference between miners and controls in the prevalence of dicentrics + rings (Fig. 1; $P > 0.2$) falls short of significance even though collectively there is a threefold increase in the number of these unstable aberrations in the miners' cells. The total number of cells affected with dicentrics + rings is small, 26, and except for the lowest-exposure group (<100 WLM; five subjects), the percentage among the miners is consistently higher than the corresponding control percentage. When either the proportion of miners with aberrant cells or the proportion of miners' cells containing aberrations is compared with similar proportions in the controls, all other aberration categories are significantly higher among the miners ($P < 0.001$).

The most curious aspect of our data is the decrease in the prevalence of aberrations in exposure Group V compared with frequencies in Groups III or IV in all aberration categories except inversions + translocations. The factors explored, both individually and in combination, to explain these results were age at the time of study, age at the beginning of mining, age at receipt of half-dose, calendar year of receipt of half-dose, rate of receipt of dose, and years since cessation of mining. Regression models which were explored to investigate these relationships produced negative results. The possibility exists that differential mortality has served to make our data a biased sample of this high-dose group, but we do not presently have access to records which would allow us to definitively answer this question.

For all aberration classifications other than dicentrics and rings (structural aberrations per 100 cells, Fig. 1), the increase in aberration frequency with estimated dose is monotonic up to an estimated dose of 3000 WLM. In each case, $r_s \geq 0.90$ and $P < 0.05$ for the data on controls and exposure groups I to IV.

TABLE II

Frequencies of Persons with a Given Number of Complex Aberrations[a] per 100 Cells Examined

Number of aberrations[c]	*Control*	*Exposure group*[b]				
		I	*II*	*III*	*IV*	*V*
0	17	3	12	5	4	6
1	2	2	8	6	5	6
2	1		5	2	1	3
3				2	1	3
4			1		2	2
5					1	
Total	20	5	26	15	14	20

[a] Complex aberrations = dicentrics + rings + inversions + translocations.

[b] See Fig. 1 for definitions.

[c] When the number of cells per person was not 100, the number of aberrations was rounded off to the nearest integer per 100 cells. This rounding off was required for eight individuals.

Table II shows the frequency distributions of the number of complex aberrations (dicentrics + rings + inversions + translocations) per 100 cells examined for individuals in each of the exposure groups studied. These distributions are typical of those seen in any of the aberration categories studied in the sense that the aberrations found are not generally confined to one or two individuals. In fact, within each exposure group the data are compatible with a binomial distribution (χ^2 goodness of fit test or Fisher's variance test for binomial frequencies). Therefore, given an estimate of the prevalence of a certain type of aberration for a given exposure category (from Fig. 1, for example), one can use that value to calculate the probability of finding various numbers of aberrant cells out of any number analyzed. With the low prevalence rates in these data, it is generally advisable to calculate individual binomial probabilities (or perhaps the probability of finding no aberrant cells or the probability of finding one or more aberrant cells per 100 screened) rather than to try to make inferences using normal approximation. No clones were observed in this population.

DISCUSSION

Retrospective bronchogenic cancer pathology (*4*), bone, blood, and hair bioassays (*16, 19*), sputum-cell cytology studies (*20*), and epidemiological follow-up of uranium miners (*17*) served to help establish radiation protection standards for this worker population. Our objective was to determine whether the prevalence of lymphocyte chromosome aberrations might provide a biological dose–response indicator of occupational exposure to irradiation or other clastogens in the miners' working environment. Our intent in this section is to review other radiation-cytogenetic studies of workers exposed to radon and thoron, factors which may have influenced our results, our specific find-

ings, and the possible application of radiation cytogenetics to other populations exposed to radon.

Other studies. There is limited value in the comparison of the biological effects of dissimilar α emitters because the results are influenced by the chemical and particulate form of the radionuclides, mode of entrance, energies and half-lives of decay products, and the biology and metabolism of different internal emitters. Two similar naturally occurring and technologically enhanced radionuclides, ^{222}Rn and ^{220}Rn, and their radioactive daughters are thought to cause the largest burdens from natural radioactivity to some tissues of man (*21*), and the cytogenetic effects of these radioactive gases have been studied.

Costa-Ribeiro *et al.* (*9*) studied the chromosomes of 58 controls and Brazilian millers of monazite sand exposed to ^{220}Rn in the work atmosphere. They concluded that the increased prevalence of dicentrics, rings, and translocations compared to control frequencies strongly suggests that the inhalation of the high-LET emitters is responsible for the chromosome aberration yield, even at levels of exposure below the maximum permissible for occupational exposure. Barcinski *et al.* (*10*) observed a significant positive correlation between the prevalence of dicentrics and rings and the place of residence among the inhabitants of Guarapari, Brazil, a town with residences on or near monazite sands containing 6.0% thorium. They concluded that the increased prevalence of two-exchange aberrations implies the persistence of internally deposited sources of high-LET radiation emitters, ^{220}Rn and ^{212}Pb.

Residents and workers in Badgastein, Austria, are exposed to high levels of atmospheric radon. A disused gold mine was converted to a thermal spa and workers in the "thermal gallery" were exposed to greatly elevated concentrations of radon and radon daughters (*22*). One hundred individuals living and working in the region were studied cytogenetically (30,000 cells), by Pohl-Rüling *et al.* (*11*). Mean estimated blood doses from inhaled radon and radon daughters varied from 0.007 to 12 rem/yr. Significant increases in the prevalence of acentric fragments + dicentric chromosomes occur between mean blood doses of 0.3 to 1 rem/yr. The authors conclude that the IAEA recommendation of 100 pCi/liter of air, 1 rem/yr blood dose, of worker radon exposure agrees very closely with their threshold for the appearance of increased chromosomal aberrations. Half-year α- plus γ-ray-dose accumulations and cytogenetic results from 122 subjects (30,590 cells) yielded a linear dose dependence in the prevalence of fragments, two-exchange aberrations, and multiple events from <100 to 200 mrad/0.5 yr, followed by a flattening of the curve out to 1300 mrad. They speculate that the shape of the curves could be the result of differential contributions by α radiation, which predominates at the lower doses, and by γ irradiation, the dominant contributor at higher doses. An alternative hypothesis is that those persons exposed to lower doses have received their irradiation continuously in the domestic and work environment, which results in a linear response, whereas those with higher radiation exposure receive the added radiation from fractionated occupational exposure for 2 to 4 hr a day. The fractionated dose would allow for more effective chromosomal repair mechanisms. Some confirmation of this hypothesis is the observation

that the highest aberration yield was recorded in four members of a single family with 200 to 300 mrad of continuous radiation exposure.

Kilibarda *et al.* (*8*) studied the chromosomes of 20 Yugoslavian uranium miners exposed to radon in the atmosphere of 3.7×10^{-10} to 2.61×10^{-9} Ci/liter of air, but no cytogenetic differences between miner and control cells were observed. In our earlier small U.S. study, Brandom *et al.* (*7*) observed a significant increase in the prevalence of chromosome changes in uranium miners' cells compared with control cells, but the populations and cell samples were insufficient to reveal intraminer differences that could be related to estimated physical dose.

Factors influencing our current results. Some of the factors which may have influenced our findings are discussed in reviews (*23–25*) and include culture conditions, age or seasonal effects, variations in individual response, number of cells analyzed, kinds of aberrations analyzed, and the accuracy of estimated physical doses in a mixed spectrum of radiations.

We knew from an earlier study (*26*) and report (*24*) that some of the uranium miners' cells would be in first, second, and even third divisions at 72 hr of culture. Mitotic yields are influenced by culture media, the mitogen used, temperature, and individual differences in response. As we have noted elsewhere (*7*), when we began the study we cultured the lymphocytes from 30 individuals at 50 and 72 hr, but the limited growth under the culture conditions then used enabled us to score only 327 cells from 8 miners at 50 hr. Chromosome aberrations were more prevalent from the 50-hr cultures (3.67 vs 2.97%), though the difference was not statistically significant ($P > 0.5$). Honda *et al.* (*27*) reported similar results in 17 atomic bomb survivors and 10 controls. Having used the 68- to 72-hr culture time early in the study, we continued this practice to keep the aberration yield data consistent throughout the project. A high proportion of the *in vivo* human radiation-cytogenetic studies done up to the time we began our study were done at 68 to 72 hr of culture time, and our results are more comparable to those studies(*28*). It has been estimated that aberration yields at 72 hr may be lower by as much as a factor of two (*24*). However, the highly significant increases in the prevalence of chromosome aberrations in subset exposure groups of miners compared to control levels suggest that the loss or derivation of aberrations may not be as strongly influenced by culture time as has been surmised from experiments and theoretical considerations.

Variation in individual response is reported for controls (*29*), in individuals exposed to whole-body γ irradiation (*30*), and in Thorotrast patients (*31*). Heterogeneity in response is to be expected because the populations for human *in vivo* studies are usually small and individuals differ in their relative sensitivity to mutagens because of age, sex, cell type, metabolism, and other factors. Our data are thus expressed by the mean prevalence of aberrations in each exposure group and not by individual response.

The accuracy of WLM dose estimates is discussed in our earlier paper on uranium miners (*7*) and in a monograph (*17*). Estimates made on the most highly exposed men in our study were made without benefit of mine air mea-

surements and are subject to the greatest error. Despite the pragmatic application of WLM estimates in other studies of the uranium miner populations, we recognize that there are limitations in the use of WLM estimates for individuals. The miners also receive external γ irradiation, the annual average absorbed dose estimated to be 1.6 rad (*32*). Since the life span of subpopulations of small lymphocytes is probably on the order of several months to several years, the external γ irradiation may, over time, contribute to the aberration yields. However, one of the major advantages of the biological-response method compared to physical dose for estimating the effects of absorbed dose is that knowledge of the relative biological effectiveness of the component radiations is not required (*24*).

We note a biological response related to estimated low-level, chronic radiation exposure in the miners' cells when all two-exchange aberrations plus deletions are scored. Therefore, it is prudent in this population to analyze thoroughly for all kinds of chromosome aberrations in 100 cells/subject, rather than to spend the equivalent time scoring for any dicentrics and rings in 300 to 500 cells/subject. Our results confirm the judgment of other researchers that reliance solely on the prevalence of asymmetrical aberrations in human *in vivo* studies may, in certain instances, result in an inadequate assessment of clastogen damage and that all aberrations should be analyzed (*33–35*).

Our uranium miner cytogenetic findings. In our uranium miner pilot study (*7*), we did not observe a consistent relationship between estimated radiation exposure and the frequency of chromosome aberrations. We speculated that a larger sample of men was necessary before cytogenetic changes might prove of value as a biological indicator of uranium miner radiation exposure. The cytogenetic data on the cells of 100 uranium miners and controls confirm our preliminary findings and, additionally, we observe a biological dose response in the prevalence of chromosome aberrations that is monotonic with estimated physical dose in all but the highest dose category. A summary of our findings follows.

(i) The marked decrease in the prevalence of asymmetrical aberrations in the most highly exposed group of uranium miners (>3000 WLM) was investigated for the factors specified under Results, but none of the quantifiable factors account for the drop in unstable aberrations in Group V compared to those in Groups III and IV. In the absence of quantifiable evidence to explain this phenomenon, there are several untestable possibilities. If the general health of miners in Group V, compared to the younger miners in Groups III and IV, was such as to promote greater immunological response, including T-cell divisions, cells containing asymmetrical aberrations may have been differentially lost in Group V individuals. Or, if there was a higher differential mortality among Group V miners, those remaining alive for sampling may have been inadvertently selected for resistance to the development of asymmetrical aberrations. But less speculative are the observations that the miners in Group V are a little older, started mining at an earlier date, and the bulk of their radiation exposure is further removed from the cell sampling date of the other miners, allowing for greater "decay" of cells containing asymmetrical aber-

rations. The miners in Group V received their half-dose by 1952. It was not until 1952–1953 that fair data were obtained on radon and radon progeny levels in most active mines (*17*), a source of greater error in the estimation of WLM for individuals in Group V than for those in Groups III and IV who received their mean half-dose in 1956 and 1955. The increased prevalance of symmetrical aberrations in Group V compared to Groups III and IV (Fig. 1) agrees with the estimate that the exposures of individuals in this group are greater than in other groups; but the earlier onset of exposure may have contributed to the decrease of dicentrics, rings, and deletions.

Trends similar to those observed in the uranium miner population are demonstrated in the extensive studies of atomic bomb survivors. Data on the survivors yield a decrease in the prevalence of dicentric + ring aberrations in cells of the most highly exposed group, as well as a dose–response relationship in the persistence of inversions + translocations in cells of the population as a whole (*36*). The A-bomb survivor population differs from the uranium miners in that the irradiation was acute, but the two populations have in common that late effects were studied.

(ii) Apart from the Group V results, the dicentrics + rings + deletions category frequencies show a consistent biological dose response from the control level through Group IV. Because of current mine standards, it is unlikely that many of the men mining currently will exceed the Group IV exposure levels, through which the dose–response relationship is monotonic.

(iii) The pericentric inversions + translocations aberration category, including the Group V individuals, shows the most consistent pattern of increase with dose. The increases do not appear to be linear with dose estimates, nor do we imply that they are, but they show a high degree of monotonicity with increasing dose (Spearman's $r_s = 0.943$; $P = 0.01$).

(iv) In all aberration categories, except dicentrics + rings, this test system is a sensitive indicator of early, low-level (<100 WLM) uranium miner irradiation.

(v) The significant ($P = 0.01$) differences in the prevalance of chromosome aberrations between miners with regular to mildly atypical bronchial cell cytology ($I–II_2$) and those with markedly atypical cells to carcinoma *in situ* ($II_3–V$) should not be construed as a cause-and-effect relationship, but this relationship should be examined in future data until a more specific hypothesis is advanced to explain it.

(vi) There is a strong correlation between WLM, SCC, and increased lung cancer in the uranium miners. The prevalence of chromosome aberrations is also highly correlated with WLM and, to a lesser degree, with SCC status. We do not imply that the lymphocyte chromosome aberrations cause lung cancer, but a marked increase in the prevalence of chromosome aberrations is probably a valid indicator of health risk in the miner *groups*. The chromosome aberrations test has only limited application to *individual* uranium miners. The overall frequency of aberrations is so small that the absence of aberrations in an individual should not be construed as evidence of lack of risk. (For example, with an aberration frequency of 1%, fully 37% of 100-cell samples

would be expected to show no aberrations. Even with a 2% aberration frequency, 13% of 100-cell samples would be expected to be negative.)

The results from the uranium miner cytogenetic study may be relevant for other populations exposed to radon daughters. Concern has been expressed, and measurements have been made, on levels of ^{222}Rn, radon daughters, or associated γ fields in other environments; in fluorspar, iron, and zinc mines (*17*), fossil-fuel energy production (*37*), underground caves (*22*, *38*), phosphate mining and processing (*39*), public and private dwellings (*40*), mill tailings (*41*), and homes built over mill tailings (*42*). Populations living or working in these environments are not strictly comparable to the uranium miners. However, based on the results of the uranium miner cytogenetic study, it may be prudent to consider the potential for risk in other populations and to anticipate protection measures wherever advisable, using physical and biological data.

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