Biomarker Monitoring of a Population Residing near Uranium Mining Activities

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We investigated whether residents residing near uranium mining operations (target population), who are potentially exposed to toxicants from mining waste, have increased genotoxic effects compared with people residing elsewhere (reference population). Population surveys were conducted, and 24 target and 24 reference residents were selected. The selected subjects and controls were matched on age and gender and they were nonsmokers. Blood samples were collected for laboratory studies. The standard cytogenetic assay was used to determine chromosome aberration frequencies, and the challenge assay was used to investigate DNA repair responses. We found that individuals who resided near uranium mining operations had a higher mean frequency of cells with chromosome aberrations and higher deletion frequency but lower dicentric frequency than the reference group, although the difference was not statistically significant. After cells were challenged by exposure to γ-rays, the target population had a significantly higher frequency of cells with chromosome aberrations and deletion frequency than the reference group. The latter observation is indicative of abnormal DNA repair response in the target population. Key words: chromosome aberrations, DNA repair, hazardous chemicals, population study, radiation. Environ Health Perspect 103:466-470 (1995)

Uranium has been mined in Texas (e.g., around Karnes County) since 1959. The process of refining the ore to produce high-grade uranium generates a large volume of hazardous residue, called tailings. This residue is often disposed of in open-air tailing piles. The tailing piles, however, contain most of the radionuclide species produced in the uranium decay chain as well as varying amounts of toxic chemicals present in the ore (e.g., heavy metals) or used in the extraction process (2). Through the tailings, radionuclides and toxic chemicals become more available for dispersal through hydrologic and atmospheric processes than in the original underground ore. An earlier investigation of the Karnes County Susquehanna mine reported radioactive contamination of soil and water in areas beyond the mining sites (2). The tailings also release radon gas into the environment. For example, a 1987 survey (3) reported that 9.54 × 10^2 Ci/year of radon gas was released from a tailings site near Pana Maria, Texas. Populations residing near tailings and mining activities may be exposed to a variety of hazardous materials which may cause them to have increased risk for health problems. We conducted a cross-sectional study of a population residing adjacent to uranium mining activities and a population residing in an area free of uranium mining operations, using biomarkers to measure differences in chromosome aberrations and in DNA repair response after their lymphocytes are challenged in vitro with γ-rays.

**Methods**

**Identification of mining sites and target residents.** Active mine/mill operations, unclaimed mine/mill sites, and sites that have been closed for less than 3 years in Karnes County, Texas, were identified, confirmed by site visits, and marked on a master map. As a result, 19 sites were selected. Households within 1.5 miles of each site were identified and marked on the same map. We identified 260 households. Residents who lived within 1 mile and downwind (in the northwest quadrant) from the uranium facilities or within 0.5 miles of the other three quadrants were defined as potentially exposed. Based on these criteria, 81 households were eligible for inclusion in this study phase.

We visited eligible households to document the residents and to inquire about their willingness to participate in our study. Volunteers were subsequently interviewed to document personal, occupational, and lifestyle information. A 37-page questionnaire was used; each interview took approximately 45 min. The interviewed participants were further selected based on our predetermined criteria.

**Location of reference area residents.** Reference (nonexposed) area residents lived south of the town of Kennedy, which is approximately 10 miles south of the mining area but within the same county. Background radioactivity in the reference areas was considered normal according to aeroradioactivity charts (U.S. Geological Survey of the Department of the Interior) provided by the Texas Department of Health. Radioactive contour lines, as indicated from the charts, ranged from 170 to 370 cps in the reference area. These background radiation levels in the reference areas were similar to those areas inhabited by our target population. From our survey of the reference area, 137 dwellings were located. Residents were interviewed using procedures described earlier.

**Selection of subjects.** Enrollment in this study was restricted to nonsmokers who had never worked in the uranium industry, had not been exposed to radiographic procedures to soft tissues such as brain and abdominal scans, and had not undergone radiotherapy or chemotherapy with potent cytotoxic drugs. Inclusion in the target group was restricted to individuals who had resided in the uranium mining target area for 10 or more years. Inclusion in the reference group was restricted to individuals who had never resided in any of the uranium mining areas that we were able to identify. We also eliminated heavy drinkers from both the target and reference populations (daily consumption of more than two shots of hard liquor or four cans of beer) and matched reference and target subjects on age (±7 years) and gender.

We selected 154 residents (73 targets and 81 references) for interview. Among the target subjects, 10 refused to participate and 30 were ineligible based on our selection criteria. This left 33 qualified target individuals for our laboratory study. Among the 81 reference individuals, 17 refused to participate and 25 were disqualified. This left 39 qualified residents for our study. Although blood samples were collected from all of the qualified participants, only 24 pairs met our matching criteria. Due to the limited number of residents in the target area, the matching age was set at ±7 years. However, 19 out of 24 pairs were matched at ±4 years.

**Radon monitoring.** Residential radon levels were measured by placing radon canisters in the homes of reference study subjects for 2–3 days during early spring of 1991. Exposed canisters were shipped to

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the Radon Testing Corporation of America (New York) for analysis. We did not monitor homes in the target areas because they have been monitored routinely by the Texas Department of Health.

Radon levels in the houses of both the target and reference subjects ranged from 0.1–2.1 pCi/L air. These levels are well below the EPA established action levels of 4 pCi/L. The levels did not differ between target and reference homes.

**Blood specimen and cytogenetic assay.** Six to eight matched individuals were asked to donate blood samples each week. The collected samples were coded and sent by air to the same day delivery to our laboratories in Galveston, Texas.

Lymphocyte-enriched cultures (from buffy coat) were set up according to the procedure of Au et al. (4). The culture medium was made up of RPMI (Roswell Park Memorial Institute) 1640 medium (Gibco) supplemented with 10% heat-inactivated fetal bovine serum, 10% autologous plasma, 2% phytohemagglutinin (Wellcome, reagent grade, 9 mg/mL), 1% glutamine (stock concentration 10,000 U and 10,000 µg/mL, respectively), and 1% sodium heparin (stock concentration 1000 USP/µL/mL). The cells from each donor and 25 mL of the culture medium were combined and mixed in a 50-mL sterile tube and then dispensed equally into five culture tubes. Three of the five tubes were uniradiated and used for the cytogenetic assay to determine the frequencies of chromosome aberrations. At 24 hr after initiation of cultures, one of the remaining two cultures was irradiated with 100 cGy of γ-rays, and the last one was irradiated with two doses of γ-rays (50 cGy per dose, separated by 1 hr). The latter two cultures were used for the challenge assay to detect abnormal DNA repair response. Bromodeoxyuridine was added to irradiated cultures immediately after irradiation and to unirradiated cultures at the same time to reach a final concentration of 5 µM. This chemical was used to label cells which have replicated DNA in culture. Only cells in the first metaphase after the beginning of culture were selected for chromosome analysis.

**Cell culture harvest and chromosome analyses.** Cell cultures were harvested according to our standardized procedures (4). Unirradiated cultures were harvested 48 hr after initiation of culture. The irradiated cultures were harvested at 51 hr. We added Colcemid (0.1 mL per tube; stock concentration 10 µg/mL) to each culture 1.5 hr before harvest to block cells at the metaphase stage of the cell cycle. Afterwards, cultures were centrifuged and culture medium was removed. Cells were treated with hypotonic solution and fixed

### Table 1. Chromosome aberrations and demographic factors in reference population*

| Individual no. | Dose (cGy) | No. of cells scored | % aberrant cells | % deletions | % dicentrics | Sex | Residency (years) |
|----------------|------------|---------------------|-----------------|-------------|--------------|-----|------------------|
| 1              | 0          | 600                 | 1.7             | 0.4         | 0.5          | F   | 18               |
| 2              | 0          | 600                 | 1.8             | 0.5         | 0.2          | F   | 12               |
| 3              | 0          | 600                 | 1.7             | 0.7         | 0.2          | F   | 28               |
| 4              | 0          | 600                 | 2.7             | 0.5         | 0            | F   | 28               |
| 5              | 0          | 600                 | 2.4             | 0.2         | 0            | F   | 13               |
| 6              | 0          | 600                 | 1.8             | 0.5         | 0.3          | F   | 14               |
| 7              | 0          | 600                 | 0.7             | 0.2         | 0.2          | F   | 12               |
| 8              | 0          | 600                 | 0.8             | 0.5         | 0.5          | F   | 15               |
| 9              | 0          | 600                 | 1.2             | 0.3         | 0            | F   | 15               |
| 10             | 0          | 600                 | 2.3             | 0.8         | 0            | F   | 15               |
| 11             | 0          | 600                 | 2.7             | 0           | 0.2          | F   | 14               |
| 12             | 0          | 600                 | 0.29            | 0.7         | 0.8          | F   | 14               |
| 13             | 0          | 600                 | 2.3             | 0.7         | 0.7          | F   | 13               |
| 14             | 0          | 600                 | 1.0             | 0.2         | 0.3          | F   | 31               |
| 15             | 0          | 600                 | 1.0             | 0.2         | 0.2          | F   | 40               |
| 16             | 0          | 600                 | 3.5             | 0.1         | 0.7          | F   | 28               |
| 17             | 0          | 600                 | 1.4             | 0.2         | 0            | F   | 17               |
| 18             | 0          | 600                 | 2.3             | 0.5         | 0            | F   | 40               |
| 19             | 0          | 600                 | 1.5             | 0.2         | 0            | F   | 20               |
| 20             | 0          | 600                 | 2.3             | 0.8         | 0.3          | F   | 19               |
| 21             | 0          | 600                 | 0.5             | 0           | 0            | F   | 12               |
| 22             | 0          | 600                 | 1.8             | 0.8         | 0.2          | M   | 26               |
| 23             | 0          | 600                 | 0.7             | 0.5         | 0            | M   | 16               |
| 24             | 0          | 600                 | 1.0             | 0.2         | 0.2          | M   | 14               |
| 25             | 0          | 600                 | 2.5             | 18.0        | 15.0         |     |                  |

*Dose = delivered dose of γ-rays from a cesium source, 50 + 50 is a split dose of 50 cGy each separated by 1 hr; % aberrant cells = % cells with any type of chromosome aberrations; % deletions = observed chromosome deletion events per 100 cells; % dicentrics = dicentric events per 100 cells. Mean age of population = 45.8 years; range, 23–71.*
**Table 2. Chromosome aberrations and demographic factors in target population**

| Individual no. | Dose (cGy) | No. of cells scored | % Aberrant cells | % Deletions | % Dicentrics | Sex | Residency (years) |
|----------------|------------|---------------------|------------------|-------------|--------------|-----|------------------|
| 1              | 0          | 600                 | 1.8              | 0.7         | 0            | F   | 19               |
| 1              | 100        | 200                 | 32.0             | 45.5        | 18.5         |     |                  |
| 2              | 50 + 50    | 200                 | 46.0             | 42.5        | 19.0         |     |                  |
| 2              | 0          | 600                 | 1.8              | 0           | 0            | F   | 26               |
| 3              | 100        | 200                 | 42.5             | 36.5        | 19.5         |     |                  |
| 4              | 50 + 50    | 200                 | 35.0             | 26.0        | 15.0         |     |                  |
| 3              | 0          | 600                 | 1.7              | 0           | 0            | F   | 21               |
| 4              | 100        | 200                 | 36.5             | 23.5        | 18.0         |     |                  |
| 5              | 50 + 50    | 200                 | 37.5             | 33.0        | 15.0         |     |                  |
| 4              | 0          | 600                 | 1.8              | 0.3         | 0            | F   | 11               |
| 6              | 100        | 200                 | 43.5             | 42.0        | 22.5         |     |                  |
| 7              | 50 + 50    | 200                 | 37.0             | 29.5        | 16.5         |     |                  |
| 5              | 0          | 600                 | 2.5              | 1.5         | 0            | F   | 23               |
| 8              | 100        | 200                 | 32.0             | 26.5        | 13.5         |     |                  |
| 9              | 50 + 50    | 200                 | 35.0             | 26.5        | 15.5         |     |                  |
| 10             | 0          | 600                 | 2.5              | 0.5         | 0.3          | F   | 34               |
| 11             | 100        | 200                 | 43.0             | 40.5        | 18.0         |     |                  |
| 12             | 50 + 50    | 200                 | 42.0             | 38.0        | 15.0         |     |                  |
| 13             | 0          | 600                 | 1.0              | 0.3         | 0.2          | F   | 34               |
| 14             | 100        | 200                 | 31.5             | 22.0        | 18.5         |     |                  |
| 15             | 50 + 50    | 200                 | 30.5             | 17.5        | 16.0         |     |                  |
| 16             | 0          | 600                 | 3.0              | 0.5         | 0.5          | F   | 14               |
| 17             | 100        | 200                 | 34.0             | 22.0        | 18.5         |     |                  |
| 18             | 50 + 50    | 200                 | 31.5             | 18.5        | 19.5         |     |                  |
| 19             | 0          | 600                 | 3.6              | 1.5         | 0.3          | F   | 48               |
| 20             | 100        | 200                 | 45.0             | 43.0        | 19.5         |     |                  |
| 21             | 50 + 50    | 200                 | 41.5             | 42.0        | 15.5         |     |                  |
| 22             | 0          | 600                 | 1.7              | 0.5         | 0            | F   | 44               |
| 23             | 100        | 200                 | 43.5             | 32.0        | 18.5         |     |                  |
| 24             | 50 + 50    | 200                 | 37.5             | 22.0        | 15.5         |     |                  |

*Dose = delivered dose of γ-rays from a cesium source, 50 + 50 is a split dose of 50 cGy by each separated by 1 hr; % aberrant cells = % cells with any type of chromosome aberrations; % deletions = observed chromosome deletion events per 100 cells; % dicentrics = dicentric events per 100 cells. Mean age of population = 46.7 years, range, 19–71.*

with Carnoy’s fixative. Cytological preparations were air-dried and stained. The stained slides were coded and divided among at least two technicians for analyses. For slides from unirradiated cultures, each technician scored 300 cells. For each of the irradiated cultures, 100 cells were analyzed by each of the two technicians. Unusual and questionable cells were reviewed before decisions were made. The data from the two scorers were added together and used for statistical analysis.

**Experimental design and statistical analysis.** Concerning the sensitivities of the study, when assuming that the dicentric frequency (from unchallenged cells) in the reference population is 0.15%, fixing the type 1 error at 0.05 and using a one-sided critical region, the study (with analysis of two metaphase cells per donor) would have had an 80% probability of detecting a target group mean frequency of 25% or larger when sample sizes of over 20 and 20 were used (5.6).

We analyzed the cytogenetic data using both parametric and nonparametric analysis of variance methods and the paired t-test to compare statistically the average chromosome aberration frequency in the target and reference groups of residents. The nonparametric method used was the Kruskal-Wallis comparison of average ranked frequencies (7). When the parametric and nonparametric significance levels differed, we used the Kruskal-Wallis test results because of the indication that requirements for the parametric analyses were not met. Usually, the violated requirements concerned different magnitudes of variability (SD) in the two groups being compared.

**Results**

Although participants who were exposed to therapeutic or excessive diagnostic radiation were disqualified, the accepted participants had diagnostic radiation to chest, hand, ankle, back, etc. The frequencies of the diagnostic radiation during the last 10 years are similar for the target and the reference groups. Only 7 out of 24 people from the target group and 8 out of 24 people from the reference group were exposed to diagnostic radiation during the last 10 years.

The collected demographic information relevant to the cytogenetic data is presented in Tables 1 and 2. The female-to-male ratios for study subjects in both the target and reference groups are identical (7:1). The reason for this high ratio is that many male residents were disqualified because of work-related exposure to uranium or other hazardous chemicals. In addition, more males than females refused to participate in the study.
The mean age of the target and reference groups were 46.7 and 45.8 years, respectively. The age ranges for the two groups were 19–71 and 23–71, respectively. The mean age and the range of ages for both populations are similar.

Our criteria required that the target residents live in the uranium belt continuously for more than 10 years and that the reference residents did not live near any uranium-mining areas during the last 10 years. The mean and range of residency data as shown in Tables 1 and 2 are consistent with our criteria. Statistical analysis of the demographic data indicates that the average and distribution of age, gender, and duration of residence are similar for the two groups.

Tables 1 and 2 show the cytogenetic data for each subject from the target and reference populations. The measured chromosome abnormalities are classified into three categories: percentage of aberrant cells, which represents the frequency of cells having any type of chromosome aberrations; deletions/100 cells, which contains the rate of chromosome-type deletions (excessive acentric fragments); and dicentrics/100 cells, which contains the rate of dicentric chromosomes.

A summary of the cytogenetic data is shown in Table 3. As shown in the table, target residents have a higher spontaneous frequency of abnormal cells and cells with chromosome deletions than reference residents (2.15 and 0.67 versus 1.75 and 0.40, respectively). The spontaneous dicentric frequencies from both groups are very low, and the target group has a lower frequency (0.13 and 0.23, respectively). None of the spontaneous frequencies between the target and the reference groups are significantly different from each other. With the challenge assay, the frequencies of aberrant cells, deletions, and dicentrics in lymphocytes from the target residents are consistently higher than those from the controls (e.g., for 100 cGy dose: 38.22, 27.80, and 18.13 versus 35.96, 26.71, and 17.31, respectively). The difference for the first two categories are significantly different from each other, whereas there is no difference in the last category.

Analyses of the cytogenetic data were conducted using both parametric and nonparametric analysis of variance methods for independent samples to compare statistically the average abnormality frequencies in the target and reference groups of residents. The results from both analyses were consistent with each other. For spontaneous chromosome aberrations, there were no significantly increased frequencies of aberrant cells, dicentrics, and deletions. For cells challenged with 100 cGy γ-rays, the significance of difference for percentage of aberrant cells, deletion per 100 cells, and dicentrics per 100 cells between the target and the reference groups are p = 0.002, 0.008, and 0.440, respectively. The p-values for the same analyses for cells irradiated with 50 + 50 cGy are 0.015, 0.033, and 0.522, respectively. The cytogenetic data were further evaluated by paired analyses. For the paired analyses, each target resident was paired with the reference counterpart. The data were evaluated using paired t-tests. A summary of the evaluation is shown in Table 3. The data show that the target group has a higher mean frequency of total aberrations and deletions but lower mean frequency of dicentrics than the reference group. The differences were not significant (p = 0.12, 0.07, and 0.06, respectively). The data from the challenge assay show that the study group had more problems in the repair of DNA damage which produced more total aberrations and deletions than the reference group (p-values range from 0.032 to 0.0004).

Discussion

Few studies have been conducted using biomarkers to monitor populations (residents) exposed to toxicants from disposal sites. Heath et al. (8) reported a lack of increased chromosome aberrations in persons living near Love Canal. Perera et al. (9) and Lakanisny et al. (10) reported increased sister chromatid exchanges in persons exposed to chemicals. To our knowledge, we are the first to report biomonitoring of a population who may have been exposed to toxicants such as radioactive particulates, radon, and heavy metals from uranium mining operations. Exposure to elevated levels of residential radon has been reported to be associated with an increase of gene mutation in peripheral lymphocytes of residents (11).

Exposure to environmental toxicants can cause DNA damage, leading to DNA repair problems. For example, lymphocytes from leukemia patients had reduced O6-alkylguanine-DNA-alkyltransferase activities after receiving methylation agents for therapy (12). Occupational exposure to toxicants caused hospital workers and tire-storage workers to be defective in the same repair enzyme (13). Lymphocytes from smokers and drug addicts have altered unscheduled DNA synthesis after in vitro challenge with UV-light or 2-acetylaminofluorene (14–16). In a series of cytogenetic challenge studies like ours, Hsu et al. (17) and Bondy et al. (18) used bleomycin, and Knight et al. (19) used X-rays in their challenge assay to detect abnormal cytogenetic response. They concluded from their studies that individuals with the abnormal response are defective in DNA repair and have an associated increased risk for cancer. We have found that cigarette smokers and butadiene workers have abnormal DNA repair responses as shown by our challenge assay (4, 20, 21). In addition, the latter study revealed a significant correlation between abnormal repair and exposure to butadiene as shown by urine metabolite analysis, suggesting a cause–effect relationship (21). Exposure to environmental toxicants can cause DNA repair problems, and our cytogenetic challenge assay can be used to identify exposure-related abnormal DNA repair response.

The results from our study, as shown in Tables 1–3, show that the target residents who reside nearby uranium mining activities have higher baseline frequencies of aberrant cells and chromosome-type deletions but lower dicentric frequency than the reference residents. These differences border on being statistically significant. Results from our challenge assay show that target residents have significantly higher frequencies of aberrant cells and chromosome deletions, indicating abnormal DNA repair response.

The data from both assays reinforce each other because increased abnormalities are often observed in the target group compared with the reference group. Our study indicates that the residents who live around uranium mining activities have exposure to hazardous agents. However, the exposure is below the level needed to
cause a significant increase in chromosome aberrations as shown by our standard cytogenetic assay. Based on the sensitivity of the standard assay, the exposure level needed is of the order of maximum permissible occupational doses (22). The exposure for the target population is, however, high enough to cause abnormal DNA repair response. Although the mechanism for induction of such response is not known, we suggest that the abnormality may be caused by mutation of genes which code for DNA repair enzymes or by blockage of repair processes on DNA (e.g., adducts) (20). These possibilities need to be investigated further using molecular assays.

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