Final Performance Report

(SERCA) Respiratory Carcinogenesis in Uranium Miners
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List of Abbreviations

1) DNA-Dependent Protein Kinase (DNA-PK)

2) New Mexico Tumor Registry (NMTR)

3) Surveillance Epidemiology and End Results (SEER)

4) Uranium Epidemiologic Study (UES)

5) Navajo Lung Cancer Study (NLCS)

6) Standardized Mortality Ratio (SMR)

7) National Death Index (NDI)

8) Motor Vehicle Division (MVD)

9) Social Security Administration (SSA)

10) Health Care Financing Administration (HCFA)

11) Institutional Review Board (IRB)

12) National Cancer Institute (NCI)

13) Uranium Miners Health Study (UMHS)

14) National Institute for Occupational Safety and Health (NIOSH)

15) Immunohistochemistry (IHC)

16) Working Level Month (WLM)

17) University of New Mexico (UNM)

18) The Lovelace Respiratory Research Institute (ITRI)

19) National Health and Nutrition Examination Survey (NHANES)

20) Specialized Program of Research Excellence (SPORE)

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Significant Findings

Uranium Mining and Lung Cancer among Navajo Men in New Mexico and Arizona, 1969-1993 (see manuscript in appendix) Uranium mining was a common occupation of Navajo men from the 1950s until the industry closed in the early 1960s. We found that over the entire 25-year period following the end of mining on the Navajo Nation, 63 (67%) of the 94 incident lung cancers among the Navajo men occurred in former uranium miners. The estimated relative risk for a history of mining compared with no history of mining was 28.6 (95% CI 13.2,61.7) and the attributable risk for uranium mining exceeded 96%. The average number of cases increased with time since exposure, from 1.9 per year during 1969-1983 to 3.4 per year in 1984-1993, with a shift in histology from excess small cell tumors to those observed in the general population. The study shows uranium mining among Navajos to be a unique example of exposures in a single occupation accounting for the majority of lung cancers in a population.

Non-malignant respiratory diseases and lung cancer risk in miners We studied the relationship of non-malignant respiratory disease and spirometric abnormalities in a cohort of former uranium miners. We found that early pneumoconioses and reduced pulmonary function were associated with an increased risk of lung cancer. Our finding indicates that clinical measures of non-malignant respiratory disease predict lung cancer risk which may be useful in identifying high-risk groups for lung cancer screening and prevention trials.

Lung cancer in uranium miners from New Mexico We conducted a cohort study of former uranium miners to assess the temporal trends in lung cancer risk following the end of exposure when the industry closed. We found that although the relative risk of lung cancer declined with time since exposure, the risk remained substantially elevated for more than 15 years after exposure.

DNA capacity in uranium miners Reduced DNA repair capacity of carcinogen-induced DNA damage is now thought to significantly influence inherent susceptibility to lung cancer. DNA-Dependent Protein Kinase (DNA-PK) is a serine-threonine kinase activated by the presence of double-strand breaks in DNA that appears to play a major role in nonhomologous recombination and transcription control. We investigated whether interindividual variation exists for DNA-PK activity in uranium miners and what impact this has on lung cancer risk. We found large interindividual variation in DNA-PK activity among miners and lower activity in patients with lung cancer than in controls. Miners with low DNA-PK activity may represent a radiosensitive subgroup. The results of this study demonstrate for the first time that reduced DNA-PK activity is associated with an increased risk for lung cancer

Usefulness of Findings

Our findings may be useful in three arenas: 1) lung cancer screening of high risk groups, 2) lung cancer prevention, and 3) risk assessment and compensation of former uranium miners.

We showed that the impact of uranium mining among Navajos is a unique example of exposures in a single occupation accounting for the majority of lung cancers in a population. These finding may be useful for the ongoing consideration of compensation issues for former miners and to focus prevention activities among former miners who are at very high risk for lung cancer.

We found that former uranium miners from the Grants, New Mexico Mineral Belt continue to be at high risk for lung cancer for more than a decade after the end of uranium mining activities.

Former miners represent a high-risk group for lung cancer, requiring ongoing screening and follow-up activities.

Our finding that clinical measures of non-malignant respiratory disease predict lung cancer risk may be useful in identifying high-risk groups for lung cancer screening and prevention trials.

Reduced DNA repair capacity of carcinogen-induced DNA damage may influence inherent susceptibility to lung cancer. We found large interindividual variation in DNA-PK activity among miners and lower activity in patients with lung cancer than controls. The results of this study demonstrate for the first time that reduced DNA-PK activity is associated with an increased risk for lung cancer. These results may be useful for screening and prevention research among miners with low DNA-PK activity who may represent a radiosensitive subgroup.

We successful demonstrated the feasibility of lead 210 methods for additional studies on larger numbers of former miners to support studies of lung cancer risk and to more comprehensively evaluate the estimation of cumulative lung dose to Rn progeny. Ultimately, these studies will allow evaluation of the usefulness of skull burdens of Pb as an alternative metric of Rn progeny exposure in future epidemiological studies of lung cancer in U.S. miners and millers. Furthermore, the data will allow evaluation of the potential utility of the method to examine hypotheses of environmental exposure to Rn from mill tailings or Rn in residences.

ABSTRACT

This final report documents an integrated program of an investigation of lung cancer based on the research opportunity afforded by former uranium miners in New Mexico and Colorado. The program included an investigation of the quantitative risks of lung cancer in relation to exposure to radon progeny, of the determinants of susceptibility, and of molecular and cellular markers of carcinogenesis.

Uranium miners have been shown to be at a markedly increased excess risk of lung cancer resulting from exposure to radon progeny and smoking. The states of New Mexico, Colorado, Arizona, and Utah have large numbers of former miners who are now at high risk for lung cancer because of these exposures. We have investigated the risks of lung cancer in a cohort of 3,500 New Mexico uranium miners and in Navajo uranium miners. We conducted a research program that extends these studies using a molecular epidemiology model. The program drew on the epidemiological resources of the New Mexico Tumor Registry, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, and the Cancer Research and Treatment Center at the University of New Mexico as well as molecular and cellular biology resources at the Lovelace Inhalation Toxicology Research Institute. Dr. Frank Gilliland continues as a principal investigator and collaborator in an interdisciplinary research team that is implementing an expanding program on the molecular epidemiology of lung cancer in uranium miners and other high risk groups.

Body of Report with Conclusions

SPECIFIC AIMS

We proposed the following specific activities:

1. Use information the New Mexico Tumor Registry's database spanning the 25-year period 1969-1993
    a. Extend the study of the lung cancer epidemic among Navajo and other American Indian uranium miners, and

b. Describe the distribution of lung cancer histologic types in Navajo uranium miners;

2. Use an existing cohort of 3,500 uranium miners employed in the Grants, New Mexico mining district, The Uranium Epidemiologic Study (UES)
   a. Determine temporal trends of lung cancer risk in relation to radon progeny exposure and smoking, and
   b. Describe the histologic distribution of lung cancers as a function of radon progeny exposure and smoking;
3. Use a newly developed cohort of high-risk uranium miners (Uranium Miners Health Study)
   a. Determine the prevalence of enrollment of cellular and molecular changes in exfoliated respiratory cells and define the relationship of these changes to radon exposure and smoking,
   b. Describe the temporal pattern of cellular and molecular events in respiratory carcinogenesis as the cohort is followed longitudinally,
   c. Quantify lung cancer risk associated with cellular and molecular markers that occur with high prevalence, and
   d. Establish a resource of biologic specimens for future molecular epidemiologic studies;
4. Use the cohort of underground miners screened through a statewide screening program
   a. Assess pulmonary function as a marker of lung cancer susceptibility and
   b. Determine lung cancer risk associated with the presence of silicosis.

STUDIES AND RESULTS

1) Navajo Lung Cancer Study (NLCS): a records-based case-control study

Uranium mining was a common occupation of Navajo men from the 1950s until the industry closed in the early 1960s. Because exposure to radon decay products in the mines was inadequately controlled, these Navajo men have an excess of lung cancer.

To characterize the long-term consequences of uranium mining in this light-smoking population, we examined lung cancer incidence among Navajo men residing in New Mexico and Arizona from 1969-1993.

We found that over the entire 25-year period following the end of mining on the Navajo Nation, 63 (67%) of the 94 incident lung cancers among the Navajo men occurred in former uranium miners. The estimated relative risk for a history of mining compared with no history of mining was 28.6 (95% CI 13.2,61.7) and the attributable risk for uranium mining exceeded 96 percent. The average number of cases increased with time since exposure, from 1.9 per year during 1969-1983 to 3.4 per year in 1984-1993.

This study shows uranium mining among Navajos to be a unique example of exposures in a single occupation accounting for the majority of lung cancers in a population.

2) <u>Uranium Epidemiologic Study (UES)</u>

   a. We have completed the initial analysis of this cohort. Computer programs were updated to account for additional time periods of study. New sex-, ethnic-, and age-specific mortality rates (cause-specific) were calculated using New Mexico vital statistics data. These rates were formatted for use in the SMR analysis program.

      NDI match and match with New Mexico vital statistics sources (MVD, SSA, HFCA, NMTR) are complete. All death certificates have been coded by two nosologists.

b. A manuscript is under preparation for submission.

c. We submitted our updated data to Dr. Jay Lubin at NCI who used the data for revision of the risk models that form the basis of the Radiation Exposure Compensation Act compensation standards.

2a) Additional studies related to the UES cohort

d. Error in exposure assessment study

We have collaborated with Drs. Dan Stram and Duncan Thomas in a preliminary study for a NIOSH-funded project to assess the effects of errors in exposure assessment for radon progeny in New Mexico uranium miners. A grant proposal is under review for a detailed assessment of the effect of error on the exposure-response relationship (Dan Stram, PI, Frank Gilliland, Co-investigator).

e. Grand Junction non-smoker study

We are collaborating with Dr. Geno Saccamanno at St. Mary's Hospital in Grand Junction, CO, to conduct a retrospective cohort mortality study of approximately 2,000 uranium miners from the Grand Junction database who were never smokers. We are currently determining exposure for a nested case-control study.

3) Uranium Miners' Health Study (UMHS)

The Uranium Miners' Health Study (UMHS) Pilot study determined the feasibility and developed methods for a cohort of uranium miners for molecular epidemiology studies. We have successfully recruited and medically screened 80 former uranium miners in the Grants and Albuquerque, New Mexico areas. High-risk miners were recruited with one mailed solicitation. Miners received the mailing if they were residents of New Mexico and if they had been seen at anytime through the Miners' Colfax Medical Center outreach program, a statewide screening and medical care program for miners (see below). Miners responded to the mailing by calling a toll-free number. A single mailing of about 400 letters resulted in an enrollment of 120 volunteers, some of whom were placed on a waiting list. A staff member interviewed the miners and determined eligibility based on the calendar year of starting underground work, a strong predictor of exposure, and cigarette smoking. In this pilot study, most subjects were current or former smokers with a lengthy history of underground work. Eligible miners received appointments for screening in Grants or in Albuquerque at the University of New Mexico's Clinical Research Center. Miners completed a structured interview that covered mining, occupation, smoking, family history, and other lung cancer risk factors and also included a standard respiratory symptoms questionnaire. Participants had a chest x-ray, pulmonary function testing (spirometry), and sputum induction. A second set of three-day sputum samples was collected by mail approximately one year later. Blood samples were collected, separated into serum, red cells, and buffy coat and frozen. Sputum was fixed for cytology and molecular assays using CytoLyt. Chest x-rays were clinically evaluated for abnormalities including lung cancer and pneumoconiosis and were read for the presence of infiltrates by two "B-readers" certified by the National Institute for Occupational Safety and Health (NIOSH) according to the 1980 protocol of the International Labor Office. Databases for study administration and data entry were developed. A manuscript is under preparation.

Sputum cytology interpretation. We found that collection of sputum by mail is feasible. We therefore have developed collaborations with Dr. Geno Saccomanno for sputum cytology interpretation. The Uranium Miners' Health Study sent 200 sputum samples to Grand Junction, CO for analysis. We found that marked and severe dysplasia was uncommon.

Detection of p53 protein in sputum. IHC analysis of the p53 protein relies on the nuclear localization and increased stability of mutant p53 protein for the identification of cells carrying

altered p53. The ability to detect aberrant p53 protein in sputum from patients with squamous cell carcinoma was evaluated in a blind study. Squamous cell carcinomas containing p53 mutations identified by sequencing were selected for this study. To date, 18 paired samples (tumor and sputum) have been examined. Sputum specimens were collected from one day to one month prior to tumor biopsy. A method was developed to double-stain sputum samples for cytokeratin and p53 to identify epithelial cells expressing mutant p53 protein and eliminate artifactual staining of nonepithelial cells by the p53 antibody. Immunoreactive p53 protein was detected in 17 of 18 tumors examined, and concordance with sputum was observed in 11 cases. In four cases where disconcordance was observed, cellularity of the sputum preparation was greatly reduced. These data were collected prior to implementing current procedures for collecting induced sputum. These preliminary data indicate that techniques have been developed to double-stain epithelial cells within sputum for p53 protein and cytokeratin and that dysfunctional p53 protein present within the tumor can also be detected in cells exfoliated from the respiratory tract. The cleanup of sputum in conjunction with the collection of induced sputum should increase the sensitivity for detection of immunoreactive p53. The results will be included in a manuscript on the cross sectional portion of the study.

Improved exposure assessment using lead-210 (210Pb) bioassay. In collaboration with Dr. Ray Guilmette, at the Inhalation Toxicology Research Institute, we conducted a pilot study of 210Pb skull counting in 20 former miners. *Annual WLM Estimates:* Overall, the working histories obtained by interview agreed almost exactly with information in the NMTR database. The earliest year of work in underground uranium mines was 1950, and the latest year was 1990 when the last operating mine in New Mexico closed (San Mateo mine operated by Chevron USA). The median first year of exposure was 1957. The median last year of work in underground uranium mines was 1982, when the price of uranium dropped dramatically and mines began to close. The mean number of years of work in underground uranium mines was 22 years (median = 21 years).

Lifetime WLM exposures ranged from 20 to 2,605. The mean lifetime exposure was 761 WLM with a standard deviation of 575. The median level of exposure was 596 WLM and the interquartile range was 465 to 708 WLM. For the purposes of this study, missing data were estimated by linear interpolation between adjacent years where information was available (e.g., the years 1958, 1959, 1960 for Subject 7) and in one case, by assigning an average value derived from State Mining Inspector records (i.e., the years 1955, 1956, and 1957 for Subject 20).

Age, Ethnicity, and Respiratory Health of Subjects: The ages of subjects ranged from 47 to 85 years, with a mean of 66 years and median of 65 years. Twelve Anglo (non-Hispanic whites) and eight Hispanic whites participated. All but one subject reported that they had never been diagnosed with chronic obstructive lung disease, silicosis, coal worker's pneumonconiosis, or other dust-related lung disease. One subject had a single episode of coughing up blood during the past year, and he is under follow-up with St. Mary's Hospital in Denver and Dr. Gino Saccomano.

Smoking: The sample included two subjects who were smoking currently, 13 former smokers, and five who had never smoked. Among smokers and former smokers the average level of consumption was one-half to one pack per day.
Diet: Dietary calcium was assessed by interviews conducted by two senior nutritionists from the UNM Clinical Nutrition. Intake of major sources of calcium and supplements was assessed for three decades corresponding to 1965, 1980, and 1995. Intake was assessed using an interview validated against seven-day diet records on other New Mexican populations. Calcium intakes were moderately correlated across these time intervals. Mean calcium intake decreased across this time period, consistent with aging and family diet as children leave the

household. The current mean calcium intake for this sample of 20 men was 80 percent of the reported U.S. mean intake.

While the primary purpose of this pilot study was to demonstrate the feasibility of measuring 210Pb levels in men whose largest exposures to Rn progeny occurred approximately 30 years ago, another important aspect was the successful demonstration that these former uranium miners could be located and recruited for measurement. Although this pilot study was limited to 20 subjects and those with the highest exposures, our experience indicates that the database maintained by the NMTR contains accurate exposure histories. Furthermore, it is feasible to collect data on smoking and dietary intakes of calcium for use in biokinetic modeling and backward estimation of lung exposure to Rn progeny.

Diet pilot. We conducted a study of dietary intake in former uranium miners. At the Clinical Research Center at UNM, we conducted dietary assessments in 100 miners, including assays for micronutrients (Vitamin A, C, E, folate/B12, ferritin). We found that miners' dietary intake of most micronutrients exceeded those in the NHANES estimates for men of the same age. We concluded that low intake of antioxidants and micronutrients are unlikely to be associated with risk of lung cancer in uranium miners. The study manuscript is under preparation.

Women uranium miners study. We collaborated with Drs. Gary Madsen and Susan Dawson from Utah State University to study the experience of women miners. We identified 800 women who were employed in the mining industry, obtained current contact information, and interviewed approximately 50 women. We found that women reported a high number of conditions that they thought were related to uranium mining. The results will be presented at an international conference and a manuscript is being finalized.

Trisomy 7. In collaboration with scientists at ITRI, bronchial cells obtained at bronchoscopy were cultured and then assessed for genetic changes commonly found in lung cancer. We found that cells from normal bronchial mucosa of uranium miners and some smokers had genetic alterations, including trisomy 7. We published two manuscripts describing our Trisomy 7 findings and another manuscript is in press describing Trisomy 20 results. Methods to examine molecular changes in sputum have been developed, and a manuscript is in press describing the p53 method. In addition, methods for assays of 9p23 LOH in sputum have been refined and are being used in our newly funded case-control study. We have also described gene promoter methylation changes in the epithelium and a manuscript is in preparation.

Grant Applications. We have submitted several grant applications based on the population of miners and the preliminary studies noted above. Several applications have been funded and studies are underway. One grant, part of the Johns Hopkins University renewal application for the Specialized Program of Research Excellence (SPORE) for lung cancer, was funded for one year. We received funding from the Budke Foundation and the Clinical Research Center at UNM. The awardee is the co-investigator for several funded studies including a case-control study of molecular markers of risk for lung cancer in smokers. Pilot funding for a prospective cohort study of respiratory carcinogeneis using sputum has been obtained from the Southern California Environmental Health Sciences Center. The awardee has also submitted an RO1 proposal to study DNA repair in uranium miners

The principal investigator is also a co-investigator for a number of pending grant applications involving former uranium miners including RO1 applications for a study of exposure error.

4) Histology of Lung Cancer in Uranium Miners Study

   a. As an investigator in NMTR, the principal investigator initiated the development of a tissue acquisition activity with two full-time employees. Currently, we are collecting slides and tissue from uranium miners diagnosed with lung cancer. We have identified new lung cancer cases and have obtained diagnostic slides.

Pathology reports were collected to determine the material to request from pathology laboratories. The protocol for review was identical to that used in previous studies. We found that the distribution of histology changed over time to become similar to that for the general population. The histology data was submitted as part of a manuscript about Navajo miners.

b. Identify and update retrieval methods for new archived lung cancer tissue: NMTR has established a system for collecting paraffin blocks and fresh tissue from cancer cases. We are obtaining samples of lung cancer tissue from uranium miners diagnosed in New Mexico for a study examining molecular markers using these specimens.

5) Silicosis and lung cancer study.

a. We have collaborated with Dr. David James, Director of the Outreach program for analyzing data from the cohort of underground miners screened through a statewide screening program operated by the Miners' Colfax Medical Center.

b. We assembled a cohort and have completed ascertainment of vital status. We have linked with New Mexico vital statistics files and SSA files.

c. Study results and conclusions

We selected all male miners interviewed between 11/5/89 and 9/29/95. Follow-up for death began at the date of interview and ended on 12/31/95 for all miners. We discarded any miner who died within 90 days of the interview date. There were 3,033 miners who met this criteria (Table 1). Of these, there were 3,023 miners with mining histories and 2,938 with both mining and smoking histories. One thousand six hundred and ninety (55.9%) of the 3,023 miners reported ever having worked below ground at an underground uranium mine (Table 2). Nine hundred and fifty eight (56.7%) worked fewer than 10 years and 732 (43.3%) worked 10 years or more.

The characteristics of the study population are presented in Table 1. Miners were interviewed from 1989 to 1995. The majority of the cohort was 50 years of age or older with equal representation of the major ethnic groups in New Mexico. Of the 158 deaths that occurred during the follow-up period, 31 percent were from cardiovascular diseases, 13.9 percent from respiratory diseases, and 12.7 percent from lung cancer.

The distribution of risk factors for lung cancer are shown for non-uranium miners and uranium miners in Table 3. Most uranium miners never smoked, reflecting the large number of American Indian and Hispanic miners in the Outreach program. Former uranium miners generally had lower pulmonary functions, more abnormalities on chest radiographs, and a higher prevalence of symptoms.

SMRs calculated using ethnic-specific mortality rates for New Mexico are shown in Table 4. The SMRs are stratified by years employed in underground uranium mines. A strong healthy worker effect is evident. The SMR for lung cancer is 5.39 for more than 10 years in underground in uranium mines. Nonmalignant respiratory diseases were not significantly increased.

Using proportional hazard models to make internal comparisons within the cohort, we found that the risk for lung cancer was elevated threefold (Table 5). Low pulmonary functions were associated with lung cancer risk and all cause mortality. Respiratory symptoms and profusion abnormalities were associated with all cause mortality. Cough and profusion changes were associated with lung cancer risk.

We conclude that uranium miners with more than 10 years employment underground are at an increased risk of lung cancer. Lung cancer risk is associated with respiratory symptoms, pulmonary function deficits, and chest radiograph abnormalities. These clinical markers of risk may be useful for identifying high-risk miners for screening and prevention trials.

6.) Reduced DNA repair capacity of carcinogen-induced DNA damage is now thought to significantly influence inherent susceptibility to lung cancer. DNA-PK is a serine-threonine kinase activated by the presence of double-strand breaks in DNA that appears to play a major role in nonhomologous recombination and transcription control. The purpose of this study was to determine whether interindividual variation exists for DNA-PK activity and what impact this has on lung cancer risk. This was accomplished by comparing DNA-PK activity in peripheral mononuclear cells from a population of individuals with lung cancer (N = 27) to a population of lung cancer-free controls (N = 27). Interindividual variability was seen within each population; however, the mean value for DNA-PK activity was significantly lower in the population with lung cancer than the control population. The odds ratio for low enzyme activity relative to high for lung cancer was 7.35. The enzyme activity in peripheral mononuclear cells reflected activity seen in bronchial epithelial cells, one of the progenitor cells for lung cancer, supporting the use of peripheral mononuclear cells for larger population-based studies of DNA-PK activity. A role for DNA-PK activity as a risk modifier for lung cancer was also established by the fact that cell killing in bronchial epithelial cells exposed to bleomycin was directly associated with enzyme activity. Thus, the results of this study demonstrate for the first time that reduced DNA-PK activity is associated with an increased risk for lung cancer most likely manifested through a reduction in DNA repair capacity.

CONCLUSIONS

The need for research in the area of respiratory carcinogenesis is evident. Lung cancer remains a pressing worldwide public health problem and indoor radon is now recognized as the second leading cause of lung cancer in the United States. Techniques of molecular and cellular biology will provide new markers for describing the longitudinal process of carcinogenesis and for screening. Further research is needed to explore the role of error in the exposure-response relationship, identify intermediate markers for use in risk assessment and for the primary prevention of lung cancer. Establishing a large cohort of former miners would provide the opportunity to validate intermediate markers and conduct clinical prevention trials.

PLANS

We have completed the specific aims that were presented in the original application. Although the awardee has moved to the University of Southern California, he continues to actively study uranium miners and has continued his research program at UNM as a faculty member. Publication of results from the multiple projects support by this SERCA are in progress including publishing the UES cohort mortality update, the silicosis and lung cancer cohort study, and the UMHS cohort study of 200 miners. Newly funded projects will continue including a case-control study of molecular markers of risk and molecular markers in lung adenocarcinomas. An additional grant application has been submitted for improved exposure assessment and to establish a long-term longitudinal follow-up study of 2000 former miners.

We anticipate that the expanding collaborative group track record and ongoing funded work in respiratory carcinogenesis will be highly productive.

Tables

Table 1: Raton Miner's Health Services 1989-1995[1]
Characteristics of cohort

		N	Percent
Year of interview	1989	55	1.8
	1990	466	15.4
	1991	817	26.9
	1992	527	17.4
	1993	551	18.2
	1994	385	12.7
	1995	232	7.6
Age at interview	20-29	41	1.4
	30-39	262	8.6
	40-49	471	15.5
	50-59	835	27.5
	60-69	867	28.6
	70-79	432	14.2
	80+	125	4.1
Ethnic group	Non-Hispanic white	774	25.5
	Hispanic	938	30.9
	Indian	1321	43.6
Vital status	Alive	2875	94.8
	Dead	158	5.2
Year of death	1990	1	0.6
	1991	17	10.8
	1992	19	12.0
	1993	31	19.6
	1994	39	24.7
	1995	51	32.2
Cause of death	Lung cancer	20	12.7
	Other cancer	23	14.6
	Respiratory disease	22	13.9
	Circulatory disease	49	31.0
	Diabetes	11	7.0
	Accidents and external	12	7.6
	Other causes	21	13.3

[1] Females and ethnicities other than Non-Hispanic white, Hispanic, and Indian were excluded. Miners who died within 90 days of interview or were interviewed after 9/30/1995 are excluded.

Table 2: Raton Miner's Health Services 1989-1995
Mining history

		No underground U mining		Ever mined U underground	
		N	Percent	N	Percent
Mining history (ever mined)	Coal	599	44.9	208	12.2
	Other metal	440	33.0	310	18.2
	Non-metal	294	22.1	62	3.6
	Other	54	4.1	49	2.9
Total years mined (any type of mine)	< 10	391	29.3	742	43.6
	10-20	383	28.7	501	29.5
	20-30	287	21.5	273	16.1
	≥ 30	272	20.4	184	10.8
Total years of underground U mining	< 10			958	56.4
	10-20			489	28.8
	20-30			212	12.5
	≥ 30			31	1.8
	unknown			10	0.6

Table 3: Raton Miner's Health Services 1989-1995
Risk factors

		No underground U mining		Ever mined U underground	
		N	Percent	N	Percent
Smoking	Never smoked	431	33.1	938	57.0
	Former smoker	611	46.9	498	30.3
	Current smoker	261	20.0	209	12.7
	Unknown	30		55	
BMI	< 25.0	320	24.6	449	26.7
	25.0-27.4	301	23.2	396	23.6
	27.5-29.9	334	25.7	401	23.9
	≥ 30.0	345	26.5	434	25.8
	Unknown	33		20	
FEV_1	≥ 70 %	1173	91.2	1559	93.6
	< 70 %	113	8.8	106	6.4
	No PFT	47		35	
FVC	≥ 80 %	1209	94.0	1565	94.0
	< 80 %	77	6.0	100	6.0
FEV_1/FVC	< 0.70	922	71.7	1271	76.3
	≥ 0.70	364	28.3	394	23.7
Profusion	None	1180	92.4	1449	86.4
	1/0 or greater	97	7.6	228	13.6
	No x-ray	56		23	
CWP	No diagnosis	1217	95.3	1569	93.6
	diagnosed on x-ray	60	4.7	108	6.4
Cough	No	915	70.9	637	55.8
	Yes	376	29.1	504	44.2
	No symptom information	42		559	
Phlegm	No	798	61.8	627	54.9
	Yes	493	38.2	514	45.1
Wheeze	No	868	53.1	676	59.3
	Yes	423	32.8	465	40.7
Dyspnea	No	574	44.5	348	30.5
	Yes	717	55.5	793	69.5

Table 4: Raton Miner's Health Services 1989-1995
SMR

Cause of death	Underground U mining	Observed deaths	SMR	(95% CI)
All causes	None	79	0.77	(0.61, 0.96)
	< 10 years	30	0.52	(0.35, 0.74)
	≥ 10 years	47	0.93	(0.68, 1.23)
All cancers except lung	None	13	0.52	(0.28, 0.89)
	< 10 years	5	0.47	(0.15, 1.09)
	≥ 10 years	5	0.47	(0.15, 1.09)
Lung cancer	None	6	0.82	(0.30, 1.78)
	< 10 years	2	1.23	(0.14, 4.44)
	≥ 10 years	12	5.39	(2.78, 9.42)
Respiratory disease	None	11	0.92	(0.46, 1.64)
	< 10 years	5	0.94	(0.30, 2.18)
	≥ 10 years	6	1.18	(0.43, 2.58)
Circulatory disease	None	28	0.69	(0.46, 0.99)
	< 10 years	8	0.45	(0.19, 0.89)
	≥ 10 years	12	0.72	(0.37, 1.25)
Diabetes	None	4	1.31	(0.35, 3.36)
	< 10 years	4	1.05	(0.28, 2.68)
	≥ 10 years	3	1.03	(0.21, 3.01)
Accidents and external	None	6	0.78	(0.29, 1.71)
	< 10 years	5	0.58	(0.19, 1.36)
	≥ 10 years	1	0.16	(0.00, 0.91)

Table 5: Raton Miner's Health Services 1989-1995
RR from Cox models (adjusted for age only)

		Any cause	Lung cancer	Any cancer except lung
Underground U mining	none	1.00	1.00	1.00
	< 10 years	0.64 (0.42, 0.97)	0.49 (0.10, 2.46)	0.67 (0.23, 1.89)
	≥ 10 years	1.10 (0.76, 1.58)	3.05 (1.12, 8.29)	0.71 (0.25, 2.04)
Ethnic group	Non-Hispanic white	1.00	1.00	1.00
	Hispanic white	0.86 (0.56, 1.30)	0.50 (0.17, 1.53)	0.76 (0.28, 2.02)
	Indian	0.82 (0.57, 1.18)	0.38 (0.13, 1.07)	0.41 (0.15, 1.13)
Smoking	Never smoked	1.00	1.00	1.00
	Former smoker	0.85 (0.60, 1.21)	1.32 (0.46, 3.83)	0.90 (0.34, 2.41)
	Current smoker	1.45 (0.92, 2.28)	2.96 (0.95, 9.23)	2.36 (0.81, 6.87)
BMI	< 25.0	1.00	1.00	1.00
	25.0-27.4	0.90 (0.61, 1.34)	0.78 (0.24, 2.45)	0.91 (0.31, 2.63)
	27.5-29.9	0.39 (0.24, 0.66)	0.47 (0.12, 1.83)	0.45 (0.12, 1.72)
	≥ 30.0	0.72 (0.46, 1.13)	0.62 (0.18, 2.16)	0.82 (0.26, 2.57)
Other metal mining	no	1.00	1.00	1.00
	yes	0.79 (0.52, 1.20)	0.17 (0.02, 1.31)	2.31 (0.99, 5.38)
FEV_1	≥ 70 %	1.00	1.00	1.00
	< 70 %	1.65 (1.08, 2.53)	3.11 (1.11, 8.73)	0.81 (0.19, 3.47)
FVC	≥ 80 %	1.00	1.00	1.00
	< 80 %	1.95 (1.22, 3.13)	3.57 (1.18, 10.81)	1.37 (0.32, 5.88)
FEV_1/FVC	< 0.70	1.00	1.00	1.00
	≥ 0.70	1.36 (0.98, 1.90)	4.99 (1.85, 13.43)	1.36 (0.56, 3.29)
Profusion	None	1.00	1.00	1.00
	1/0 or greater	1.80 (1.25, 2.59)	2.73 (1.02, 7.32)	1.86 (0.72, 4.81)
CWP	No diagnosis	1.00	1.00	1.00
	diagnosed on x-ray	1.28 (0.78, 2.11)	2.13 (0.61, 7.44)	1.39 (0.41, 4.76)
Cough	No	1.00	1.00	1.00
	Yes	1.88 (1.31, 2.68)	2.72 (1.08, 6.86)	0.97 (0.41, 2.32)
Phlegm	No	1.00	1.00	1.00
	Yes	1.80 (1.25, 2.60)	2.27 (0.90, 5.73)	1.18 (0.50, 2.81)
Wheeze	No	1.00	1.00	1.00
	Yes	1.95 (1.37, 2.77)	2.27 (0.93, 5.57)	1.88 (0.79, 4.47)
Dyspnea	No	1.00	1.00	1.00
	Yes	2.01 (1.26, 3.19)	1.34 (0.49, 3.71)	1.00 (0.39, 2.60)

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8. Gilliland FD, Hunt WC, Padilla M, Key CR. Uranium Mining and Lung Cancer Among Navajo Men in New Mexico and Arizona, 1969-1993. (submitted for publication)

Present and Future Publications

1. Gilliland FD, Hunt WC, Padilla M, and Key CR. Uranium Mining and Lung Cancer among Navajo Men in New Mexico and Arizona, 1969-1993, (submitted for publication).

2. Neft, R, Belinsky, S, Gilliland FD. Trisomy 20 in lung cancer patients and Uranium miners, (in preparation)

3. Uranium Mining and Stomach Cancer among Navajo Men in New Mexico and Arizona, 1969-1993

4. DNK-PK activity as a risk factor for lung cancer

5. Temporal trends in lung cancer risk in New Mexico uranium miners

6. Clinical risk factors for lung cancer among uranium miners and non-uranium miners

7. Genetic abnormalities in exfoliated respiratory epithelial cells from sputum of former uranium miners

8. Diet and abnormalities in exfoliated respiratory epithelial cells from sputum of former uranium miners