LUNG CANCER EPIDEMIOLOGY IN NEW MEXICO URANIUM MINERS

PROGRESS REPORT

FOR THE PERIOD

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JONATHAN M. SAMET

PRINCIPAL INVESTIGATOR

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UNIVERSITY OF NEW MEXICO SCHOOL OF MEDICINE

DEPARTMENT OF MEDICINE

NEW MEXICO TUMOR REGISTRY

CANCER CENTER

ALBUQUERQUE, NM 87131

MASTER

ABSTRACT

This investigation assesses the health effects of radon progeny exposure in New Mexico uranium miners. Cumulative exposures sustained by most New Mexico miners are well below those received earlier in the Colorado Plateau. This project utilizes the research opportunity offered by New Mexico miners to address unresolved issues related to radon progeny exposure: (1) the lung cancer risk of lower levels of exposure, (2) interaction between radon progeny exposure and cigarette smoking in the causation of lung cancer, (3) the relationship between lung cancer histologic type and radon progeny exposure, and (4) possible effects of radon progeny exposure other than lung cancer.

A cohort study of 3,300 men with at least one year of underground uranium mining experience in New Mexico is in progress. The investigation began in 1977 and since 1983 has been funded by the Department of Energy. To date, we have assembled large data bases that describe the exposure of the miners to radon progeny, and their smoking and mining histories. Mortality in the cohort has been assessed periodically and a four-fold excess of lung cancer has been observed. A case-control study of incident cases of lung cancer as well as analysis of mortality in the full cohort have been completed and the findings reported. The estimated excess relative risks were 1.1% per WLM and 1.8% per WLM in the case-control and cohort analyses, respectively. The data were consistent with a multiplicative interaction between cigarette smoking and exposure to radon progeny. The risk of lung cancer increased smoothly for

exposure categories above 100 WLM. A panel of pathologists reviews the histopathology of all lung cancer cases and review of cases available through 1990 has been completed.

We have implemented a case-control study within the cohort for lung cancer cases and a control group of miners deceased from other causes. The case-control study will provide a lifetime history of cigarette consumption and permit more careful assessment of the interaction between smoking and radon progeny. In preparation for the case-control study, mortality was searched through December 31, 1988 using the National Death Index and permission secured, when possible, from the states for follow-back interviews with next-of-kin. Continued follow-up of the cohort is needed to describe the temporal evolution of the lung cancer risk associated with exposure to radon progeny.

INTRODUCTION

This cohort study was initiated in 1977 to examine lung cancer and other causes of death in Grants, New Mexico area underground uranium miners. Funding from the Department of Energy began in 1983; this progress report covers the second year of the third cycle of funding from the Department of Energy. Major data collection tasks were completed during the first two funding periods, terminating in 1989. Work proposed for the period of this award (6/1/90-5/30/93) includes further follow-up of the cohort and implementation of a nested case-control study and continued review of lung cancer histopathology. A number of collaborative projects are also in progress. Additionally, analysis of the full cohort data has been completed and a manuscript accepted for publication in Health Physics (see Appendix A). The activities are reviewed separately below.

COHORT FOLLOW-UP AND CASE-CONTROL STUDY

We have conducted further follow-up of the cohort through the National Death Index, adding the years 1986-1988. The results of the follow-up have been received and death certificates obtained from the states (Table 1). The underlying causes of death are now being coded by the nosologist who has coded all deaths to date. The newly identified deaths include 23 from lung cancer; this large number of new lung cancer deaths points to the high mortality from lung cancer that the cohort is likely to experience as its members enter the fifth and sixth decades of age.

The case-control study will involve follow-back to surviving spouses or family members of deceased uranium miners. Obtaining permission for follow-back interviews required submission of a

revised application to the National Death Index (NDI) and obtaining approval from the NDI before proceeding to ask for approval from the individual states as well. We have submitted a revised protocol to the National Death Index for follow-back which has been approved. We have now requested permission from the individual states for the follow-back; this step is mandatory before interviewing can begin. This step proved lengthier than anticipated as many states required the completion of specific applications and supporting materials.

Some states do not permit any follow-back: Arizona, Iowa, Kansas, Maryland, Montana, North Dakota, and Wyoming. Only limited follow-back effort may be made in several states including Colorado, Oregon, Pennsylvania, South Carolina, and Texas. Approximately one-third of the deaths will not be available for any attempts at contact. The follow-back protocol is now completed and the interviewing will begin in January, 1992.

In planning the design of the case-control study, we have examined alternative approaches for control selection. A recently reported case-control study conducted within the Beaverlodge Uranium Miners Cohort included 46 lung cancer cases and 95 controls (L'Abbe et al. 1991). In this study, controls were matched to cases by birth year and year of death, comparable to the approach that we have planned to use; the controls included only miners who had died of causes other than lung cancer. Our original strategy had proposed to use any eligible control, even if the selected control(s) later developed lung cancer. We were concerned about potential bias, however, because of the high proportion of deaths attributable to lung cancer.

In a methodologic exploration of the potential bias associated with including or excluding controls with death due to lung cancer, we used existing data on cigarette smoking to simulate the situation of a case-control study (Table 2). Including controls who ultimately died of lung cancer tended to bias estimates of risk downwards, particularly at higher levels of exposure. Recently we have become aware of alternative approaches to the case-control design for this analytic problem. In "two-stage" studies, information from the full cohort is utilized for independent variables available for the full cohort with confounding and interaction assessed using data available for a smaller sample (Cain and Breslow 1988). This design offers a more efficient approach for assessing confounding and interaction with cigarette smoking, the primary objective of collecting the additional data on cigarette smoking. We are presently examining use of these two-stage designs.

REVIEW OF HISTOPATHOLOGY

A panel of four pathologists has reviewed available materials for lung cancer cases in the cohort as well as materials from a comparison study of Navajo uranium miners. Small cell carcinoma remains the predominant histologic type in the cohort. We plan to report these descriptive findings during the next year.

DATA ANALYSIS

Analysis of data from the full cohort is completed (see manuscript in Appendix A). With assistance from Dr. Jay Lubin, National Cancer Institute, conventional and multivariate modeling was used. The availability of new software from Dr. Lubin facilitated comparison of alternative models (exponential relative

risk, excess relative risk, and absolute risk). Overall, mortality in the cohort was significantly increased (Standardized Mortality Ratio (SMR) = 1.1, 95% confidence interval (CI) 1.0-1.2). A substantial excess was evident for lung cancer (SMR = 4.0, 95% CI 3.1-5.1). The risk of lung cancer increased smoothly for exposure categories above 100 WLM; the excess relative risk increased by 1.8% per WLM.

OTHER PROJECTS

A number of other collaborative projects are underway, based on the research opportunities afforded by the data set. We have been working with Dr. Curtis Harris, National Cancer Institute, on a project directed at the molecular and cellular biology of lung cancer in uranium miners. We have supplied paraffin blocks of lung cancer tissue from smoking and non-smoking uranium miners and from smokers and non-smokers in the general population. These tissues are being examined for oncogene expression and mutations at the National Cancer Institute. Analyses have been completed on the mutational spectrum of the p53 suppressor gene and the K-ras oncogene in 19 lung tumors from the cohort. The initial analyses suggest patterns of genetic damage different from lung cancer observed in tobacco smokers in the general population. Tissues have also been made available to Dr. Fred Leung, Battelle Pacific Northwest Laboratory, for assessment of growth factor receptors.

We are also working with Dr. Sarah Darby, Oxford University, in an international effort to pool data from radon-exposed miners; the emphasis is on causes of cancer death other than lung cancer. Data have been supplied from our cohort for the analysis which should pool nearly all available studies of miners. The National Cancer

Institute, with Dr. Jay Lubin as the lead investigator, initiated an additional collaborative pooled analysis designed to replicate and expand the work of the Biological Effects of Ionizing Radiation (BEIR) IV Committee. We are also contributing to this analysis which will combine the data from 11 studies that have exposure estimates for radon progeny. Finally, we continue to explore use of the data to assess consequences of measurement error. Our collaborations include Dr. Duncan Thomas, University of Southern California, and Dr. Donna Spiegelman, Harvard University.

PROJECT PLANS FOR 1992-1993

We will complete data collection in the case-control study and analyze and report the data. Histopathology review and our collaborative projects will be ongoing.

REFERENCES

1. Cain KC, Breslow NE. Logistic regression analysis and efficient design for two-stage studies. Am J Epidemiol 1988; 128:1198-1206.
2. L'Abbe KA, Howe GR, Burch JD, et al. Radon exposure, cigarette smoking, and other mining experience in the Beaverlodge Uranium Miners Cohort. Health Physics 1991; 60:489-95.

TABLE 1
1986-1988 Deaths by State of Death

AZ 8

AR 4

CA 3

CO 12

KS 1

MO 2

MT 2

ND 1

OK 7

OR 1

TX 2

UT 4

WA 1

WV 3

NM 52

TABLE 2

Comparison of estimates for exposure effects on lung cancer based on two types of matching
a) cases allowed to be controls for preceding risk sets and b) only non cases allowed to be controls.

Cases allowed to be controls

Exposure(WLM)	Smoking unadjusted			Smoking adjusted		
	O.R.	95% C.I.	p-value	O.R.	95% C.I.	p-value
0- 99	1.0			1.0		
100-199	1.02	0.45 - 2.32	.92	0.96	0.42 - 2.20	.93
200-299	1.72	0.81 - 3.65	.15	1.63	0.75 - 3.49	.21
300-399	2.65	1.16 - 6.06	.021	2.60	1.13 - 5.96	.024
400-499	3.92	1.31-11.64	.014	3.81	1.28-11.29	.016
500-749	6.12	2.22-16.85	<.001	5.49	1.96-15.37	.001
750-999	3.03	0.52-17.85	.22	3.06	0.51-18.40	.22
≥1000	2.05	0.61 - 6.95	.25	2.40	0.66 - 8.66	.18
EVER				1.77	0.64 - 4.92	.27
MISSING				1.56	0.46 - 5.34	.48

Only non cases allowed to be controls

Exposure (WLM)	Smoking unadjusted			Smoking adjusted		
	O.R.	95% C.I.	p-value	O.R.	95% C.I.	p-value
0- 99	1.0			1.0		
100-199	0.93	0.41 - 2.09	.86	0.89	0.39 - 2.02	.79
200-299	1.83	0.85 - 3.95	.12	1.72	0.79 - 3.73	.17
300-399	2.93	1.23 - 6.96	.015	2.76	1.15 - 6.60	.023
400-499	7.58	2.12-27.09	.002	7.35	2.06-26.24	.002
500-749	14.71	4.21-51.34	<.001	13.05	3.67-46.46	<.001
750-999	6.16	0.87-43.64	.069	5.88	0.81-42.97	.081
≥1000	4.11	1.08-15.67	.039	4.78	1.16-19.71	.031
EVER				1.64	0.59 - 4.56	.34
MISSING				1.35	0.38 - 4.72	.64

DISCLAIMER

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