LUNG CANCER IN

THE NATIONAL COAL WORKERS' AUTOPSY STUDY

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Summary

The 2410 cases in the National Coal Workers' Autopsy Study were analyzed to determine whether factors in the underground mining environment influenced the incidence or histogenesis of lung cancer. The major factor in the development of lung cancer in coal workers appeared to be cigarette smoking. We could find no effect due to duration of underground exposure. An interesting finding was an apparent increase in the number of cases with adenocarcinoma. This latter finding supports the concept that the histogenesis of bronchial neoplasm is influenced by environmental factors.

Introduction

It is being increasingly recognized that most respiratory cancers are associated to some extent with environmental factors. Among the environmental factors, cigarette smoking, asbestos exposure and exposure in the metal and mineral mining industries have been considered significantly influential in the development of lung cancer. (Stocks, 1966; 1967; Selikoff, et al. 1974; Axelson and Sundell; 1976, Archer, et al. 1973; Newman, et al. 1974; Auerbach, et al. 1975; Wagoner, et al. 1967; 1973). There is also evidence suggesting a direct relationship between air pollution and pulmonary cancer (Carnow and Meier, 1973; Hagstrom, et al. 1967; Schneiderman and Levin, 1972; Levin, et al. 1960).

There are many reasons for suspecting that the environment of the coal mine may influence the incidence of lung cancer. Several studies have been reported in the literature mainly based on death certificate and necropsy data (Kennaway and Kennaway, 1947; 1953; James, 1955; Carroll, 1963; Enterline, 1964; 1972; Liddell, 1973; Costello, et al. 1974; Ortmeyer, et al. 1974; Rooke, et al. 1979; Scarano, et al. 1972; Mooney, 1975; Abraham, 1978; Cochrane, et al. 1979). The majority of these studies have shown a slightly decreased incidence of lung cancer in coal workers. It is difficult to draw firm conclusions from these studies as most of them have suffered from important epidemiological limitations, for example, the majority of studies have not been adequately controlled for smoking.

In the United States squamous cell carcinoma is considered the most common type of lung neoplasm (Clifton and Luomanen, 1968). Also, squamous cell carcinoma is known to be the most prevalent

type of cancer in smokers (Kreyberg, 1962; Doll, et al. 1957; Vincent, et al. 1965; Weiss, et al. 1972). On the other hand, small cell carcinoma has been reported to be the most prevalent type of lung neoplasm in uranium miners (Archer, et al. 1973; Auerbach, et al. 1975) and adenocarcinoma is more prevalent in asbestos workers (Spencer, 1977; Whitwell, et al. 1974; Heuper, 1966; Hourihane and McCaughey, 1966). Thus, knowledge of the frequency distribution by histological type in a given population may provide valuable clues to the etiology of lung cancer.

The purpose of this study was to determine whether there is an association between histological type of coal workers' lung cancer and factors in the underground mining environment. The study was based on the material in the National Coal Workers' Autopsy Study (NCWAS). Comparisons were made between histological type, years of underground exposure, specific occupation within the mine and the type and severity of coal workers' pneumoconiosis (CWP).

Materials and Methods

In 1969 the United States Congress passed the Coal Mine Health and Safety Act, which provides free autopsies for all underground coal workers. Since its inception from 1972 through 1977 we have collected 2410 cases from 22 states. Each case submitted to this program included full demographic data, occupational and smoking histories together with a detailed autopsy report and pulmonary tissue. The NCWAS population is similar to the general working miner population with regard to geographic distribution, occupation within the mines and smoking history. However, the mean age, total number of years worked and the smoking history are higher than the

general working miner population (Abraham, 1978).

The pathological material consisted of 3 or more histological sections (1 x 1.5 cm) with 3 corresponding or different blocks of tissue which had been prepared from post-mortem tissues. Histologic evaluation of the type of neoplasm was determined by 4 pathologists according to the WHO classification (Kreyberg, et al. 1967) with minor changes as outlined below.

1. Epidermoid or squamous carcinoma:
   a. Squamous cells with keratin, keratin pearls and intracel lular bridges (well differentiated).
   b. Squamous cells with intracellular bridges or pre-keratin (moderately differentiated).
   c. Squamous cells with characteristic growth pattern, sheet-like arrangements and occasional cells with pre-keratin (poorly differentiated).
2. Small cell anaplastic carcinoma.
   a. Small cell lymphocytic (oat cell) type.
   b. Small cell polygonal type.
   c. Small cell fusiform type.
3. Adenocarcinoma
   a. Acinar type with mucin.
   b. Papillary type bronchoalveolar adenocarcinoma with mucin.
   c. Poorly differentiated acinar type with occasional mucin containing cells.
4. Mixed squamous cell and adenocarcinoma with keratin and mucin.
5. a. Large cell carcinoma with mucin.
   b. Large cell carcinoma without mucin.

c. Large cell carcinoma with giant cells.

d. Clear cell carcinoma.

6. Mesothelioma.

a. Diffuse.

b. Localized.

7. Others (Leiomyosarcoma, fibroscarcoma, etc.

In 202 cases there was sufficient material available to make a microscopic assessment. Evaluation on a minimum of 3 histological slides were made independently by all the members of the panel; that is, without prior knowledge of autopsy findings or smoking histories or years of mining history; and results recorded. The same group of slides were re-evaluated simultaneously by the panel one week later using a multi-headed microscope and the results of earlier independent interpretations were compared. When disagreements were found among the members of the panel or when mixed tumor patterns and poor differentiation were observed, additional slides stained with a battery of special stains were obtained. The histological sections, stained with H & E, keratin stain, Fontana stain and mucicarmine stains were re-examined by the panel. When these preparations were studied by the panel a unanimous opinion on the type of carcinoma was usually reached. The total number of cases disputed or demanding further characterization by special stains for a unanimous opinion was 66.

Histopathological evaluation of the pneumoconiosis was performed on all the 202 cases by two of the panel members (V.V. and F.H. Y.G.). In this evaluation it was assumed that at post-mortem the lung tissues selected for microscopic examination by the partici pating NCWAS pathologists were representative of the whole lung

for the purposes of determining the extent, severity and type of pneumoconiosis. Classification and grading of coal workers pneumoconiosis was made according to standards established by a panel of the College of American Pathologists (Kleinerman, et al. 1979).

The 221 cases identified with lung cancer were matched with cases without lung cancer. The following groupings were chosen:

1. Lung cancer cases matched with all non-lung cancer cases. The matching variables were: race, exact age, mining regions represented by eastern Pennsylvania (anthracite) the rest of appalachia and the mid west (bituminous) and west, smoking status (non-smoker, cigarette smoker (current or ex), pipe or cigar smoker). A total of 175 matches were found.
2. The same as (1) above with the exception that smoking status was replaced by pack years (5 pack-year intervals). A total of 135 matches were found.

Statistical tests were performed to determine the relationship between occupational exposure, smoking, job differences and the prevalence of lung cancer. The analyses were made using the matched pair t-tests.

Results

Table I presents relevant descriptive information for the entire sample. The 2410 miners in the NCWAS had an average age at death of 64.0 ± 11.0 years with 27.0 ± 13.0 years of underground mining. Seventy-two percent of the total sample had a history of cigarette smoking with a mean pack year smoking history of 25.0 ± 19.0. Two hundred and twenty one (221) cases were identified in which carcin-

oma of the lung was mentioned on the autopsy report. This represented 8.8% of the total sample. The mean age at death of miners with lung cancer was 65.0 ± 10.0 years. In the 221 lung cancer cases 200 (90%) smoked cigarettes, 3 were pipe or cigar smokers only and 18 were non-smokers. In 183 cases lung cancer was determined by the pathologist to be the underlying cause of death. Table II shows the distribution of lung cancer cases and cases with cancer at other sites in 22 coal mining states. The proportion of lung cancer cases in Illinois and Ohio appears to be increased.

Analysis of matched group 1 showed a significant difference ($P = 0.03$) in mean pack years between the smokers in the two groups. The mean pack years for lung cancer cases was 31.0 ± 20.0 compared to 24.0 ± 22.0 for non-lung cancer cases.

Among the 175 matched lung cancer cases 13 were non-smokers with an average underground work history of 26.0 ± 17.0 years. The average underground work history of the matched control population was 35.0 ± 12.0 years. This difference was not statistically significant ($P = 0.12$).

As there was a significant difference in the amount smoked between the lung cancer and non-lung cancer cases we felt a more precise matching of smoking history was required to determine an independent effect due to occupation. Group 2 illustrates this matching. In both smoking and non-smoking miners no significant differences were detected between years underground, specific occupation and the presence of lung cancer.

Table III shows the relationship between the histological type of lung cancer and age, mining and smoking histories in 202 cases on which histological material was available. The predominant

cell type was adenocarcinoma (30%), followed by small cell (28%) and epidermoid (24%) carcinomas. For each of these three major histological types of lung cancer no significant differences were detected in mean age, pack years smoking history or years in underground mining.

The type of CWP lesion and its frequency of occurrence with the different cellular types of lung cancer are shown in Table IV. There appears to be a lower incidence of macular CWP in cases with small cell carcinoma.

Due to the unexpectedly high incidence of adenocarcinoma in this series an attempt was made to determine the site or origin of these tumors within the lung. These details were extracted from the clinical, surgical and autopsy reports. Out of a total of 60 cases of adenocarcinoma 23% of the tumors originated in the upper lobes, and 16% originated in the lower lobes. The remaining tumors either originated from the trachea, right middle lobe, main stem bronchi or the site of origin could not be determined.

Discussion

Whether exposure to coal mine dust increases the chances for developing carcinoma of the lung is a matter of considerable importance which has not been resolved in spite of several investigations (Green and Laquer, 1980). There are many reasons for suspecting the environment of the coal mine may influence the incidence of lung cancer. Coal mine dust is known to contain polycyclic aromatic hydrocarbons and several metal carcinogens such as beryllium, cadmium, chromium, cobalt, lead, maganese and nickel (Berg and Burbank, 1972). Moreover, coal dust due to its high adsorbing ability may facilitate the transportation of polycyclic hydrocarbons from

cigarette smoke. It has been shown that cigarette smoking miners have an 8 fold increase of lung cancer deaths as compared with non-smoking coal miners (Jacobson, 1976). Several studies suggest that carcinoma of the lung is less frequent in coal miners than in non-miners of a similar age group (James, 1955; Doll, 1959; Goldman, 1965; Costello, et al. 1974; Ortmeyer, et al. 1974; Liddell, 1973; Kennaway, and Kennaway, 1947; Rooke, et al. 1979; Cochrane, et al. 1979). In contrast to these reports other mortality studies conducted in the United States have shown an increased SMR for lung cancer in coal workers (Enterline, 1964; 1972; Mooney, 1975). The cause of this disparity in findings is a reflection on the complexity of the problem. The difficulties in determining the true incidence of lung cancer in coal miners are mainly due to regional variations in coal mines and dust concentrations, difficulties in obtaining control populations from the same areas, and separation of the influence of mining independent of smoking.

In this study we could find no evidence that the development of lung cancer is influenced by duration of underground exposure. However, we have confirmed the well recognized etiological relationship between cigarette smoking and lung cancer.

We found a greater percentage of adenocarcinoma and small cell carcinoma in the NCWAS cases than reported in comparable studies. There is some evidence that lung cancers due to smoking are mainly squamous or small cell in type and adenocarcinomas are endogenous growths (Kreyburg, 1962; 1967; Weiss, et al. 1972). In this study 90% of the NCWAS cases with lung cancer had a history of cigarette smoking. Thus, the descrepancy noted in this study between predominant histological type and smoking history may be related to

occupation. In a study of histological cell types in asbestos workers with lung cancer, adenocarcinoma was also found to be the most common type (Whitwell, et al. 1974). Ionizing radiation, on the other hand, is known to induce predominantly small cell, undif ferentiated type of carcinomas and the relative frequency of this type of tumor rises with cumulative radiation exposure (Saccomanno 1971; Archer, et al. 1973; Horacek, et al. 1977;Auerbach, et al. 1975). The relative predominance of adenocarcinoma in the NCWAS cases raises the interesting possibility that factors in the coal mining environment influence the histogenesis of bronchial carcinomas. However, this conclusion cannot be drawn with certainty as a suitable control group of non-miners with lung cancer were not available for us to study. There is also some evidence that the incidence of adenocarcinoma of the lung in the general population is increasing (Vincent, et al. 1977).

In conclusion, we would like to stress that this report is provisional. We are currently updating the study to include cases submitted during 1978 and 1979, and are tracking down additional material on cases lacking histological sections of the lung tumor. We hope to better define the relationship between smoking and lung cancer in coal workers and to compare the severity of CWP in lung cancer cases with matched controls.

TABLE I

NCWAS CASE DESCRIPTION

SAMPLE SIZE	2410
MEAN AGE ± S.D.	64 ± 11
SMOKERS	1709 (72%)
NON - SMOKERS	619 (26%)
PIPE SMOKERS	47 (2%)
MEAN PACK - YEARS ± S.D.	25 ± 19
MEAN MINING YEARS ± S.D.	27 ± 13

TABLE II

PREVALENCE OF LUNG CANCER AND CANCER OF OTHER ORGANS BY STATE

STATE	TOTAL DEATHS	ALL CANCERS EXCEPT LUNG	%	LUNG CANCER	%
ALABAMA	3	0	-	1	-
ARKANSAS	3	1	-	1	-
CALIFORNIA	1	1		0	-
COLORADO	33	5	15	2	6
DIST. OF COLUMBIA	1	0	-	0	-
ILLINOIS	88	13	15	16	18
INDIANA	8	1	-	0	-
KANSAS	8	4	-	1	-
KENTUCKY	120	9	8	8	7
MARYLAND	6	1	-	1	-
MISSOURI	1	0	-	0	-
NEW MEXICO	5	1	-	0	-
OHIO	89	10	11	16	18
OKLAHOMA	4	1	-	1	-
PENNSYLVANIA	1176	163	14	103	9
TENNESSEE	3	0	-	1	-
TEXAS	1	0	-	0	-
UTAH	9	0		0	-
VIRGINIA	71	6	8	5	7
WASHINGTON	1	9	-	0	-
WEST VIRGINIA	666	91	14	56	8
WYOMING	38	9	24	1	3
TOTALS	2336	316	14	213	9

TABLE III

CARCINOMA OF THE LUNG: CELL TYPES BY AGE, SMOKING AND MINING

	%	Age	Pack Yrs.	Mining Yrs.
Adeno-Carcinoma	30	$63^{\pm}$	$28^{\pm}$	30^{+}_{-}
		10*	20	14
Epidermoid	24	$68^{\pm}$	$33^{\pm}$	31^{+}_{-}
		10	19	12
Small Cell	28	$64^{\pm}$	$30^{\pm}$	32^{+}_{-}
		9	23	11
Large Cell	9	$67^{\pm}$	$35^{\pm}$	33^{+}_{-}
		10	16	14
Mixed Adeno-Carcinoma Epidermoid	8	$65^{\pm}$	$30^{\pm}$	41^{+}_{-}
		9	18	14
Broncho-Alveolar	1	$62^{\pm}$	$37^{\pm}$	19^{+}_{-}
		10	27	13
All Cases	100	$65^{\pm}$	$32^{\pm}$	31^{+}_{-}
		2	3	7

*MEAN ± 2 STANDARD DEVIATION

TABLE IV

THE TYPE OF LESION AND ITS FREQUENCY OF OCCURRENCE IN THE CASES WITH LUNG CANCER

Cell Type	No-CWP Lesions %	Macule %	Nodule %	PMF %	Silicosis %
Adenocarcinoma (60)	23	77	23	5	8
Epidermoid (48)	17	83	35	8	8
Small Cell (56)	34	64	23	5	2
Large Cell (19)	16	74	32	16	16
Mixed Adenocarcinoma (16) Epidermoid	12	88	44	19	6
Broncho-Alveolar (3)	33	67	--	--	--

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Dr. Lingeman: I would like to know if there is any correlation between the type of cancer and the amount of silicon present in the coal. For example, do you know how much silicon is present in the coal mined in Pennsylvania, versus that mined in Ohio or in Illinois? Is there a high level of silicon in the coal from these states?

Dr. Vallyathan (NIOSH): Yes, there is a difference in the amount of silicon present in the different types of coal. We have not determined whether there is any correlation between the frequency or type of cancer and the silicon content of the coal mine dust.

Dr. Spirtas (NCI): From the abstract I take it for granted that this is a case control study. Is that correct?

Dr. Vallyathan (NIOSH): No, it is not a case control study. We have not been able to obtain a suitable control autopsy population. Therefore all our comparisons are internal.

Dr. Spirtas (NCI): What is your study design? Is there some way that you will try to determine whether this series of cases are representative cases or is this a report on a series of cases?

Dr. Vallyathan (NIOSH): The National Coal Workers' Autopsy (NCWAS) cases represent only about ten percent of the deaths in the Nations' coal workers. It is a selected population due to its voluntary nature. The NCWAS population is demographically similar in many respects to the living miners in our National coal study.

Dr. Spirtas (NCI): I take it that the voluntary part of the program is on the part of the physician. Is there some reason to suspect that certain types of physicians or certain types of cases are volunteered for autopsy?

Dr. Vallyathan (NIOSH): No, it is not the physician who determines whether to submit a case or not. An autopsy is requested and submitted by the next-of-kin.

Dr. Spirtas (NCI): Is this for a claim for benefits under the Coal Mining Act?

Dr. Vallyathan (NIOSH): Yes.

Dr. Marcy (EPA): I presume these cases represent a stable population in terms of their work history in the industry and residency in a state. Have you verified their residency and other occupational exposures?

Dr. Vallyathan (NIOSH): Yes, these cases do represent a stable population with a coal mining history of 10 or more years in the individual states. We have ascertained the residency of all cases included in this study. However, details of occupational histories other than in the coal mining industry are not available.

Dr. Kraybill (NCI): Did you make any radioactivity measurements? I understand when coal is burned an effluent of radioactive material is released. Is there any radium or uranium type ores connected with coal? Is there a difference in the radioactivity levels of coal mine to coal mine from state to state?

Dr. Vallyathan (NIOSH): No, we did not make any radioactivity measurements in the different mines. There is some information available to us on the radon daughters in different coal mines. This level of radioactivity seems to be insignificant. I am not aware of the presence of any uranium or radium ores in the coal mining areas.

Dr. Blot (NCI): Other than the proportional histology analyses that you have presented today, could you say again how you might be able to use this data to get at the question of whether or not coal miners have an increased lung cancer risk?

Dr. Vallyathan (NIOSH): We hope to answer that question by a case control epidemiological study. However, I have mentioned some of the difficulties that we have encountered. If all the variables are adequately controlled, the question of whether the coal miners have an increased risk of lung cancer can be ascertained. Some of the earlier studies have attempted to differientiate the effect of cigarette smoking and a limited number of cases have shown a low incidence of lung cancer in coal miners. In this respect it is important to note that the latency period for the inorganic type of minerals to induce lung cancer is probably in the range of 20 to 30 years. Induction of cancer by coal dust may not be evident if other causes such as smoking or shortened lifespan from pneumoconiosis occurs before the expression of the cancer.

Dr. Blot (NCI): How are you going to use the data that you have available? I think I am getting at the question that Bob Spirtas was bringing up. How are you going to use that data to answer this question?

Dr. Vallyathan (NIOSH): It can be answered only by a case control study.

Dr. Blot (NCI): A case control study among all coal miners and their autopsies and then looking for differences in lengths of employment?

Dr. Vallyathan (NIOSH): Yes, that is what we plan to do, and we are also in the process of getting a case control series of lung cancer cases from non-mining populations.

Dr. Fraumeni (NCI): I would just like to ask one question for the future. I would be very cautious in saying, as you have a number of times, that you have evaluated the incidence of lung cancer. The data that you have, is some sort of a proportionate frequency series; but does NIOSH have any plans to conduct a cohort analysis of coal miners to determine once and for all whether or not the risk of lung cancer is increased or decreased or the same as the general population? Because I think without a cohort study and lifetable analysis, you will never be able to evaluate the issue. Can anybody answer that?

Dr. Vallyathan (NIOSH): As far as I know, there are no cohort studies which have been initiated. Regarding your first comment, I definitely agree that incidence is the wrong term to be used. I probably should have said "prevalence".

Dr. Bridbord (NIOSH): First of all, there was a recent cohort mortality study sponsored by NIOSH, which did not clarify the lung cancer issue but did suggest an increase in stomach cancer. The second point to note is that the recent Mine Safety and Health Amendments Act does give NIOSH considerable new responsibilities in the area of mining in general, which is not exclusively coal mining but really reaches out to the total spectrum of mining. I think we would have to weigh the answer to that question in terms of the opportunities that would be available to do that additional study and look at our total mining responsibilities. But I do not think that the Institute is completely satisfied that we have resolved the question. So, at some point in the future, I think there might be a chance to embark upon a larger study, but that would be a competing issue in terms of the total mining research needs.

Dr. Fraumeni (NCI): Is there any evidence with regard to the relationship between the cell types and the amount of pulmonary fibrosis? For example, with the cases of adenocarcinoma of the lung, did they have more pulmonary fibrosis or any evidence of what has been called Caplan's syndrome, which is a hypersensitivity reaction with pulmonary fibrosis and rheumatoid arthritis?

Dr. Vallyathan (NIOSH): This was illustrated by the last slide. May I have the last slide again, please? The extent and severity of pneumonconiosis, which has been graded based on the type and presence of the different types of lesions, that is; simple macule, nodule, PMF, which is progressive massive fibrosis and silicosis, are scored for each type of cancer. We have not found any definite association with adenocarcinoma and PMF. However, there is a lower prevalence of pneumoconiosis with small cell carcinoma. In small cell carcinoma only 64% of the cases had pneumoconiosis. Caplan's syndrome was not observed in these coal workers.

NIOSH

PROCEEDINGS OF THE
FIRST NCI/EPA/NIOSH COLLABORATIVE WORKSHOP:
PROGRESS ON JOINT ENVIRONMENTAL AND
OCCUPATIONAL CANCER STUDIES

MAY 6-8, 1980

SHERATON/POTOMAC, ROCKVILLE, MARYLAND

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Appropriate portions of the discussions, working groups and plenary session were sent to the participants for editing. The style of editing varied, as could be expected. To the extent possible, we have attempted to arrive at a consistent format.

PROCEEDINGS OF THE FIRST NCI/EPA/NIOSH COLLABORATIVE WORKSHOP: PROGRESS ON JOINT ENVIRONMENTAL AND OCCUPATIONAL CANCER STUDIES

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