The Etiology of Lung Cancer in Northeastern Oklahoma

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A GREAT DEAL of speculation exists concerning the role of the environment in the current epidemic of lung cancer. The controversy of the causal relationship between smoking and lung cancer has not been resolved to the satisfaction of everyone concerned, nor has the extent been determined to which air pollution contributes to the rising trends from the disease.

The literature on occupational mortality reveals differences in the prevalence of lung cancer. In two groups, the Schneeberg and Joachimsthal miners, lung cancer accounted for 75 and 40 to 50 percent of the total deaths (*1*). Compared with the death rates for all U.S. males, lung cancer death rates were 29 times greater among employees of six chromate plants (*2*). The risk also was five times greater among all nickel workers in the nickel-producing districts of South Wales (*3*), and 15 times greater among workers employed 20 years or more in dusty areas of asbestos plants in Great Britain (*4*). Mortality among the retired employees of a London gas company who were 60 years old and over exceeded 80 percent for a 10-year period. Those actually engaged in the work had an excess risk of 100 percent (*5*).

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A number of investigators have suggested that genetic factors may play a role in the etiology of lung cancer (*6–8*). A biological basis for the habit of smoking also has been postulated (*9, 10*). Friberg and associates (*6*) and Fisher (*11*) found a higher degree of concordance in smoking among monozygotic than among dizygotic twins. Several studies have shown that smokers tend to aggregate in families (*7, 8*).

In a study of the geographic and secular variations of mortality from cancer of the respiratory system (*12, 13*), cancer of the lung, trachea, and bronchus (combined) among white males was most prevalent in Oklahoma from Ottawa County in the northeastern corner of the State to Hughes County in the east central region. The same area, excluding Tulsa and Creek Counties, reported the lowest per capita sales of cigarettes. Several coal mines and minable coalfields are in this area.

The average annual age-adjusted death rates per 100,000 population during the 1956–65 period studied were Ottawa County 50.0, Okmulgee County 57.0, and Washington County 40.2. These three counties have either zinc smelters or lead-zinc mines.

Our current epidemiologic study was aimed at (*a*) investigating the relationship, if any, between the very high mortality of cancer of the lung, trachea, and bronchus in northeastern Oklahoma and the patients' occupations and smoking habits; (*b*) determining if the low per capita sale of cigarettes in northeastern Oklahoma is a true indicator of low per capita consumption or an artifact influenced to a great degree by the habit of purchasing cigarettes across the State line in Kansas, Missouri, or Arkansas; and (*c*) determining if cancer of the lung, trachea, and bronchus aggregates in families.

Method of Procedure

We will attempt to explain the high mortality from histologically confirmed cases of cancer of the lung, trachea, and bronchus among patients admitted to 27 accredited hospitals in 12 northeastern Oklahoma counties: Craig, Creek, Hughes, Mayes, Muskogee, Nowata, Okfuskee, Okmulgee, Ottawa, Rogers, Tulsa, and Washington. We also will attempt to separate occupational factors from human habits, familial factors, and environmental factors.

The average annual age-adjusted death rates for 1956–65 in these 12 counties were in the upper quartile, based on the study of the geographic and secular variation of mortality from cancer in Oklahoma (*13*).

The index patients included those whose diagnoses were histologically confirmed at the hospitals in the 12-county area during the calendar year 1969. No distinction was made between the specific types of tumors.

By systematically screening adjacent households in the blocks where the patients lived, we selected a group of healthy men and women as controls, matched for race, sex, age (plus or minus 5 years), and usual residence. In addition to information abstracted from the hospital records, data were obtained by personal interviews of the patients still living and of the controls and their immediate family members. The specific information requested of them concerned—

- Race, age, sex, and marital status
- Family history, including consanguinity of parents
- Smoking history
- Residential history
- Occupational history (usual and last)
- Information concerning deceased members of family
- Place of purchasing cigarettes or other tobacco

In addition to the cases identified from the hospital records, we also obtained information, filed by the 12 counties at the State health department for the same 1-year period, concerning all deaths attributed to cancer of the lung, trachea, and bronchus. The mortality data were compared with the incidence data ascertained from the patient-control study.

These data were transferred to IBM cards for analysis. Age, sex, and race specific rates and crude incidence and mortality rates were tabulated by using the case data obtained from the hospitals and the death records filed at the State health department for 1969. Data from the 1970 Oklahoma census were used for the appropriate populations at risk.

After initial screening we classified 533 cases as cancer of the lung, trachea, and bronchus, but in a more detailed review we rejected 313 cases for one or more of the following reasons:

1. Diagnosis by X-ray or clinical symptoms only
2. Duplication of charts
3. Duplication of patients by more than one hospital
4. No bona fide histological report on (*a*) surgery (like pneumonectomy), (*b*) biopsy, (*c*) cytology of sputum, and (*d*) exfoliative cytology of bronchial washing.

Only 220 cases therefore had the histologically confirmed diagnoses required for this study. An additional 41 cases were rejected because the patients resided outside the 12 counties; thus only 179 cases were eligible for the study.

Results and Discussion

Of the 533 identified cases 41 percent were histologically confirmed. The proportion varied within each hospital, but generally the larger the hospital the greater the proportion of confirmed cases. Most patients were admitted to the hospitals in Tulsa. (The 179 patients included in this study were 137 white men, 32 white women, eight Negro men, and two Negro women.)

Obviously, many of the diagnosed cases of lung cancer in the 12 counties were not histologically confirmed. The larger hospitals in Tulsa and Muskogee Counties had the greatest proportion of the total cases that were histologically confirmed. This fact perhaps indicates that the availability of pathological services influences to some degree the frequency with which physicians use pathological services to confirm clinical diagnoses.

Table 1. Lung cancer incidence and mortality rates, by county of residence, Oklahoma, 1969

County	Rates per 100,000 population	
	Incidence [1]	Death
Craig	61.1	54.3
Creek	19.8	41.7
Hughes	....	22.7
Mayes	17.2	51.5
Muskogee	25.2	45.4
Nowata	20.5	61.4
Okfuskee	56.2	46.8
Okmulgee	22.6	42.4
Ottawa	16.8	57.0
Rogers	14.1	35.2
Tulsa	27.1	32.9
Washington	18.9	37.9
Total	25.1	37.8

[1] Based on histologically confirmed cases.

From a study limited to one geographic area in a State that has experienced excessive mortality from lung cancer, it is difficult to conclude that the increased mortality reported in the area resulted from fewer deaths of patients with histologically confirmed cases than in other geographic areas of the State. To reach such a conclusion we would have to assume gross misdiagnoses by physicians who relied on clinical judgment alone. A larger proportion of deaths or histologically confirmed cases in an area of low mortality might suggest that the high mortality from respiratory cancer in another area could be partially explained by the diagnostic practices concerning the disease in that area.

Both incidence and mortality data are included in tables 1 and 2. Distribution of lung cancer incidence and death rates in 1969, by county of residence, are shown in table 1. Although all the deaths are not of the study patients, the trend in most counties seems to indicate that a larger number of deaths were attributed to cancer of the lung, trachea, and bronchus than the number of histologically confirmed cases identified. For the 12 counties in 1969, there were 270 deaths reported to the State health department and only 179 histologically confirmed cases. Most cases and deaths occurred, in order, in Tulsa, Muskogee, and Creek Counties. The age-specific incidence and mortality rates for lung cancer in the 12 counties are given in table 2.

The practice of diagnosing lung cancer also is reflected in the increased mortality over incidence of newly diagnosed cases reported in 1969. Some patients whose cases were diagnosed in 1969 died the same year, but most cases were diagnosed before 1969. For a disease such as lung cancer, where the period between diagnosis and death may be short, the death rates should approximate the incidence rates. Had we included other cases of lung cancer with those histologically confirmed, the incidence rate would have been higher than the death rate.

Adenocarcinoma was the most frequent cell-type cancer that occurred in the women; squamous cell carcinoma occurred most frequently in the men (table 3). Other major cell-type carcinomas were epithelial and epidermoid.

Among a group of 70 patients we surveyed concerning smoking habits and occupation, 69 were smokers. The one nonsmoker, an executive of an oil refinery, had an alveolar-type adenocarcinoma. Squamous cell cancer occurred proportionately more in the men than in the women—as did smoking among these men and women. The pathologists reported about 20 cell types of cancer, which may indicate varied use of the terminology.

The usual occupation of both groups, patients and controls, by major categories, is given in table 4. The frequency of lung cancer among

Table 2. Age-specific incidence and mortality rates for lung cancer in 12 northeastern Oklahoma counties, 1969

Age group (years)	Rates per 100,000 population	
	Incidence	Death
35–44	10.7	17.9
45–54	37.4	51.9
55–64	97.7	118.1
65–74	112.2	185.0
75 and over	58.6	136.8
Total	57.0	85.9

Table 3. Histologically confirmed lung cancer cases, by cell type and sex of patients

Cell type	Men		Women	
	Cases	Percent	Cases	Percent
Adenocarcinoma	21	14.4	9	26.4
Epithelial cell carcinoma	14	9.6	6	17.6
Epidermoid carcinoma	12	8.2	2	5.8
Squamous cell carcinoma	49	33.7	7	20.5
Squamous cell plus other cell types	6	4.1	3	8.8
All other	43	29.6	7	20.5
Total	145	99.6	34	99.6

Table 4. Distribution of 70 patients and controls surveyed by occupation

Type of work	Cases	Controls	Relative risk
Not working	2	1	2.0
Professional	1	4	.2
Managerial	13	13	1.0
Nonmanagerial	11	18	.5
Artisans	23	13	2.2
Carpenters	5	1	3.3
Farmwork	9	12	.7
Oilfield	6	5	1.2
Mine or factory	4	3	1.4
Glass factory	4	1	4.2
Other	...	1	...
Unknown	1	...	...
Total	70	70	...

artisans and among nonmanagerial controls is perhaps significant. Interesting, too, are the four cases of lung cancer reported among glass factory workers. Only one control was employed in a glass factory. Five lung cancer patients and only one control were carpenters.

In attempting to explain the association between lung cancer and occupation, relative risks were tabulated for each major occupational category and for each specific occupation within a major category. Of all the occupations, artisan is most associated with an increased risk of lung cancer. The relative risk for this occupation was 2.2 as opposed to 1.0 for managers, 0.2 for professionals, 0.5 for nonmanagers, 0.7 for farmworkers, 1.2 for oilfield workers, and 1.4 for patients in either mining or factory work. Within the artisan group, the relative risk for carpenters was 3.3, though their number (six) was small. The relative risk for workers in glass factories was 4.2.

Occupational influence on lung cancer in northeastern Oklahoma is interesting, considering that 69 of the 70 patients and only 55 of the 70 controls smoked. Although smoking was not controlled for in determining the relative risk for each occupation, the synergistic effect of smoking on certain occupational groups, such as some artisans, miners, and factory workers, should not be overlooked.

Data on the smoking histories of patients and controls with respect to ever smoking, current smoking, and type, amount, and duration of smoking are presented in table 5. Only eight patients were currently smoking as compared with 28 controls.

Most smokers among the two groups smoked cigarettes; 59 of 70 among the patients and 44 of 70 among the controls. Seven controls smoked cigars and pipes as compared with one patient. The amount of tobacco smoked indicated that more patients than controls were heavy smokers.

The mean age when smoking was started was 16.5 years for patients and 18.6 years for controls. The mean duration of smoking was 44.1 years for the patients and 41.0 years for the controls. The 3-year difference is short, but it is significant because we do not know if any controls who continue to smoke will eventually develop lung cancer.

The mean number of years of smoking has been used as a measure of the latent period for lung

Table 5. Smoking histories of lung cancer patients and controls

Smoking histories	Patients		Controls		Relative risk
	Number	Percent	Number	Percent	
Ever smoked	69	98.6	55	78.6	18.8
Current smoker	8	11.4	28	40.0	...
Type of smoking:					
Cigarettes	59	84.3	44	62.9	1.5
Pipe or cigar	1	1.4	7	10.0	.02
Combination	8	11.4	4	5.7	1.7
Amount smoked daily	70	100.0	70	100.0	...
Once in a while	...	...	1	1.4	...
1–10 cigarettes or 1–4 pipes or cigars	6	8.6	7	10.0	...
11–20 cigarettes or 5–10 pipes or cigars	25	35.7	17	24.3	...
21–40 cigarettes or 11 or more pipes or cigars	28	40.0	22	31.4	...
More than number shown	9	12.8	6	8.6	...
Unknown	1	1.4	2	2.9	...
Never smoked	1	1.4	15	21.4	...
Age (years) when smoking began	69	100.0	55	100.0	...
Under 16	34	49.3	21	38.2	...
16–19	13	18.8	9	16.4	...
20 or over	16	23.2	19	34.6	...
Unknown	6	8.7	6	10.9	...

Table 6. Observed and expected deaths of patients' relatives, by total, cancer, and lung cancer mortality

Patients' relatives	Total mortality		Cancer mortality		Lung cancer mortality	
	Observed	Expected	Observed	Expected	Observed	Expected
Fathers	39	36	6	5.4	2	2.7
Mothers	29	24.2	8	3.6	1	0
Brothers	23	22	9	8	4	6
Sisters	15	20.4	8	12	1	1.2
Total	106	102.6	31	29.0	8	9.9

cancer and also has been used to explain the peak in the age-specific lung cancer death rates in the 60- to 69-year age group. This peak in the age-specific death rates is present only in cross-sectional age-specific mortality curves, as indicated in this study. It disappears when cohort age-specific mortality curves are plotted, indicating an association of mortality from the disease with time. The percent distribution of smokers among patients and controls, by age group, also shows that a greater proportion of smokers began smoking earlier among the patients than among the controls.

Our study showed that the risk of developing lung cancer is 18.8 times greater among smokers than among nonsmokers. The amount of smoking was not considered. The data clearly showed that among those who smoked, patients smoked more cigarettes and in heavier quantities than the controls.

Among those who stated where they had purchased their tobacco, most patients and controls named the local store. No crossovers to other counties or neighboring States were reported.

In a previous mortality study (*13*), Asal and Lindeman had hypothesized that the low per capita sales of cigarettes in northeastern Oklahoma was an artifact influenced by the habit of purchasing cigarettes from Kansas, Missouri, or Arkansas, whose sales tax is less than Oklahoma's. In this study, the crossover hypothesis was refuted, but the legal implications of crossing over may have prevented the subjects from telling the truth about the place of purchase.

The expected total, cancer, and lung cancer mortalities for the patients' relatives were estimated by using the death rates for the controls' relatives as the standard. The expected number of deaths of the patients' relatives was then compared with the observed deaths. The subjects for whom cause of death was unknown were excluded from this tabulation. Since the total number of cases was small, the age factor was not considered; only the crude death rates for specific causes were used (table 6).

Deaths from all causes occurred more frequently than expected among the relatives of the patients except the sisters. Although the numbers were extremely small, the same pattern was observed for total cancer; that is, the relatives of the patients experienced more deaths than expected except among the sisters. The expected deaths from lung cancer were too few to evaluate.

For a large percentage of fathers and mothers of both the patients and controls year of birth was unknown. The distribution of the remaining fathers and mothers, by age, showed no unusual differences between patients and controls. Among the brothers and sisters, fewer unknown years of birth were reported. The siblings of the controls were older than those of the patients; most siblings were born before 1900.

There were 214 siblings in the families of the patients, excluding the patients; the average was three siblings per family. The controls reported 189 siblings, or an average of 2.7 siblings per family. No marked differences were found between the smoking history and lung cancer experience of relatives of the patients and controls.

Information was collected concerning current diseases or causes of death among the relatives of both the patients and controls. No unusual differences were noted except that the percentage of neoplasms was 11.4 among the mothers of the patients as compared with 4.3 percent among the mothers of the controls. Diseases of the circulatory system were present about twice as often among the mothers of the patients as among the mothers of the controls. The percentage of mothers with unknown disease reported was greater for the controls than for the patients.

The birth year of the blood relatives and the smoking histories of both patients and controls showed no unusual distribution. From the numerical distribution of total cancer mortality and lung cancer mortality among relatives of the controls, the expected mortality in the appropriate category among the patients was tabulated and compared with the observed mortality. Total mortality and cancer mortality increased among the fathers, mothers, and brothers of the patients but not among the sisters. No patients or controls reported consanguineous marriages of their parents or spouses.

Drawing definite conclusions concerning the influence of familial factors on mortality from lung cancer in northeastern Oklahoma is difficult. More data are needed. Perhaps a statewide study would be the ideal answer to the question of familial aggregation of the disease. From our study we can conclude that lung cancer does not aggregate in families, but there appears to be an effect in total cases of cancer.

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An epidemiologic study was conducted to explain the high mortality from lung cancer in northeastern Oklahoma. The descriptive phase of the study revealed that a high proportion (59 percent) of the diagnosed lung cancer cases was not histologically confirmed. Mortality rates also were higher than histologically confirmed incidence rates for 10 of the 12 counties as well as for all age groups.

The death rates for Craig County were 54.3, Creek 41.7, Hughes 22.7, Mayes 51.5, Muskogee 45.4, Nowata 61.4, Okfuskee 46.8, Okmulgee 42.4, Ottawa 57.0, Rogers 35.2, Tulsa, 32.9, Washington 37.9, and the total was 37.8.

The incidence rates were Craig 61.1, Creek 19.8, Hughes 0.0, Mayes 17.2, Muskogee 25.2, Nowata 20.5, Okfuskee 56.2, Okmulgee 22.6, Ottawa 16.8, Rogers 14.1, Tulsa 27.1, Washington 18.9, and total 25.1.

The death rates by age groups were 35–44 years 17.9, 45–54 years 51.9, 55–64 years 118.1, 65–74 years 185.0, 75 years and over 136.8, and the total was 85.9. The incidence rates by age groups were 35–44 years 10.7, 45–54 years 37.4, 55–64 years 97.7, 65–74 years 112.2, 75 years and over 58.6, and the total was 57.0.

In the second phase of the study, 69 of the 70 patients were smokers as opposed to 55 of 70 neighborhood controls. More patients (84.3 percent) than controls (62.9 percent) smoked cigarettes. The relative risk of disease development in carpenters was 3.3, glass factory workers 4.2, and artisans 2.2.

No crossover to other States for the purpose of purchasing tobacco was reported by any patients, controls, or their families. The findings of this study do not support the hypothesis that lung cancer aggregates in families. The findings from this study do emphasize, however, the need for a further statewide study of the epidemiology of lung cancer in Oklahoma.