

An Epidemiological Study of Lung Cancer in Asbestos Miners
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PLAINTIFF'S EXHIBIT

W-8

Reviewed by
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LITERATURE MATERIAL

Affirmative
Association:

1. Early literature refers to cancer cases which occurred simultaneously with asbestosis. In other words, reviewed those cases of asbestosis to find what percent of cancer (lung) occurred in this group.

2. Example:

Merewether (1954) 16.0%

Gloyme (1951) 14.1%

Reviews:

1. Hueper (1952) states 7-17% of cases of asbestosis, after 1 1/2 to 20 years latent period, develop lung cancer.
2. Hordasewski and Sorge - animal experiments - produced lung cancer in mice which were exposed to asbestos dust.

Negative:

1. Saunders (1939), found no cases of lung cancer among 620 cases of asbestosis he examined.
2. Holleb (1942), found the number of cases of asbestosis with lung cancer too small for statistical evaluation.
3. Wegelin (1947), in 126 x-rayed cases of asbestosis among 476, found no lung cancer associated in the group.

Mancuso:

Lung cancer occurs in asbestos workers with and without asbestosis. All studies were related to cases of lung cancer associated with asbestosis and when this simultaneous requirement occurs, it is usually a smaller percentage. The Wegelin study makes the assumption

that for lung cancer to occur, this would be only when asbestosis is present by x-ray evidence. This may or may not be true. Lung cancer can occur in these workers as a cause of death, without asbestosis as a secondary cause. By considering ~~only the simultaneous occurrence of lung cancer and asbestosis, the investigator is automatically excluding a large potential of deaths with no diagnosis of asbestosis, even though exposure and duration of exposure have been established.~~

Doll:

Doll (1955) studied records of men who worked for at least 20 years in exposed situations; found that in workers after 20 years of exposure, the risk is 10 times as great as general population (Found 61 cases of lung cancer-studied 113 men who had worked for 20 years or more.)

Mancuso:

In Doll's study, he excluded those who died from other causes, after shorter employment. It is evident that lung cancer cases could have occurred among employees with less than 20 years employment exposure, depending, of course, on what is found to be the minimum number of years exposure required and the latent period.

Braun:

Cites selective factor of Dr. Gloyne's series of 14.1% of autopsy cases saying these came as part of unusual group of lung cases to autopsy. Also cites percent of lung cancer at London Chest Hospital was 21.37%.

Mancuso:

This could very well relate to all the lung cancer cases which come to the hospital, like coming to Dr. Ochsner's Clinic, so this part of the criticism is valid. However, association of asbestosis with lung cancer is not a bias that exists by virtue of the Clinic-so observation of Gloyne is still an unusual and valid suggestive lead.

3. Lung Cancer in Asbestos Miners

Braun: Refers to Klotz : he found only 4 cases of lung cancer in 473 cases of asbestosis.

Mancuso: Initial observation in regard to the limitations of this interpretation still holds. Other cases could have occurred but not simultaneously. (The simultaneous requirement places a restrictive bias in a real situation.)

EPIDEMIOLOGICAL APPROACH - by Braun

Source of Data:

1. Braun used all persons who had been processed through the company clinic at Thetford Mines since 1947 in Quebec.
2. Established cohort, with total exposure of 5 or more years who were on employment rolls in 1950. The office force and non-exposed were not included.

Mancuso:

~~I question whether Braun is allowing sufficient number of years for latent period required for lung cancer.~~ If the cutoff date is 1955, then the cohort latent period is only being tested against a period of 11 years, 1945-1955; question whether there is enough of this population in the cohort with exposure of 10 years or more. For example, if they (the number of workers with 10 or more years exposure) represented only 20% of the cohort, the expectancy of lung cancer would definitely be diluted by the other 80%. The cohort followed through 1955, whether alive or dead, he states--all but a small number of these were accounted for as either living or dead." This was 133 out of 6,091. If the 133 were found and only 1 lung cancer recorded had occurred, the entire conclusion of the study would have been different. Certainly a very slight thread to draw such definite conclusions.

4. Lung Cancer in Asbestos Miners

Braun:

1. Through Office of Vital Statistics tabulated lung cancer rates by sex for years 1950-1955, inclusive.
2. Group policy coverage of one company studied for all cancers of lung and Braun states: "Very few not covered by this policy- and those who leave industry and are not covered, are a small number."

Mancuso:

How many? This may affect results. Braun states "few cases in which lung cancer is strongly suspected but not proved as the cause of death were considered separately."

Mancuso:

Deaths from lung cancer were determined from clinical records in the medical service of industry and checked by means of death certificates and the insurance company records. However, he refers to only the group insurance plan coverage of industry.

Braun:

Cohort-5,958, placed in three (3) categories according to increasing degrees of exposure based on weighted average of years, etc.

Mancuso:

Table 1-66% of cohort in 20-44 age group

Population weighted to the young age group will not show usual incidence of lung cancer found in the older age groups, therefore, rates of this group as a total for cancer will be low and biased, a dilution factor of considerable proportion. However, the age specific rates for 20-44, if higher than the control, would be significant. Again, however, one must determine how many in this group worked for 20 or more years, since this is probably the latent period, otherwise the rate becomes markedly diluted. The number of this group by the very nature of the ages, 20-44, would indicate that the number of workers of 20 or more years would be very small, too small to use statistically since the cohort was only followed for 11 years. How many were there with 11 or more years exposure in the age group of 20-44 comprising 66% of the total cohort?

5. Lung Cancer in Asbestos Miners

Mancuso:

Table 2. The number and percent distribution by length of employment showed only 30% with 20 years or more exposure; 70% less than 20 years. If it takes 20 or more years to develop lung then the dilution factor is 70%; the lung cancer rates should be based on the 30%. Even should we consider that 10 or more years are required then there is still 30% of the cohort which would not be included in the population when the rates are calculated. Materially, would increase the rates. Notice, however, in addition that the length of employment is not given by age groups. Could be as high as 50% in the age group with less than 10 years of employment. Don't know actual percent but represents a high dilution factor.

Mancuso:

Table 3. Exposure categories.

Again, in categories not related to the age groups like 20-44.

Mancuso:

Table 4. Smoking habits.

Not related to age groups. Definition of smokers-5 cigarettes a day. This is not the definition usually used which refers to a pack a day, etc.

Mancuso:

Table 5. Number of Cases.

Defined proved cases of lung cancer as "diagnosis suggested by autopsy, surgical section. Microscopic examination." "Suspected cases-3, diagnosis in doubt but evidence points to cancer."

Basic error here. In comparing this type of ~~proved cases~~ ~~criteria of autopsy, or surgical section, which does not apply to~~ ~~the control of the general population,~~ the rates for lung cancer in the control are derived from lung cancer as listed on the death certificates. There is ~~no indication that the same criteria are~~ ~~applied to the general control population.~~ Actually, this would be (impossible without reviewing all the lung cancer cases of the county)

re-establishing their entire clinical record. Secondly, the general population may not have same opportunity of medical care. This could work both ways, excludes other cases without such confirmation. Controls include both confirmed and nonconfirmed, usually nonconfirmed group is larger because of medical or available medical care.

Fraum:

In discussion states "If he uses the 3 suspected cases, Table 12 would be statistically significant."

Mancuso:

He goes on to analyze the 3 questionable cases because this makes the study so close to the significant level.

Mancuso:

Table 8. Lung Cancer Deaths by Age Groups.

There was only 1 case of the 9 proved cases in the 20-44 age group. Recall that this age group had 66% of the population of the cohort.

The rate for 20-44, per 100,000 more years of exposure, was only 4; and rate for 45-54 was 15. (Comprised 17% of cohort).

Rates are based on very small numbers, one each in 20-44 and 45-54. Cannot use total average rate of 25 because of marked dilution factor of age 20-44 rate of 4 which comprised 66% of population; must make age specific comparisons with the control.

Mancuso:

Table 9. Lung Cancer Deaths by Length of Employment.

~~Shows that only 1 proved case was found in the less than 20-year-length of employment and this group comprised 70% of the cohort.~~

The rates under 20 years length of employment were 7 per 100,000. This again dilutes total rate and lowers average rate to 25.

Note that the rates were high in 20-29 yrs. length of employment group which was 54, and the 30-39 yrs. length of employment was ⁴13/100,000 man employment years.

Fraum:

Discussion of 240 men over 40 years of age, followed for 6 years, did not develop lung cancer.

Braun: Table 10. Lung Cancer Deaths by Exposure Category

States rates do not increase by category of exposure. "Thus this is proof that asbestos is not a carcinogenic agent."

Mancuso: Categories, however, are not related to age distribution of the population; for example, 66% of population in the 20-44 age group. Do not know how much a contribution is made to these various categories, I, II and III. This may be the reason why the rates did not rise with category increase from I to III. ✓

Secondly, workers are so small, 2 cases in category III; the addition of 1 or 2 cases makes sizeable difference.

Mancuso: Table 11.

Categories I, II and III were comprised of 1,795 persons with employment only of 5-9 years and comprised 30% of cohort population; adding the 10-19 yrs. length of employment group gives 70% of the population. However, of these groups at least 66% must have been in age group 20-44; 1300 out of 1772 were in category III-from employment group less than 20 years; 1400 out of 2,150 were in category II; 1300 out of 2,000 in Category I. It is obvious that these categories are biased by contributions of different age groups and higher numbers under 20 years in these categories.

Therefore, one cannot use this approach because the categories are weighted by a larger number in the younger age group; even in category III which would be less likely to have cases of lung cancer occurring. Braun states "Average number of years of employment in each exposure category is almost identical." He does not take into consideration distribution by age group.

Braun.

Table 12.

States not a single case of lung cancer occurred in 1,265 non-smokers of both "proved" and "suspected" cases.

Tables 13, 14, 15.

States "With longer exposure average (2.3 ^{years} ~~yr~~ these smokers) and greater age (data does not show this) one would expect the non-smoking group to show a higher rate if lung cancer was due to asbestos."

Mancuso:

Actually he does not show in what ages these cases occur in the "smokers."

Braun:

Table 16, Comparison of Cohort Experience with Province of Quebec.

Gives -

Annual rate per 100,000

Province	22.5
Cohort	
(Excluding Asbestos workers)	
Total	33.8
Proved	25.3

Mancuso:

He gives no reason why the suspected cases should not be included. This would be statistically significant since same exclusion factors are not applied to the controls. Secondly, he feels that the general population is not studied as diligently as the miners and, therefore, the rate may be low in the control, implying that the difference, therefore, is not real.

The fact that the cohort did not necessarily show a progressive increase in these years is not a valid argument because variations occur depending upon the latent period; and recalling the 66% in younger age groups, one may find that in the next 10 years there would be a rise in lung cancer after the latent period is fulfilled.)

9. Lung Cancer in Asbestos Miners

Mancuso: Table 17.

Braun uses a classification of "primary" and "proven" as determining whether death certificate carried the inclusion of autopsy or surgery, etc. This is not a valid comparison. There not the same degree of accuracy in recording data on death certi

Braun: Table 13.

Gives comparison of actual and expected number of lung cancer deaths by age among asbestos miners.

Mancuso: First, Braun uses the 1954 and 1955 province rates rather than 1 years of actual study from which the population was studied. This had a higher rate, and with the control higher, it becomes less likely to pick up the difference in the cohort because of the small numbers involved. In the 65 years and over group, there were 5 older deaths compared to the expected of 2. He, however, points out and emphasizes that this includes 1 of the "suspected" cases to indicate what appears to be a suggestion of statistical evidence. He adds that "it is rather likely that the rate for the general population is understated in this age group for the obvious reason that the exact cause of death in the very old is not a matter of the same intensity of interest as it is in the younger person." This is not true. He expects to imply that the rate for this group would be higher in the control and, therefore, the differences observed by the cohort in this age group would not mean anything.

Braun: In Table 18, says members of cohort have not died from lung cancer at an age earlier than general population.

Mancuso: ~~What he has left out is,~~ that the cohort consists of 66% of age groups of 20-44, and 4,000 out of 5,700 have less than 20 years

10. Lung Cancer in Asbestos Miners

Mancuso: experience; so, if the 30-44 group did not have a sufficient latent period, they would not have lung cancers. Recall too that the cohort was followed only for 6 years. As to the comment about the 243 with more than 40 years of employment, this may be a selective factor with the hardy survivors. There is some question whether he really got all the miners who retired, those who left the area, etc.

Braun: Discussion-page 647.

Mancuso: Braun makes his case again on the total rates-all ages, 20.3 per 100,000 for Canada. Compares to 25.3 per 100,000 proven cases. The 33.3 for total cases included the suspected.

✓ |
Feel that Table 13, age suspected, tends to prove rather than disprove, particularly when recognizing that 66% of the cohort in 20- age group were in the 72% under 20 years exposure. Large population cohort without sufficient follow-up has automatically diluted the results. Actually by age specific rates, the controls are lower than the cohort study as it now stands. If cohort was followed longer this would show up more strikingly that limitation of time period of follow influences absence of cases.

Do not agree with statement he makes that "there are no important differences between the rates for asbestos miners and general population of Quebec and Canada."

Then proceeds to compare with United States rates which are higher. This is not valid because of marked industrialization in our country compared to Canada.

Braun: Page 648 of discussion.

Mancuso: Wow! Speculates that about 50,000 persons exposed throughout the world have 1,000,000 man years of exposure. Since only 150 cases reported in the literature, gives rate 15 per 100,000.

Mancuso:

(continued)

This is ridiculous because many cases of lung cancer never are reported in the literature simply because studies were not made in the asbestos plants. Example: United States reports in literature are not an accurate gauge as to what has or has not occurred as far as lung cancer is concerned.

Mancuso:

Table 22.

check
This table shows that lung cancer rate of the county in which the asbestos plants were located has rate 2 times the adjacent counties, 13.9 to 9.4. This is a valid comparison, certainly makes a better control. He has been using the Province of Quebec as a control which I believe includes Montreal which raises the overall rate of the control.

Brown:

Refers to additional cases not included in the cohort. For example the 9 deaths prior to the beginning of study due to lung cancer.

Mancuso:

Brown refers again to "at least 7 of 19 proved lung cancers were not accompanied by asbestosis." This is not the point about dealing only with the histologically proven cases. He should have used as a control, the age specific rates of the surrounding counties instead of the total Province which was weighted with other industrial areas, which raised the total rate of the control.

If he had compared with the adjoining counties on an age specific basis, it would have been statistically significant because the one county was already 2 times the rate of the adjoining county.

~~The case is too weak. Entire conclusion hinges on the addition of~~
~~cases. The conclusion is that the rate of lung cancer is~~
~~disproportionately high in the county in which the asbestos~~
~~plants are located. This is not a valid answer. The rate of lung cancer is~~
~~not significantly higher in the county in which the asbestos~~