Attributability in the Face of Uncertainty

*Philip E. Enterline, Ph.D.**

A frequent question asked of physicians in occupational medicine and in other specialties is whether, in their opinion, an individual with a particular disease or set of symptoms has this as the result of a particular occupational exposure. This situation usually arises when workman's compensation is involved or where legal suits are filed against employers and others for disease caused by employment with them or caused by use of their products. The purpose of this paper is to illustrate how epidemiologic data can be used to make statements about causality in a particular case. I will deal with the relationship between asbestos exposure and lung cancer, since this illustrates the methodology I wish to present and, in addition, permits me to draw upon a wealth of data now available about asbestos dust exposure and lung cancer.

The central problem is that the lung can respond in only a limited number of ways to external agents. Since such agents far outnumber these responses it is not always clear, given a specific response, what agent was involved. Diseases such as asbestosis, where the name of the disease specifies the etiology, may be notable exceptions. Even here, however, if (in the case of asbestosis) only the effects of the physical properties of fibers are responsible, some fiber other than asbestos might be etiologically important.

Where lung cancer is seen in an asbestos worker, or a person otherwise exposed to asbestos, it cannot be stated *with certainty* that a cause-effect relationship is present. To do so would imply that the asbestos exposure somehow blocked the possible effects of all other cancer-causing agents. On the other hand, some statements can be made, based on epidemiologic studies, as to the probability that a particular case was caused by this exposure.

Probability Statements

To illustrate how epidemiologic data may be used here, a number of years ago I studied a large group of men exposed to asbestos in connection with manufacturing asbestos products.[1] I found that they were dying from lung cancer at a rate of 64 per 100,000 per year; whereas, in the general population of males during the same period, the death rate for lung cancer was only 31 per 100,000 per year. Thus, it could be estimated from these data that for every 64 lung cancer cases among asbestos workers, 33 were due to the asbestos exposures and 31 were due to something else. For a given case of lung cancer in an asbestos worker, it could be stated *from this experience* that the odds were about 50-50 that it was caused by asbestos. That is, there was about a 50 percent probability that the case was caused by asbestos.

While the concept of probability is most often used in a predictive sense, there is nothing in this concept that specifies whether the events need to be future or past. There is, of course, a truth about past events; however, this can be just as unknown to an observer as the truth about future events.

Since these early observations on asbestos and cancer, we have learned about many additional factors that influence these probabilities. I think the most important of these are the time between the first exposure to asbestos and the appearance of lung cancer, and the intensity of the asbestos exposure. This is illustrated in Table 1. These data are taken from a study of 1,348 men who retired from the asbestos industry during the years 1941-67.[2] Shown are relative risks for lung cancer—that is, the ratio of lung cancer death rates in asbestos workers to comparable U.S. lung cancer death rates. For workers first exposed less than 20 years prior to death, and exposed at levels under 10mppcf, the relative risk was 1.2. This translates into the prediction that only about 1 in 6 or 17 percent of such lung cancer cases are due to asbestos exposure.† At the other extreme,

†Where the relative risk (RR) exceeds 1, this is calculated as Percent Pr $= \left(\frac{RR-1}{RR}\right)$ 100 due to asbestos exposure.

Table 1—*Relative Risk for Respiratory Cancer Among Retired Asbestos Workers*

Years Since First Exposure	Mean Dust Level	
	<10 mppcf	10 mppcf+
Under 20	1.2	3.1
20-29	1.8	3.6
30 or more	2.8	4.7

*Professor and Chairman, Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh.
Reprint requests: Dr. Enterline, 130 DeSoto Street, Pittsburgh 15261

men first exposed 30 years or more earlier and at levels in excess of 10 mppcf had a relative risk of 4.7. This translates into the prediction that 79 percent of such men have lung cancer because of asbestos exposure and, in an individual case, the probability of .79 or 79 percent that the cause was asbestos dust exposure.

Asbestos and Smoking

One rather surprising thing recently reported by Selikoff[3] on the basis of his study of 17,800 asbestos insulators in the United States and Canada is the fact that the relative risk of lung cancer for cigarette smokers exposed to asbestos is about the same as the relative risk for non-smokers.[3] In this sense, that is, on a relative scale, there apparently is no interaction. Earlier publications had suggested that in the absence of cigarette smoking, asbestos produced no increase in lung cancer.[4] Table 2 shows death rates observed among asbestos insulators during the years 1967-76. Men with and without a history of cigarette smoking are shown separately, and then death rates compared with their counterparts in the general population. For smokers and non-smokers alike, the relative risk associated with asbestos is roughly the same, between 4.4 and 4.9.

If we consider *only* the population of smokers and the population of non-smokers, then we can estimate from data in Table 2 the probability that asbestos caused lung cancer in an asbestos worker who smokes and in an asbestos worker who does not. For the population of smokers this probability is .79 or 79 percent, while for the population of non-smokers this probability is .77 or 77 percent. Thus, a smoking history does not appear to be an important piece of information in estimating the probability that asbestos exposure played a role in the occurrence of lung cancer in an individual case.

While this finding with regard to cigarette smoking seems a bit curious, it relates to an unusual property of asbestos that I've commented on previously—that is, its ability to multiply the effects of other carcinogens in the environment.[5] As seen in Table 2, asbestos exposure simply multiplied the death rates in smokers by 4.9 and in nonsmokers by 4.4. This curious property seems to explain the somewhat diverse findings observed in several epidemiologic investigations, but more importantly, it explains the rise in the importance of asbestos lung cancer throughout the world. When lung cancer was a rare disease, asbestos apparently acted simply to multiply the risk by some factor—say 4. A four-fold increase in a rare disease is likely to produce a rare disease. So, we didn't really see much lung cancer in asbestos workers until lung cancer became fairly common.

Table 2—*Lung Cancer Death Rates by Smoking History (Rates per 100,000 Per Year)*

Cigarette Smoking	Asbestos Insulators	U.S. Males*	Relative Risk
Yes	362.0	74.4	4.9
No	40.4	9.2	4.4

*Estimated by the American Cancer Soc (from Selikoff, 1978[3])

In summary, while in a given instance we cannot attribute an individual case of disease to a particular occupational exposure, we can, based on epidemiologic observations, make a statement as to the probability that a particular occupational exposure was the cause. Moreover, we can modify this probability by taking into consideration various aspects of a specific case. To illustrate this in the case of asbestos exposure and lung cancer I've mentioned two: time since first exposure, and the intensity of exposure, and there are others. Two factors that do not seem to effect these probabilities in the case of asbestos exposure are smoking history and the point in time about which we are talking. That is, the probability that for a given exposure a particular case of lung cancer was due to asbestos exposure is about the same for cigarette smokers as for noncigarette smokers, and is no different now than it was 10, 20, or 30 years ago.

Addendum

The interpretation of causal probability associated with two variables such as smoking and asbestos requires some clarification as to what is meant by causation, since here there is an absolute interaction between smoking and asbestos exposure. In calculating the probability (.794) that an asbestos worker with lung cancer who smoked had lung cancer as the result of asbestos exposures, for example, I have followed the traditional public health concept of a prior or predisposing condition which, if removed, would have prevented the disease. Clearly, however, smoking magnifies the effect of asbestos, and it can also be calculated for the same asbestos worker that the probability his lung cancer was due to smoking is .888. Moreover, it can be calculated, again for the same workers, that the probability that either smoking or asbestos exposure was responsible for his lung cancer is .975. The latter can be calculated as before, but with the relative risk calculated as the ratio of the death rate among asbestos insulators who smoke to the death rate for U.S. males who don't smoke:

$$RR = \frac{362.0}{9.2} = 39.3$$

The desired probability is therefore .975. If relative risks are actually independent of smoking and of

asbestos exposures (Table 2) this can also be calculated in a more conventional way:

$$P(S \text{ or } A) = P(S) + P(A) - P(S \text{ and } A)$$

While this requires an estimate of relative risks under the condition of independence, substituting the probabilities of .794 and .SSS gives a good approximation:

$$\begin{aligned} Pr &= .794 + .8SS - (.794)(.SSS) \\ &= .794 + .888 - .705 \\ &= .977 \end{aligned}$$

The second method is informative since it shows clearly the large interaction between asbestos exposure and smoking. For an asbestos worker with lung cancer who smoked cigarettes, the probability that both asbestos and cigarettes played a role is .705.

References

1 Enterline PE. Mortality among asbestos products workers in the United States. Ann NY Acad Sci 1965; 132:156-65

2 Enterline P. DeCoufle P, Henderson V. Respiratory cancer in relation to occupational exposures among retired asbestos workers. Br J Industr Med 1973; 30:01-05

3 Selikoff I. Testimony presented at OSHA generic cancer policy hearings, Washington, D.C., June 1, 1978

4 Hammond EC, Selikoff IJ. Relation of cigarette smoking to risk of death of asbestos-associated disease among insulation workers in the United States. *In* Biological effects of asbestos. Proceedings of a Working Conference held at the International Agency for Research on Cancer, Lyon, France, Oct. 2-6, 1972. Lyon: International Agency for Research on Cancer, 1973: 312-17

5 Enterline PE. Pitfalls in epidemiological research: an examination of the asbestos literature. J. Occupat Med 1976; 18:

STATE OF FLORIDA

COUNTY OF _____

AFFIDAVIT OF PHILIP E. ENTERLINE

PHILIP E. ENTERLINE being duly sworn deposes and says:

1. I reside at 37 St. Clair Drive, Pittsburgh, Pennsylvania 15228.

2. I am a Professor Emeritus of biostatistics at the University of Pittsburgh.

3. My field of specialty is biostatistics.

4. I have reviewed all the medical literature published on asbestos and cancer during the period 1934-1964.

5. In 1978, I prepared a book entitled Asbestos and Cancer which summarized that review.

6. That book was updated in 1980.

7. The review was conducted at the request of the Asbestos Information Association ("A.I.A.").

8. As part of this review, I read an article entitled "Experimental Studies of Asbestosis" published in the Archives of Industrial Hygiene and Occupational Medicine, Volume 3, dated 1951.

9. This article was authored by A. J. Vorwald, T.M. Durkin and P.C. Pratt ("Vorwald Article").

10. As a result of my review of the published literature, I concluded that in the United States there was a twenty-year lag in the acceptance of the causal connection between asbestos exposure and cancer.

11. I have recently reviewed a document entitled "Outline of Proposed Monograph on Asbestosis" written by Dr. Leroy Gardner ("Monograph Outline"). (A copy of which is attached as Exhibit 1.)

12. This Monograph Outline contained information not contained in the Vorwald article.

13. In his Monograph Outline, Dr. Gardner included his findings of an 81.8% tumor incidence in mice exposed to asbestos.

14. Dr. Gardner stated: The incidence rate of 81.8% is excessive." (Emphasis in the original)

15. Dr. Gardner's findings of an 81.8% tumor incidence was not reported in the Vorwald article.

16. I am not qualified as an experimental pathologist, toxocoligist or medical doctor, and therefore can offer no opinion about the design, conduct or scientific adequacy or inadequacy of the Gardner mice/cancer findings ("Monograph Outline").

17. It is my opinion that if the Gardner findings of an 81.8% tumor incidence in mice exposed to asbestos had been published in a reputable scientific journal, it would have accelerated in this country the acceptance of a casual relationship between asbestos and cancer.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

PHILIP E. ENTERLINE

Sworn to and Subscribed before me
this 7th day of March, 1991

NOTARY PUBLIC
STATE OF FLORIDA

My commission expires: Notary Public, State of Florida
My Commission Expires June 17, 1991