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Estimating Health Risks in Studies of the Health Effects of Asbestos[1,2]

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SUMMARY

Epidemiologic studies of respiratory cancer hazards associated with asbestos exposure in working populations should provide some estimate not only of whether an excess of cancer exists but of the magnitude of this excess. While most studies seem to be in agreement as to the existence of an excess, there is considerable disagreement as to its magnitude. For 11 studies, estimates of relative risk for respiratory cancer range from about 1.2 to 9.2. Four features of these 11 studies can be identified that account for some of the variation in results: some studies include workers whose exposure to asbestos was too recent to be likely to produce cancer by the end of the follow-up period, and results are diluted by the presence of these workers; in most studies, the wrong population was used for estimating expected numbers of deaths; in some studies, death certificates for the study population were corrected based on a review of other medical records, but then comparisons were made with expected deaths derived from uncorrected death certificates; finally, in most studies, level and duration of exposure is unknown, and this is clearly a factor that determines the magnitude of the respiratory cancer risk. For 6 of the 11 studies it was possible from published material to correct results roughly for the first 3 of these factors and much of the variation disappeared. Problems in the 11 studies reviewed here should be considered in planning and reporting on epidemiologic investigations in the future.

Asbestos represents an interesting environmental hazard in that it is apparently sufficient for the production of one disease (cancer), and both necessary and sufficient for that of another (asbestosis). That is, asbestosis is caused only by asbestos exposure, whereas cancer has many causes, one of which is apparently asbestos exposure. In the instance of asbestosis, a single case represents the health risk, whereas for cancer, the risk can be measured only in relation to all other risks. This paper is confined to a discussion of the problem of estimating cancer risks associated with asbestos, because it is here that there appear to be some methodologic difficulties in work that has been done to date.

When a number of agents contribute to a single disease, as for respiratory cancer, it is customary to measure the contribution of a single agent by calculating the ratio of the risk with the agent present to the risk with the agent absent. This calculation is illustrated in table 1, where death is the measure of risk. The relative risk can be estimated by calculating the ratio of the probability of dying among persons exposed to the agent of interest to the probability of dying among those not so exposed. This can also be expressed as the ratio of an observed number of deaths in an exposed population to an expected number based on the experience in a non-exposed population. There is also another way of measuring risk, and that is the absolute risk, i.e., the absolute difference between the two probabilities. Both of these measures are of interest in studies of the health effects of asbestos.

In 11 studies in the United States and Canada,

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TABLE 1

METHODS FOR CALCULATING EXCESS MORTALITY IN A PROSPECTIVE STUDY

	Dead	Not Dead	Total
Exposed	a	b	a+b
Not exposed	c	d	c+d
Total	a+c	b+d	N

$P_1 = \frac{a}{a+b}$ $P_0 = \frac{c}{c+d}$

Relative risk $= \frac{P_1}{P_0}$

Absolute risk $= P_1 - P_0$

the risk of developing respiratory cancer has been estimated in a prospective way among workers exposed to asbestos. These studies should provide some estimate not only of whether an excess in respiratory cancer exists but of the magnitude of this excess. The latest published results from these studies, summarized in table 2, are expressed as relative risks (1–14). Twelve studies are shown; however, my 1964 and 1967 reports relate to subgroupings from a single large cohort. All show an excess; however, the magnitude varies widely. At least 4 features of the published data account for this variation in results and, in a more general sense, can be regarded as problems in epidemiologic studies.

(1) Some studies included workers with a very low probability of developing asbestos-related cancer. These were workers whose exposure to asbestos was too recent to be likely to produce cancer by the end of the follow-up period. This can be labeled the latent period problem.

(2) In most studies, the wrong population was used for estimating the expected number of deaths, i.e., the probability (P_0) shown in table 1 of developing cancer in the absence of exposure to asbestos.

(3) In some studies, death certificates were corrected based on a review of other medical records; but comparisons then were made with expected deaths derived from uncorrected death certificates.

(4) In most studies, the level and duration of exposure were unknown, so that relative risks could not be related to levels and duration of exposure. Exposure levels and duration are clearly factors that determine the magnitude of the health risk associated with asbestos (10, 12).

The latent period problem can probably best be demonstrated by looking at the experience of a *population with a single exposure* that is now known to be cancer-inducing, e.g., the incidence of leukemia in the population near the hypocenter of the atomic bomb exploded at Hiroshima and Nagasaki (figure 1). Leukemia did not appear immediately, and, in fact, until 1948 few cases occurred. The peak year was 1951, after which the incidence declined.

The underlying distribution of cases of leukemia shown in figure 1 is probably the log normal distribution shown in figure 2. This illustrates how a single dose of asbestos may work. For the exposure intensity represented here, little cancer would be observed in the first 6 years. The maximal response and the highest relative risk after the single exposure would be observed between 18 and 24 years. Whether the risk would, in fact, decline 25 years or more after cessation

TABLE 2

RELATIVE RISKS FOR RESPIRATORY CANCER OBSERVED IN STUDIES OF WORKERS EXPOSED TO ASBESTOS

Reference	Date First Presented or Published	Population Studied	Relative Risk
BRAUN and Truan (1)	1958	Miners	1.5
DUNN and associates (2,3)	1959	Insulators	3.6
DUNN and Weir (3)			
MANCUSO and Coulter (4)	1963	Manufacturing	3.4
SELIKOFF and associates (5,6)	1963	Insulators	9.2
ENTERLINE (7)	1964	Manufacturing	2.3
ENTERLINE and Kenwick (8)	1967	Manufacturing	1.2, 1.3
COOPER and Balzer (9)	1969	Insulators	7.3
MCDONALD and associates (10,11)	1971	Miners	1.4
ENTERLINE and co-workers (12)	1972	Manufacturing	2.7
WAGONER and co-workers (13)	1972	Manufacturing	2.3
SELIKOFF and associates (14)	1972	Manufacturing	8.2
SELIKOFF and associates (16)	1972	Insulators	5.6

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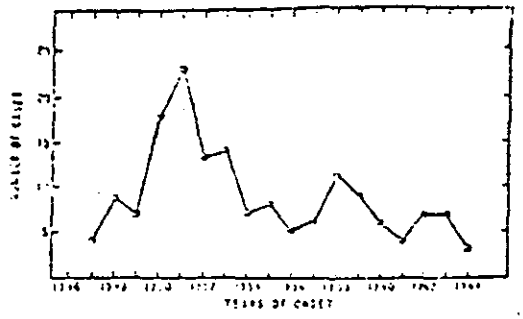

Fig. 1. Incidence of leukemia at Hiroshima and Nagasaki.

of exposure is conjectural. In the absence of any good epidemiologic observations on this, it will be assumed in this discussion that the lung clearance mechanism or selective factors are operative in such a way as to reduce the risk approximately as shown in figure 2. For a succession of doses—as for workers exposed continuously to asbestos (and in the absence of any interaction)—we might think of a succession of curves. The area to the left of the dotted line in figure 2 would probably be approximately as shown, whereas the area to the right probably would look somewhat different.

The point is that the relative risk observed is partly dependent on when the exposure took place in relation to the period in which follow-up studies were carried out. The studies shown in table 2 varied widely in this regard. For some, follow-up did not start until 20 years after exposure began. For others, follow-up began close to the time of first exposure to asbestos. Termination times and ages also differed. Clearly, results should differ, and statements as to the magnitude of the cancer risk associated with asbestos cannot be made without reference to some latent period and termination times.

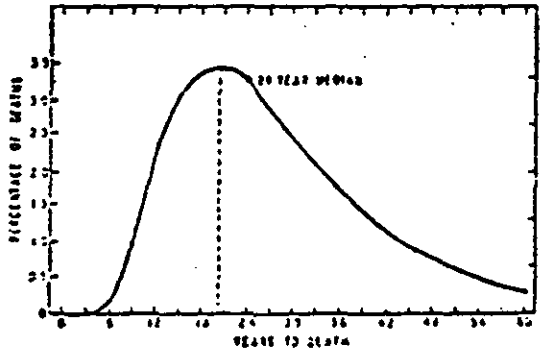

Fig. 2. Respiratory cancer resulting from a single exposure to asbestos.

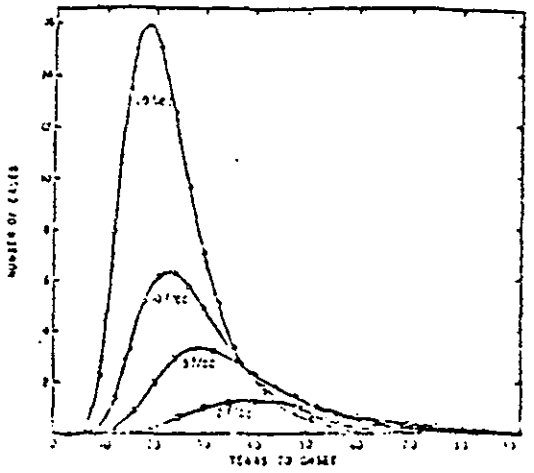

Fig. 3. Respiratory cancer resulting from single asbestos exposure at 4 levels.

The problem is further complicated by the probable relationship between the intensity of exposure and the length of the latent period. This is illustrated in figure 3, which shows a family of log normal curves corresponding to single-dose exposures at various intensities. Four assumptions were made in constructing these curves: (*1*) response to asbestos exposure is linear, (2) an intensity of 20 fibers per ml corresponds to a median latent period of 20 years, (*3*) response to a single dose has a log normal distribution with a geometric standard deviation of 1.5, and (*4*) latent period is related to the inverse cube root of dose. These assumptions are based on papers by Jones and Grindon (15), Albert and Altshuler (16), and available data on asbestos-exposed populations. From these data, the effects of applying various starting and stopping rules in epidemiologic studies can be estimated. A requirement for entry into a study of 20 years since first exposure would ensure missing nearly one half of the cases of respiratory cancer resulting from a very high exposure. Stopping follow-up at any point because of age or time limitations would also provide a misleading picture, a picture with a different kind of bias for each level of exposure. Obviously, follow-up must be stopped at some point, if only because all of the study population has died. This leads to the interesting notion that even if the relationship between asbestos and respiratory cancer is linear there is a kind of threshold limit value, defined as that dose for which the latent period exceeds the life span of man (15).

From this, it would appear that when exposure levels are uncertain, epidemiologic studies

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should probably include the experience of all workers, regardless of the number of years since first exposure; follow-up should continue for a very long time, and results should be reported in relation to the number of years since first exposure.

The second problem, that of using the wrong population for estimating the expected numbers of deaths, is illustrated by the data shown in table 3, derived from a study of retired asbestos workers (12). This shows the risk of dying from respiratory cancer 10 years after retirement during 2 time periods, 1941 to 1957 and 1958 to 1969. The risk of dying was nearly 3 times greater after 1957 than before 1957. There is no explanation for this insofar as the intensity of duration of exposure to asbestos is concerned. The reason seems to lie simply in what was happening in the general population during this period, i.e., a 3-fold increase in respiratory cancer mortality. Asbestos was apparently interacting with other causes of respiratory cancer, so that the effects of other factors increased the effect of asbestos.

Some data from an early study by Selikoff and associates (5) seem to show this quite well, and are given in table 4. The men in this study had all first been exposed 20 years earlier on entry to the cohort, and for each of the 4 time periods shown the population at risk was approximately the same size. Also, for men living in the 4 time periods shown, it's unlikely that exposure levels differed very greatly. One of the things that did change, however, was time, and with it, the effects of factors other than asbestos on incidence of respiratory cancer. Note that both observed and expected deaths increased at the same rate (a 3-fold increase in each case). There was also a 3-fold increase in the absolute risk associated with respiratory cancer. The relative risk, however, was unchanged. During this period, time multiplied the mortality rate by a factor of 3; asbestos, by a factor of 7. The combined effect

TABLE 3

RESPIRATORY CANCER DEATHS AND DEATH RATES AMONG MEN 65 TO 74 YEARS OF AGE

Study Period	No. of Deaths	Rate per 1,000 Persons
1941–1957	8	2.3
1958–1969	37	6.6

of time and asbestos, then, was approximately 21, i.e., 0.3 expected deaths in the period 1943 to 1947, and 13 observed deaths in the period 1963 to 1967. Asbestos apparently has the ability to multiply the effects of other agents in producing respiratory cancer. This has been observed by Berry and associates (17) with regard to asbestos and cigarette smoking.

The interaction between asbestos and other factors that cause respiratory cancer probably applies to geographic as well as temporal variations. Thus, the absolute lung cancer risk associated with asbestos exposure would be higher in an area with a high lung cancer death rate than in an area with a low lung cancer death rate. The relative risk would probably be the same, however. In nearly all U.S. studies, the expected number of deaths from respiratory cancer was based on the level of mortality that characterized the entire United States, rather than the local area in which the asbestos workers lived. The result was that the relative risk observed was directly related to the local death rate for respiratory cancer. This relationship is shown in figure 4 for 6 studies in which men whose first exposure occurred 20 years previously were followed, i.e., where the latent periods are roughly comparable on entry to the study. As might be expected, this shows that if asbestos interacts with other factors that cause lung cancer, and if local death rates are ignored in calculating expected deaths, when the local death rate is

TABLE 4

RELATIVE AND ABSOLUTE RISKS FROM RESPIRATORY CANCER*

Study Period	Observed	Expected	Relative Risk	Absolute Risk (rate/1,000 persons)
1943–1947	6	0.8	7.5	2.6
1948–1952	8	1.4	5.7	3.3
1953–1957	13	2.0	6.5	5.5
1953–1962	18	2.4	7.5	7.8

*Data from Selikoff and associates (5).

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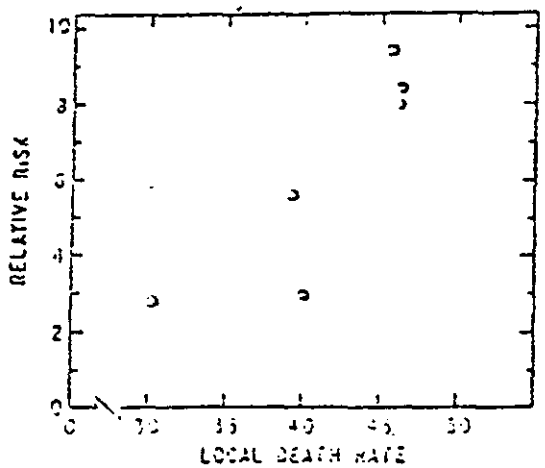

Fig. 4. Relative risk for respiratory cancer and local death rates in 6 studies.

high, the relative risk is high; when the local death rate is low, the calculated relative risk is low. If local rates of respiratory cancer death, rather than the U.S. death rate, had been used in calculating the expected deaths, variation in relative risk due to variation in local death rates would have been eliminated.

The third problem is that in most studies, cause-of-death statements on death certificates were corrected by checking hospital records, pathologic reports of biopsies and autopsies, and coroners' reports. In some cases, data on respiratory cancer were published both as they were recorded on death certificates and as corrected, and these show that corrected death certificates produce larger numbers of respiratory cancer deaths than uncorrected death certificates. A comparable correction cannot be made, however, for calculating the expected death rate. As a result, some of the published comparisons between observed and expected deaths are also comparisons between corrected and uncorrected death certificates, and this inflates the relative risk.

The relative risks, with the death certificate correction removed, are shown in table 5. The table includes data from 6 studies for which latent periods were roughly comparable. For the studies by Selikoff and coworkers, observed lung cancer deaths were reduced by multiplying by 0.575, based on a reported correction for their U.S. Insulation Workers Study, and pleural mesothelioma deaths by a factor of 0.133, based on a study by Ducic (18, 19). The first column of figures in table 5 shows relative risks as calculated from published reports. The second column shows the relative risks that would have been calculated if death certificates had not been corrected. The last column estimates the relative risks that would have been observed if, in addition, local, rather than national, death rates had been used in calculating expected deaths. These adjustments bring the findings from the various studies much closer together.

Finally, some of the variation in the relative risk for respiratory cancer among studies is undoubtedly due to differing exposure levels. As shown in figure 3, studies that include only workers with 20 years since first exposure would result in higher relative risks than studies in which workers were included with shorter times since first exposure, owing to fulfillment of latent period requirements—particularly at lower dose levels. In addition, however, relative risks would be higher because of the longer period of exposure and, thus, the larger dose. Intensity of exposure appears to make an additional but independent contribution. The latter is illustrated in table 6. These data are based on the retired population of asbestos workers mentioned earlier; relative risks are shown by number of years since first exposure at time of entry to the cohort (time of retirement) and average exposure levels during work. Both factors clearly contributed to the respiratory cancer risk. Actually, 3, rather than 2, factors were probably operating here: latent pe-

TABLE 5

RELATIVE RISKS AND CORRECTED RELATIVE RISKS FOR RESPIRATORY CANCER FOR 6 STUDIES, 20 YEARS AT ENTRY SINCE FIRST EXPOSURE

Reference	Relative Risk	Death Certificate Corrected	Death Rate Corrected
Selikoff (6)	9.2	7.6	6.2
Enterline	3.0	3.0	2.9
Cooper (9)	7.8	7.8	6.7
Wagoner (13)	2.8	2.8	2.6
Selikoff (14)	6.2	6.8	5.5
Selikoff (15)	5.8	4.7	4.7

TABLE 6

RELATIVE RISK FOR RESPIRATORY CANCER AMONG RETIRED ASBESTOS WORKERS

Time Since First Exposure (years)	Mean Dust Level	
	< 10 mppcf	> 10 mppcf
< 20	1.2	3.1
20–29	1.8	3.6
≥ 30	2.8	4.7

riod, dose expressed as time, and dose expressed as intensity. Thus far, the effects of the first 2 have been impossible to separate.

References

1. Braun, D. C., and Truan, T. D.: An epidemiological study of lung cancer in asbestos miners, AMA Arch Ind Health, 1958, *17*, 634.
2. Dunn, J. E., Linden, G., and Breslow, L.: Lung cancer mortality of men in certain occupations in California, Am J Public Health, 1960, *50*, 1475.
3. Dunn, J. E., and Weir, J. M.: Cancer experience of several occupational groups followed prospectively, Am J Public Health, 1965, *55*, 1367.
4. Mancuso, T. F., and Coulter, E. J.: Methodology in industrial health studies, Arch Environ Health, 1963, *6*, 210.
5. Selikoff, I. J., Churg, J., and Hammond, E. C.: Asbestos exposure and neoplasia, JAMA, 1964, *188*, 22.
6. Selikoff, I. J., Hammond, E. C., and Seidman, H.: Cancer risk of insulation workers in the United States, in *Proceedings of IARC Working Group to Review the Biological Effects of Asbestos, Lyon, France, 1972*, International Agency for Research on Cancer, Lyon, 1973, p. 209.
7. Enterline, P. E.: Mortality among asbestos products workers in the United States, Ann NY Acad Sci, 1965, *132*, 156.
8. Enterline, P. E., and Kendrick, M. A.: Asbestos-dust exposures at various levels and mortality, Arch Environ Health, 1967, *15*, 131.
9. Cooper, W. C., and Balter, J. L.: Evaluation and control of asbestos exposures in the insulating trade, in *Proceedings of a Working Conference on the Biological Effects of Asbestos*, Dresden, Germany, 1963.
10. McDonald, J. C., McDonald, A. D., Gibbs, G. W., Siemiatycki, J., and Rossiter, C. E.: Mortality in the chrysotile asbestos mines and mills of Quebec, Arch Environ Health, 1971, *22*, 677.
11. McDonald, J. C., Becklake, M. R., Gibbs, G. W., McDonald, A. D., and Rossiter, C. E.: The health of chrysotile asbestos mine and mill workers of Quebec, Arch Environ Health, 1974, *28*, 61.
12. Enterline, P. E., Decouflé, P., and Henderson, V.: Respiratory cancer in relation to occupational exposure among retired asbestos workers, Br J Ind Med, 1973, *30*, 162.
13. Wagoner, J. K., Johnson, W. M., and Lemen, R.: Malignant and nonmalignant respiratory disease mortality patterns among asbestos production workers, in *Congressional Record-Senate Proceedings and Debates of the 93rd Congress, First Session*, vol. 119, pt. 5, March 14, 1973, U.S. Gov't. Printing Office, Washington, D. C., p. 7328.
14. Selikoff, I. J., Hammond, E. C., and Churg, J.: Carcinogenicity of amosite asbestos, Arch Environ Health, 1972, *25*, 183.
15. Jones, H. B., and Grindon, A.: Environmental factors in the origin of cancer and estimation of the possible hazard to man, Fed Cosmet Toxicol, 1975, *18*, 231.
16. Albert, R. E., and Altshuler, B.: Considerations relating to the formulation of limits for unavoidable population exposures to environmental carcinogens, in *Radionuclide Carcinogenesis*, J. E. Ballou, R. H. Busch, D.-D. Mahlum, and C. L. Sanders, ed., AEC Symposium Series, CONF-72030, NTIS, Springfield, Va., 1973, p. 233.
17. Berry, G., Newhouse, M. L., and Turok, M.: Combined effects of asbestos exposure and smoking on mortality from lung cancer in factory workers, Lancet, 1972, *2*, 276.
18. Rossiter, C. E.: Discussion summary, in *Proceedings of the IARC Working Group to Review the Biological Effects of Asbestos, Lyon, France, 1972*, International Agency for Research on Cancer, Lyon, 1973.
19. Ducić, S.: L'exactitude des causes de décès : une comparaison avec les diagnostiques a l'autopsie dans une serie de mesotheliomes et autres tumeurs malignes du poumon, Can J Pub Health, 1971, *62*, 395.

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