H. A. ESCHENBACH

6/7/84

JUN 8 1984

To: J. W. Wolter

F.Y.I.

Harry

10002209

Declining Relative Risks for Lung Cancer After Cessation of Asbestos Exposure

Alexander M. Walker, M.D., Dr. P.H.

All studies that provide follow-up information for workers more than 35 years after initial exposure to asbestos show a declining ratio of observed to expected lung cancer deaths at the end of follow-up. The most parsimonious explanation of this finding is that relative risk for lung cancer begins to decline sometime after cessation of asbestos exposure.

The ratio of observed to expected lung cancer deaths among North American insulation workers studied by Selikoff et al[1] peaked 30 to 34 years after first employment and declined by about 10% in each succeeding quinquennium. This phenomenon was interpreted recently[2] as possibly resulting from a biologic process of progressively diminishing relative risk for lung cancer following termination of asbestos exposure through retirement. From detailed mathematical review of the time course of disease risk in Quebec miners, Thomas[3] has furthermore derived models of incidence that imply an eventual diminution of relative risk for lung cancer in workers who have ceased asbestos exposure. Since the problem of future lung cancer incidence in asbestos-exposed workers will affect workers, regulators, and industry at least through the remainder of this century, there is an important need to document as thoroughly as possible the late effects of asbestos exposure. What follows is a review of published observations on very-long-term follow-up of asbestos-exposed workers, with the goal of summarizing what is known about the late evolution of lung cancer risk.

Evolution of Risk After Short-term Exposure

The follow-up of 820 workers in a New Jersey amosite asbestos factory by Seidman et al[4,5] provides the clearest and most often cited evidence on disease evolution. These men were employed principally for short periods during World War II, and were not, in general, career asbestos workers. Death certificates were obtained for all 528 decedents through the end of 1976; for 78% of the deaths additional pathological or clinical information was used to supplement the death certificate diagnosis. Table 1 gives the progression of the observed lung cancer risk as originally presented by Seidman et al and as reexpressed for the present analysis. (The methods employed for the reexpression are given in the footnote to Table 1.) With the exception of the period 20 to 24 years after the onset of work, the observed-to-expected (O/E) ratio shows a pattern of monotonic increase to a peak (at 15 to 19 years) and monotonic decline thereafter.

In fact, the data of Table 1 represent the superposition of a collection of events seen in subcohorts defined by age at onset of work and by duration of employment. As seen in Table 2, also from Seidman et al,[5] in every subcohort there is a decline in the O/E ratio over the last two periods of observation. The peaks, as noted by the original authors, come earlier for those of older ages at start of work. The numbers of deaths observed for each subcohort are small, and no single one could be viewed as providing much useful information; however, on a null hypothesis of no expected change in the O/E ratio between the last two time intervals, the probability of observing a decline in all six instances is $(1/2)^6$, i.e., $p = .02$.

Risk as a Function of Time Since First Employment

When date of termination of asbestos exposure is not available, some inferences can be made about the evolution of risk from data on time since first exposure. Very long times after first employment, i.e., times approaching or after retirement, are unlikely to be associated with heavy concurrent asbestos exposure for two reasons: many such workers will have retired and, for the remainder, exposure will have taken place in the comparatively recent past, under improved dust control conditions. By far the richest source for this kind of data is the analysis of deaths in the 10 years beginning Jan. 1, 1967, among 17,800 North

From the Unit of Analytical Epidemiology, Division of Epidemiology & Biostatistics, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, Lyon, France.

Table 1 – Observed and Expected Cumulative Probabilities of Death From Lung Cancer Five Through 35 Elapsed Years Since Onset of Work in an Amosite Asbestos Factory 1941-1945, by Length of Time Worked in 820 Men Followed for at Least Five Years*

	Elapsed No. of Years Since Onset of Work					
	5-10	5-15	5-20	5-25	5-30	5-35
	Original Data					
Observed %†	0.25(2)	1.84(15)	4.43(36)	6.41(52)	9.13(74)	11.92(93)
Expected %‡	0.21	0.53	0.95	1.47	2.09	2.82
	5-9§	10-14	15-19	20-24	25-29	30-34
	Transformed to Discrete Intervals					
Observed No.‖	2	13	21	16	22	19
Expected No.¶	1.68	2.62	3.41	4.20	5.01	4.97
O/E#	1.19	4.97	6.17	3.81	4.39	3.82

* Data from Seidman et al,[5] Table 7A
† Observed numbers of deaths shown in parentheses (attribution of death to lung cancer is based on review of all available evidence)
‡ Expectation based on age- and year-specific death rates for New Jersey white males, as routinely obtained from death certificates and census data
§ Intervals assumed to be five years in length and relabeled accordingly
‖ Taken as successive differences in observed cumulative counts
¶ Ratio of observed to O/E
# Taken as the ratio of successive differences in the cumulative observed % and expected % given in "Original Data" section

American insulation workers carried out by Selikoff et al,[1] who identified 2,271 deaths by death certificate, with further clinical data on 86% of these. There are also four smaller cohorts with onset of exposure sufficiently far in the past to have allowed some analysis of O/E ratios 35 years or more after onset of exposure. Data have been reported for two of these cohorts by Nicholson et al.[6] The first consisted of 544 men in Quebec who in 1961 had been employed for at least 20 years in one of four companies mining or milling chrysotile asbestos in Thetford Mines. In this group all individuals were eventually traced; death certificates were obtained on 97% of the 178 decedents and hospital records for 73%. The second was a factory cohort of men who in 1959 had been employed for at least 20 years and whose experience has so far been presented in only a summary fashion. Selikoff et al[7] ascertained the vital status of all 632 men registered in two New York-New Jersey union locals of insulation workers through the end of 1976, with cause of death abstracted from death certificates of the 478 who had died. Some of these men are members of the larger insulation workers cohort described above. Weill[8] and co-workers have reported the experience of 6,328 men working in two asbestos cement plants in New Orleans, with date of employment at least 10 years prior to the close of follow-up in 1974. Data discussed below are for the portion of that cohort with at least 100 million-particles-per-cubic-foot-years of exposure.

Results from these four cohorts are given in Table 3. Each, like the amosite asbestos factory workers described in Tables 1 and 2, shows a late decline in the O/E ratio. From the point of view of statistical stability, the insulation workers' study is overwhelmingly the most important, but the presence of the same finding in each of the other cohorts suggests that the results of Selikoff et al[1,7] are not simply the product of an unspecified underlying bias.

Models of Temporal Variables

Thomas[3] has analyzed data on 223 lung cancer cases and a matched sample of 669 noncases from an historical cohort study of 10,939 males that covered every man born between 1891 and 1920 and employed in the Quebec chrysotile asbestos mining and milling industry.[9] Thomas used a variety of methods to model the combined effects of asbestos exposure, smoking, and variables related to time: age at risk (i.e., age at the various follow-up times examined), average age at exposure, average interval from exposure to time at risk, and duration of exposure.

Thomas' models revealed phenomena similar to the ones noted above but in the form of parametric estimates of temporal effect. In a linear relative risk model, increases in the average interval between exposure and follow-up time decreased the apparent effect of a given cumulative asbestos exposure on lung cancer risk, as did increasing age at follow-up. When further adjusted for smoking patterns, these effects led to a steady increase in the estimated lung cancer relative risk associated with a given total asbestos exposure up through age 64, and an abrupt decline thereafter. When a time course of the effect of asbestos on lung cancer risk was parameterized directly, the maximum risk after a given asbestos exposure was estimated to occur at 16 years following exposure, on the average, with high doses being associated with shorter and low doses with longer intervals. An equivalent result appeared when the disease model was based on the multistage theory of carcinogenesis[10]: maximum likelihood estimates indicated that asbestos operated at a late stage of lung carcinogenesis, which implies that the recency of exposure is a strong determinant of risk and that

Table 2 — Ratio of Observed to Expected Probabilities of Death From Lung Cancer in 10-Year Periods Starting at Five-, 15-, and 25-Year Points After Onset of Work in an Amosite Asbestos Factory, 1941-1945, by Age at Onset of Work and Whether Worked <9 or 9+ Months*

Months Worked	Age at Onset of Work, yr	Elapsed No. of Years Since Onset of Work		
		5-14	15-24	25-34
<9	15-24	0.00† (0/0.02)‡	6.85 (1/0.15)	2.73 (2/0.73)
	25-34	0.00 (0/0.14)	4.27 (3/0.70)	4.03 (6/1.49)
	35-44	3.75 (2/0.53)	2.91 (4/1.37)	... ...
	45-54	0.00 (0/1.11)	... ...	... ...
9+	15-24	0.00 (0/0.02)	19.07 (2/0.10)	13.13 (6/0.46)
	25-34	0.00 (0/0.09)	11.45 (5/0.44)	7.41 (8/1.08)
	35-44	11.94 (4/0.34)	5.62 (5/0.89)	... ...
	45-54	9.93 (8/0.81)	... ...	... ...

* From Seidman et al,[5] Table 11, rearranged and relabeled
† Ratio of observed to expected (see footnotes to Table 1)
‡ Number of deaths observed/number of deaths expected (expected death derived from reported observed divided by reported O/E ratio, except when that ratio was 0.00, in which case the reported expected percent was multiplied by the number of men at risk)

exposures in the distant past should have a diminishing, although never negligible, influence on current risk.

Implications

A decline in relative risk for lung cancer resulting from cessation of asbestos exposure is the most parsimonious interpretation of the data reviewed here. This is analogous to the reduction in lung cancer relative risk noted after the termination of cigarette smoking,[11] although the decline is slower and less dramatic after the presumed elimination of asbestos exposure. Declining carcinogenic potential with the passage of time is consistent with the clearance or encapsulation of asbestos fibers in the lung, processes whose completeness and rapidity are very likely to be affected by particle dimensions and, thus, will vary according to fiber type.[12]

A late decline in the O/E ratio attributable to previous asbestos exposure is inconsistent with the often noted linearity of the standardized mortality ratio for lung cancer as a function of accumulated dose.[9,13-18] One resolution may lie with the diminished time to onset of risk with increasing age, shown in Table 2. Age is in general a very strong correlate of accumulated dose. As continuously exposed persons age, their current risk reflects a more than proportionate accumulation of risk, due to increasingly short latent periods. Thus a diminished effect of exposures in the distant past is compensated for by the accelerated appearance of risk from recent exposure. A rising O/E ratio with accumulated dose during working years would then reflect partly an age-exposure interaction and only partly a summation of effects of past exposure.

There are a variety of possible extraphysiologic explanations for a decline in the O/E with very long follow-up. Elderly cases may be poorly ascertained. However, of the studies cited here, diagnosis was ascertained on the basis

Table 3 — Changes in the Ratio of Observed to Expected Deaths With Time Since First Employment in Four Cohort Studies

Years Since Initial Exposure	North American Insulators*		Quebec Miners and Millers†		Factory Workers‡		New York-New Jersey Insulators§		Asbestos Cement Workers‖	
10-	2.55	(7)¶	...	...	...	...	0.00	(0)	0.77	(1)
15-	3.40	(29)	...	...	...	...	...	...	1.25	(3)
20-	3.48	(59)	0.00	(0)	2.38	(4)	8.67	(26)	1.54	(6)
25-	5.00	(105)	...	...	...	...	...	...	2.33	(7)
30-	6.08	(112)	1.94	(7)	3.73	(23)	...	...	3.33	(5)
35-	5.68	(65)	...	...	...	...	6.63	(67)	3.08	(4)
40-	4.93	(40)	4.19	(16)	1.37	(6)	...	...	...	...
45-	3.89	(69)	...	...	...	...	...	...	...	...
50+	...	...	1.67	(5)	...	...	...	...	...	...
Total No. of Deaths	...	(486)	...	(28)	...	(33)	...	(93)	...	(26)

* Data from Selikoff et al,[1] Table 5
† Data from Nicholson et al,[6] Table 7
‡ Data from Nicholson et al,[6] Table 9
§ Data from Selikoff et al,[7] Table 4
‖ Data from Weill et al,[8] Table 3
¶ Number of deaths given in parentheses

of the least information in the asbestos cement workers,[7] the cohort showing the smallest drop in Table 3, and the group in which ascertainment bias would be expected to make the decline most pronounced. Exposure to asbestos might be hypothesized to have been substantially lower in the 1920s and 1930s than during subsequent years for persons in similar occupations, so that workers reaching 35 years or more since first employment in the 1970s would have had lower total exposures than younger cohorts with shorter durations of exposure. However, detailed reviews of historical exposure patterns in British[15,19] and American[20] factories suggest that conditions improved rather than deteriorated in the decades following 1930, and studies of chrysotile mines and mills in Quebec[21] have indicated amelioration of dust levels at least since the late 1940s. Peto et al's[22] analysis of exposure histories in Los Angeles mesothelioma cases furthermore suggested no temporal trends between 1922 and 1946 in exposure intensity among persons presumably using asbestos, although the data are consistent with diminished intensity of exposure both before 1922 and after 1946. Together these reports make an hypothesis of low cumulative exposure among older workers unattractive. They do however suggest that cessation of exposure is not an all-or-none phenomenon, but rather has been taking place in continuously exposed workers for several decades.

Changes in the prevalence of smoking may have affected the reported figures. Successive birth cohorts of U.S. males from 1881 to 1920 showed progressively higher peak prevalences of smoking,[23] so that the oldest worker populations reported may well have lower smoking rates than the younger cohorts; in every cohort, the smoking rate declines after reaching a peak in middle-aged men. However, to the extent that asbestos-exposed workers track the general population in their smoking habits, changes in smoking pattern should enter into the denominator of the O/E ratio. The ratio itself should be unaffected, provided that a multiplicative joint effect of smoking and asbestos exposure on lung cancer rates[24] actually holds.

Is the decline in the O/E ratio due simply to the early death of essentially all smokers in asbestos-exposed cohorts?[7] The published data are too sparse for us to be sure. Given the very high mortality rates in smoking asbestos workers,[24,25] such an effect would be plausible for former workers of retirement age; chance would have to be invoked rather than depletion of the populations at risk to account for drops in the O/E ratio among workers in the 40- to 60-year age range, as observed in the youngest of the amosite cohorts.[5] From the point of view of prognostication of the future experience of once heavily exposed workers,[2,26-30] the question may be unimportant: the decline is present, and little matter what its origin. A more final judgment as regards the mechanism of carcinogenesis implied by these observations may depend on further analysis of data that fortunately are already in hand.

Acknowledgment

Drs. N. Day and L. Simonato provided valuable advice in the development of this report.

References

1. Selikoff IJ, Hammond EC, Seidman H: Latency of asbestos disease among insulation workers in the United States and Canada. *Cancer* 46:2736-2740, 1980.

2. Walker AM, Loughlin JE, Friedland ER, et al: Projections of asbestos-related disease 1980-2009. *J Occup Med* 25:409-425, 1983.

3. Thomas DC: Statistical methods for analyzing effects of temporal patterns of exposure on cancer risks. *Scand J Work Environ Health* 9:353-366, 1983.

4. Seidman H, Lilis R, Selikoff IJ: Short-term asbestos exposure and delayed cancer risk, in H.E. Niebergs (Ed.): Proceedings of the Third International Symposium on Detection and Prevention of Cancer. New York: Marcel Dekker, Inc., pt. 1, vol. 1, 1977, pp 943-960.

5. Seidman H, Selikoff IJ, Hammond EC: Short term asbestos work exposure and long term observation. *Ann NY Acad Sci* 330: 61-89, 1979.

6. Nicholson WJ, Selikoff IJ, Seidman H, et al: Long term mortality experience of chrysotile miners in Thetford Mines, Quebec. *Ann NY Acad Sci* 330:11-21, 1979.

7. Selikoff IJ, Hammond EC, Seidman H: Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann NY Acad Sci* 330:91-116, 1979.

8. Weill H, Hughes J, Waggenspack C: Influence of dose and fiber type on respiratory malignancy risks in asbestos cement manufacturing. *Am Rev Respir Dis* 120:345-354, 1979.

9. McDonald JC, Liddell FDK, Gibbs GW, et al: Dust exposure and mortality in chrysotile mining, 1910-1975. *Br J Ind Med* 37: 11-24, 1980.

10. Armitage P, Doll R: The age distribution of cancer and a multi-stage theory of carcinogenesis. *Br J Cancer* 8:1-12, 1954.

11. Doll R, Peto R: Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health* 32:303-313, 1976.

12. Morgan A, Holmes A: Concentrations and dimensions of coated and uncoated asbestos fibres in the human lung. *Br J Ind Med* 37:25-32, 1980.

13. Enterline PE, Henderson V: Type of asbestos and respiratory cancer in the asbestos industry. *Arch Environ Health* 27:312-317, 1973.

14. Peto J, Doll R, Howard SV, et al: A mortality study among workers in an English asbestos factory. *Br J Ind Med* 34:169-173, 1977.

15. Newhouse M, Berry G: Patterns of mortality in asbestos factory workers in London. *Ann NY Acad Sci* 330:53-60, 1979.

16. Berry G: Dose-response in case-control studies. *J Epidemiol Community Health* 34:217-222, 1980.

17. Dement JM, Harris RL, Symons MJ, et al: Estimates of dose-response for respiratory cancer among chrysotile asbestos textile workers. *Ann Occup Hyg* 26:869-887, 1982.

18. Dement JM, Harris RL, Symons MJ, et al: Exposures and mortality among chrysotile asbestos worker: Part II. Mortality. *Am J Ind Med* 4:421-433, 1983.

19. Skidmore JW, Dufficy BL: Environmental history of a factory producing friction material. *Br J Ind Med* 40:8-12, 1983.

20. Dement JM, Harris RL, Symons JM et al: Exposures and mortality among chrysotile asbestos workers: Part I. Exposure estimates. *Am J Ind Med* 4:399-419, 1983.

21. Gibbs GW, Lachance M: Dust exposure in the chrysotile asbestos mines and mills of Quebec. *Arch Environ Health* 24:189-197, 1972.

22. Peto J, Henderson B, Pike MC: Trends in mesothelioma incidence in the United States and the forecast epidemic due to asbestos exposure during World War II, in Peto R, Schneiderman M (Eds.): Quantification of Occupational Cancer, Banbury report 9. Cold Spring Harbor Laboratory, Cold Sping Harbor, N.Y.: 1981, pp 51-69.

23. Harris JE: Cigarette smoking among successive birth cohorts of men and women in the United States during 1900-1980. *J Natl Cancer Inst* 71:473-479, 1983.

24. Saracci R: Asbestos and lung cancer: An analysis of the epidemiological evidence for the asbestos-smoking interaction. *Int J Cancer* 20:323-331, 1977.

25. Selikoff IJ, Seidman H, Hammong EC: Mortality effects of cigarette smoking among amosite asbestos factory workers. *J Natl Cancer Inst* 65:507-513, 1980.

26. Hogan MD, Hoel DG: Estimated cancer risk associated with occupational asbestos exposure. *Risk Analysis* 1:67-76, 1981.

27. Enterline PE: Proportion of cancer due to exposure to asbestos. in Peto R, Schneiderman M (Eds.): Quantification of Occupational Cancer, Banbury report 9. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.: pp 19-36.

28. Blot WJ, Fraumeni JF: Cancer among shipyard workers, in Peto R, Schneiderman M (Eds.): Quantification of Occupational Cancer, Banbury report 9 Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.: pp 37-49.

29. Nicholson WJ, Perkel G, Selikoff IJ, et al. Cancer from occupational asbestos exposure: Projections 1980-2000, in Peto R, Schneiderman (Eds.): Quantification of Occupational Cancer, Banbury report 9. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.: pp 87-111.

30. Nicholson WJ, Perkel G, Selikoff IJ: Occupational exposure to asbestos: Population at risk and projected mortality - 1980-2030. *Am J Ind Med* 3:259-311, 1982.

Outcasts in Our Culture

When we deal with the impaired we always do so patronizingly. We treat the dwarf as a child because of his smallness; we ask the blind man's wife whether he takes sugar in his coffee instead of asking him; we yell and reduce our vocabularies to the level of a six year old when speaking with the deaf which both successfully scrambles sound in their hearing aids and demotes the conversational content to stupidity. *We cannot seem to deal with any single visible impairment without assuming that the entire person is impaired in intelligence, in all sensory dimensions, in personality.*

There is another side to this coin. Professionals experienced in working with the blind have information to give us. The born-blind who have had to rely on senses other than sight all their lives are often particularly skillful at sorting people out for what they are. Not distracted by the beautiful woman or the handsome man, they comfortably accept the amputee though they may rapidly discard the anorexic. They do not reject the obese and they "see" the dwarf for what he really is, whether gifted or stupid.

I do not envy the blind because I cherish color and form and art and clothes too much. But I wish I could disencumber myself of some of the prejudices my society has imposed on me and not on them. I wish I felt as comfortable with a dwarf or a facially scarred person or an amputee as someone who either never "saw" them or as someone who hadn't been acclimatized to shun. I don't mind some of my prejudices but I do mind this one.

— From "Editorial: A Question of Visibility" by Frances L. Drew, M.D., in *Bulletin of the Allegheny County Medical Society*, November 12, 1983.