R.S. 301-ASBEST-TX-CER

SHORT-TERM ASBESTOS EXPOSURE AND DELAYED CANCER RISK

Herbert Seidman, M.B.A.*, Ruth Lilis, M.D.**
and Irving J. Selikoff, M.D.**

From the *American Cancer Society
777 Third Avenue, New York, New York 10017
Environmental Sciences Laboratory**
Mount Sinai School of Medicine
of the City University of New York
Fifth Avenue and 100th Street, New York, New York 10029

I. INTRODUCTION

The relationship of lung cancer and mesothelioma of the pleura and peritoneum with asbestos exposure has been well documented by numerous epidemiologic studies in various countries. The awareness of this risk has led to concern regarding relatively low-level and/or short-term asbestos exposure, especially since experiences with "neighborhood" and "household" exposures have been reported to result in mesothelioma (Newhouse(1), Wagner(2), Anderson(3).

Cancer of the lung, while less specific for the asbestos carcinogenic effect is, nevertheless, several times more frequent a cause of death in asbestos-exposed workers. Definition of the minimum asbestos exposure that would lead to a significant increase in lung cancer is an unanswered question of high theoretical and practical importance.

II. MATERIALS AND METHODS

The requirements of the U.S. Navy for asbestos insulation for pipes, boilers and turbines of its ships led to the establishment of an amosite asbestos factory in Paterson, New Jersey just before the entry of the United States into World War II. From 1941 through 1945, 933 men were

---

Supported in part by Grants from the National Institute of Environmental Health Sciences, ES 00928 and the American Cancer Society, R-53C.

recruited to work in this plant which continued in operation through 1954. Though non-whites were employed in the latter years of the plant's operation, the initial group was almost entirely white. Wartime conditions had a marked influence on the composition of this work force. Younger and fitter men having been siphoned off by the Armed Services, these men tended to be older than is usual for men entering a new line of work. There were very few "career" men and only 19 had worked with asbestos previously; they have been omitted from the present analysis. In contrast to other groups of asbestos workers that have been studied, composed largely of those who continued to work in the industry once they started, a large proportion of the remaining 914 men drifted off to other employment after a while, and others left to enter the Armed Services, as the need for men increased.

This resulted in a unique body of data; experiences of men with a very limited duration of asbestos work exposure. Thus, there were 65 who worked in the plant less than a month; 101, worked one month; 103, two months; 165, 3-5 months; and 151, 6-11 months. We know that this plant had poor ventilation as detailed by review of conditions with workers and management, and examination of ventilation engineering plans. Examination of tissues obtained at autopsy (A.M. Langer) has shown that even short periods of exposure sufficed to leave the men with a lifetime burden of a large number of asbestos fibers in their lungs.

Our approach in this study has been to examine the mortality experience of these men in each year through 30 years after onset of work, in comparison with a hypothetical group of men of identical age at outset, subject to age specific death rates prevailing for white males in the general population of New Jersey in each relevant calendar year 1941-1974.

Table I shows the status of the 914 men at various intervals subsequent to entry. We took 1943 as the average starting point, 1948 as the 5 year point, etc. The setting in time has great significance for many reasons including the kinds of cigarettes available at the particular time.

Age 40 may be taken as roughly the age at which the frequency of cancer begins to be of appreciable magnitude. Despite the dwindling total number of men, we can see that for much of the period of observation there was actually an increase in the number of "effective" men (i.e., those 40 or over) at risk, as the younger men became older.

The "withdrawals alive" include 52 men lost to followup, mostly in the early years of the study, 17 men terminated from observation in this study at a time at which they accepted asbestos work elsewhere, and 36 men who had begun work in 1945 but who had not yet finished their 30th year of observation by December 31, 1974.

The "expected" number of men at risk are the number of survivors from the original group of 914 men depleted on the basis of mortality for white males in New Jersey,* allowing for "withdrawals alive." Subtracting the actual number of men at risk from the "expected" number yields what we have termed "net susceptibles", or more precisely "net susceptibles at the level of asbestos exposure experienced." Besides being a measure of the excess mortality among the asbestos workers, the fact that these "susceptibles" were not available for observation in subsequent time periods means that some understatement was likely in such periods in the cumulative probabilities of death data we will show for the asbestos workers.

We have used followup study life table methods to estimate the probabilities of death in various parts of the first year after onset of work, and year by year thereafter. To obtain these probabilities we adopted the approach by Chiang(11) and Littel (12) in which P_t, the probability of surviving a small time interval t was computed from λ, the death rate per man-year for the interval, through the relationship $P_t = e^{-t\lambda}$. Chain multiplication of these probabilities gave the cumulative probability of surviving from some initial point of time to some later point of time. Subtracting the cumulative probability of surviving from 1 results in the cumulative probability of dying from all causes.

The cumulative probabilities of death for cancer and lung cancer were derived by summing over the various intervals the products obtained by multiplying the part of the probability of death during that interval attributable to cancer or lung cancer by the cumulative probability of surviving to that interval.

---

*The depletions were calculated by interpolation and extrapolation of single year of age l_x from published life tables for New Jersey white males for 1940(4), 1950(5) and 1960(6). The 1970 life table is not yet available so we developed one(7,8) from mortality data for the years 1969-1971(9) and population data from the 1970 census(10).

In order to start the cumulative probabilities of death for all subgroups from the date of onset of work, each subgroup was given the mortality experience for all men during the period less than one month after onset. Subgroups which worked one month or more were given the mortality experience of all such men for month 1. Subgroups which worked two months or more were given the mortality experience of all such men for month 2.

Through 1971, mortality data for New Jersey were available from the annual vital statistics publications of the National Center for Health Statistics (9). Annual populations were estimated by interpolating and extrapolating decennial population data(10,13-15). The kind cooperation of the National Center for Health Statistics provided us with unpublished mortality data for 1972-1973(16). The 1974 data not yet being available, we extrapolated for 1974 from 1967-1973.

The coding for cause of death in this study is that of the VI through VIII revisions of the International List in use in the United States from 1949 on. The observed deaths were coded in two ways. First, according to death certificate information but then also according to verified diagnosis, established from additional information available for the decedent from autopsy, surgical specimens, x-ray films and clinical information. For this analysis we have utilized the verified diagnosis. To obtain total cancer death rates on a consistent basis for New Jersey prior to 1949, we extrapolated from rates for 1949-1955.

For New Jersey white males, age specific death rates were available for total cancer of the respiratory system but not for lung cancer specifically, although this neoplasm constitutes the major part of the category. However, the all ages total for lung cancer were at hand. We estimated the age-specific lung cancer rates as follows: For each age group, to the United States lung cancer death rates for 1949 on, we applied the ratio of New Jersey to United States total respiratory cancer rates in order to obtain first estimates of lung cancer rates for New Jersey. These first estimates were multiplied against population figures for New Jersey and the resulting implied numbers of deaths were summed to obtain the totals. These were then compared with the actual total numbers. There was excellent agreement and only small adjustments were required between the first and final estimates.

III. RESULTS

The results for small subgroups are subject to substantial sampling variation. Even so, for the 65 men who worked less than a month, the indications were for favorable mortality for all causes of death during the 30 year period of observation(Fig. 1). No cancer death was observed until the 22nd year and no lung cancer death until the 25th year but in the probabilities thereafter there is the hint that even in these men the time bomb of "residence asbestos exposure" (residual retained asbestos in tissues) was ticking away.

When we proceed to the findings for the men who worked a month or more, the mortality after a number of years was consistently unfavorable (Figs. 2-7).

Table II provides a summary for all causes of death at various points of time after onset of work, of the absolute and the relative differences between the observed and expected cumulative probabilities of death for the several subgroups. Underneath the lines and in the unshaded area, the observed mortality is consistently unfavorable. For those who worked 1, 2 and 3-5 months, this became evident at 20 years while for those who worked longer, it is evident earlier.

Table III provides a similar summary for total cancer. The absolute differences were smaller and the relative differences larger than those for all causes of death. The smaller absolute differences for cancer compared with all causes means that cancer did not account for all of the excess mortality in these asbestos workers. For those who worked 1-11 months it took longer for cancer than for all causes for the excess mortality to become evident.

In the summary for lung cancer in Table IV the relative differences are clearly much larger than those in Tables II and III. As compared with the respective absolute differences for total cancer, lung cancer sometimes accounted for all of the excess cancer mortality and sometimes for only a part of the excess.

Figure 8 shows the relative differences 30 years after onset of work in the observed compared with expected cumulative probabilities of death from all causes for the various subgroups. Relative differences of observed to "expected" of 1.3, 1.4 and 1.5 may not seem impressive, but it must be remembered that as "expected" cumulative probability of death approached 50%, the largest possible relative difference was 2. Figure 9 shows these data for all cancer and Figure 10 for lung cancer.

IV. DISCUSSION

The fact that direct asbestos exposure of short duration (less than one year), results in significant excess risk of lung cancer, together with the development of mesothelioma after minor (neighborhood or household) asbestos exposure, is of considerable interest for the evaluation of the "minimum carcinogenic dose" for asbestos.

It is also evident that the asbestos exposure in "residence" is immensely important. Calculations of asbestos dose which consider only the initial direct exposure dose deal with the visible tip of the iceberg and ignore the bulk of the mass which is out of sight(17).

Since tissues continue to be exposed after cessation of the individual's direct exposure, the disease outcome is influenced by the duration of post-employment tissue exposure ("residence time"); epidemiologically, this becomes evident only with long post-employment observation.

The lengthy interval between the direct dosage and the emergence of cancer poses the challenge to use this time in some way to intervene and abort the cancer process in those we know to be high risk persons. To date, the opportunity may be there, but not the know-how of how to take advantage of it.

In coding cause of death using all of the information compiled for the 494 decedents among this group of 914 men, we classified 142 deaths in the category "total cancer" including 76 as lung cancer. Based on death certificate information alone, 135 deaths would have been classified as cancer and 65 as lung cancer. Some investigators assert that for greater comparability only death certificate information for coding causes of death should be used. Of course, it would be optimal if causes of death in the general population were also to be coded with all of the relevant records at hand. This not being feasible, we believe our approach is well justified because of the unique problems in asbestos workers. For instance, with careful effort it is not unusual to detect mesothelioma in an asbestos worker, mesothelioma which was probably unrecorded on death certificates. In the general population with equal effort it would be rare to detect mesothelioma because it simply is only rarely there to be detected and recorded.

V. SUMMARY

Workers exposed to amosite asbestos for merely a month showed a clear excess risk of cancer. With longer direct exposure (i.e., 2 months, 3 months, 6 months, etc.) the cancer risk became greater. Moreover, with very brief direct exposure, increased cancer risk was found only after 25 years. Longer employment resulted in cancer after shorter post-exposure observation.

Thus, brief asbestos employment (less than one year) resulted in important excess cancer mortality.

In evaluating cancer hazards of asbestos exposure, it is necessary to include post-employment observation of adequate duration, since the retained asbestos results in tissue exposure long after employment ceases.

Acknowledgements: We wish to thank Stephen L. Smith, Ashley Bodden and Edwin Silverberg of the American Cancer Society, for their assistance in processing the data of this study.

TABLE I. Status of All 914 Men With Respect To Elapsed Time After Onset of Work, 1941-1945

Item	Number of Elapsed Years Since Onset of Work						
	0	5	10	15	20	25	30
Middle calendar year	1943	1948	1953	1958	1963	1968	1973
Number of men at risk	914	814	760	686	584	472	337
Mean years of age per man	37.3	42.0	46.1	49.9	53.0	56.0	59.1
Number of men age 40 or more at risk	382	440	487	521	522	472	337
Number of deaths in ensuing 5 years	38	51	74	101	110	108	...
Number of withdrawals alive	62	3	0	1	2	37	...
"Expected" number of men at risk	914.0	814.9	767.0	712.5	647.9	573.7	458.3
Cumulative "net susceptibles" already dead	...	0.9	7.0	26.5	63.9	101.7	121.3

TABLE II. Observed Compared With Expected Cumulative Probability Of Death Through 30 Elapsed Years Since Onset Of Work In An Amosite Asbestos Factory, 1941 - 1945, by Length of Time Worked.
ALL CAUSES OF DEATH

Length Of Time Worked	Elapsed Number Of Years Since Onset Of Work											
	5		10		15		20		25		30	
	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E
<1 Month	-1.72	0.48	-5.39	0.23	-8.58	0.27	-14.70	0.18	-14.23	0.44	-7.71	0.77
1 Month	0.19	1.04	-0.88	0.91	-0.94	0.94	5.32	1.22	8.45	1.26	9.44	1.23
2 Months	1.63	1.26	2.01	1.16	2.34	1.11	4.10	1.14	9.00	1.23	15.31	1.32
3-5 Months	2.53	0.53	-3.10	0.73	-0.09	1.00	4.54	1.17	15.76	1.44	15.19	1.34
6-11 Months	1.57	1.36	4.56	1.49	4.50	1.30	15.12	1.68	16.21	1.54	17.42	1.47
1 Year	2.22	1.62	-1.95	0.97	4.79	1.38	5.40	1.29	7.36	1.29	17.92	1.54
2+ Years	-2.45	0.53	1.06	1.09	5.71	1.29	10.76	1.37	15.27	1.39	21.04	1.43

TABLE III. Observed Compared With Expected Cumulative Probability Of Death Through 30 Elapsed Years Since Onset Of Work In An Amosite Asbestos Factory, 1941 - 1945, by Length of Time Worked.
ALL CANCER

Length Of Time Worked	Elapsed Number Of Years Since Onset of Work											
	5		10		15		20		25		30	
	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E
<1 Month	-0.50	0.00	-1.19	0.00	-2.15	0.00	-3.40	0.00	-1.74	0.63	-0.28	0.96
1 Month	0.23	1.29	0.26	1.15	0.03	1.01	3.79	1.84	2.07	1.33	2.34	1.29
2 Months	-1.01	0.00	0.05	1.02	-1.34	0.60	0.19	1.03	3.07	1.41	7.16	1.76
3-5 Months	-0.22	0.75	-1.37	0.33	-1.46	0.58	0.95	1.19	5.24	1.75	5.46	1.62
6-11 Months	0.02	1.03	-0.19	0.89	0.12	[illegible]	3.14	1.76	5.24	1.92	7.29	1.99
1 Year	-0.55	0.00	-1.29	0.00	1.04	1.46	1.48	1.43	4.15	1.84	10.79	2.63
2+ Years	-0.84	0.00	0.41	1.20	5.35	2.42	9.09	2.62	11.10	2.45	16.65	2.72

TABLE IV. Observed Compared With Expected Cumulative Probability Of Death Through 30 Elapsed Years Since Onset Of Work In An Amosite Asbestos Factory, 1941 - 1945, by Length of Time Worked.
LUNG CANCER

Length Of Time Worked	Elapsed Number Of Years Since Onset of Work											
	5		10		15		20		25		30	
	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E	O-E (%)	O/E
<1 Month	-0.09	0.90	-0.24	0.00	-0.48	0.00	-0.83	0.00	0.26	1.19	2.93	2.52
1 Month	-0.14	0.00	-0.35	0.00	0.39	1.59	3.13	3.96	2.62	2.66	3.09	2.44
2 Months	-0.18	0.00	-0.45	0.00	-0.83	0.00	-0.14	0.89	1.75	1.95	5.95	3.49
3-5 Months	-0.15	0.00	-0.40	0.00	-0.74	0.00	0.17	1.14	1.68	1.99	1.79	1.78
6-11 Months	-0.12	0.00	-0.31	0.00	0.15	0.28	1.39	3.15	4.42	4.13	4.62	3.37
1 Year	-0.09	0.00	-0.24	0.00	2.00	5.20	3.33	5.15	4.54	4.62	7.34	5.10
2+ Years	-0.43	0.00	-0.20	1.25	3.77	3.92	8.33	7.45	10.80	6.84	15.27	7.22

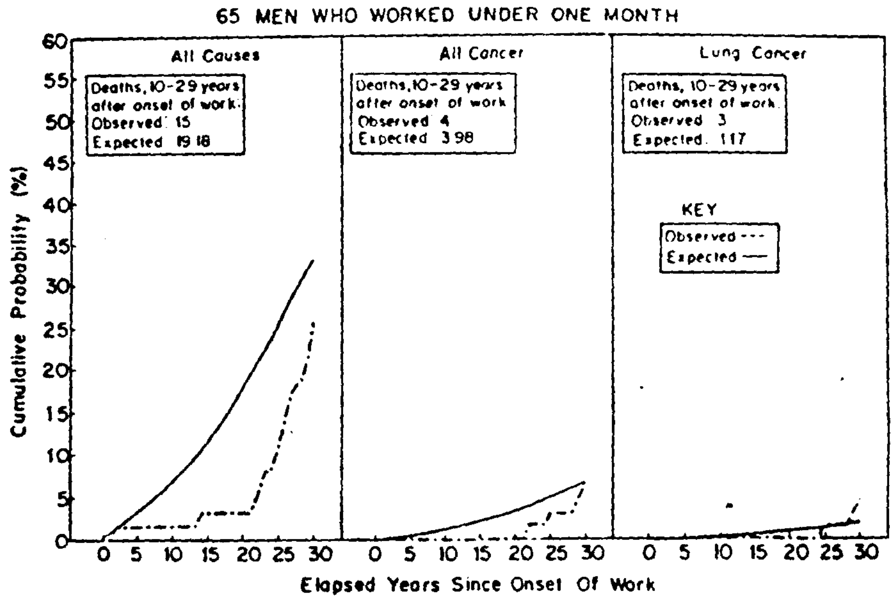

FIG. 1. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 65 men who worked less than 1 month, through 30 elapsed years since onset of work in an amosite asbestos factory, 1941-1945.

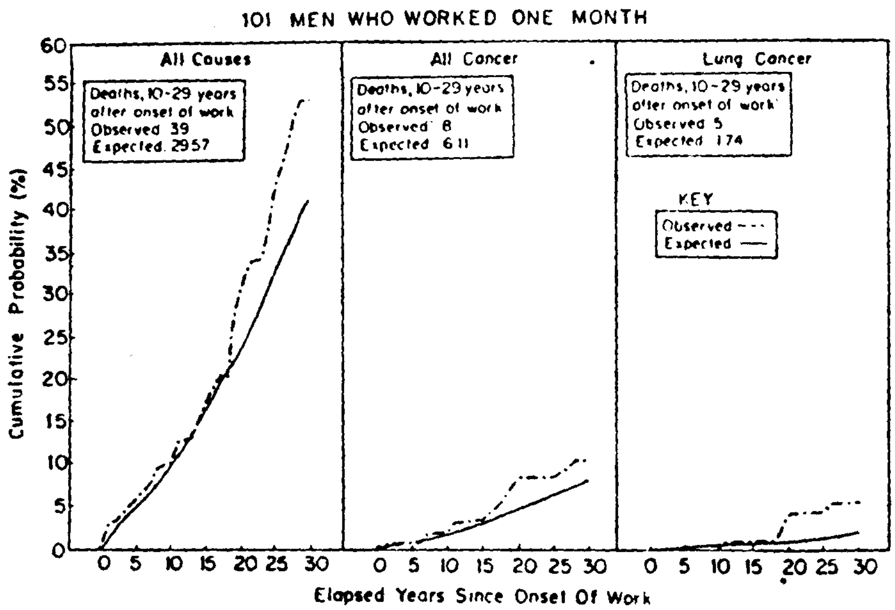

FIG. 2. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 101 men who worked one month, through 30 elapsed years since onset of work in an amosite asbestos factory, 1941-1945.

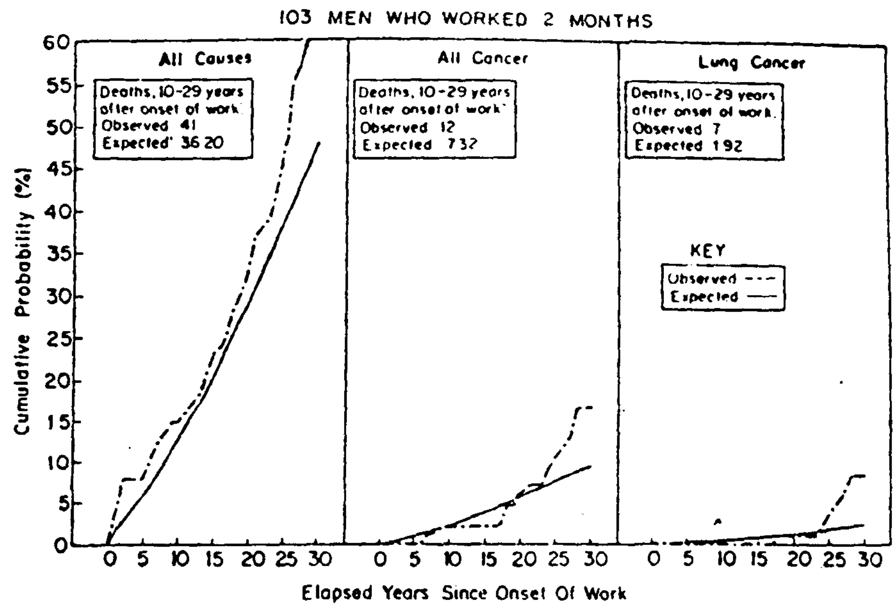

FIG. 3. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 103 men who worked 2 months, through 30 elapsed years since onset of work in an amostie asbestos factory, 1941-1945.

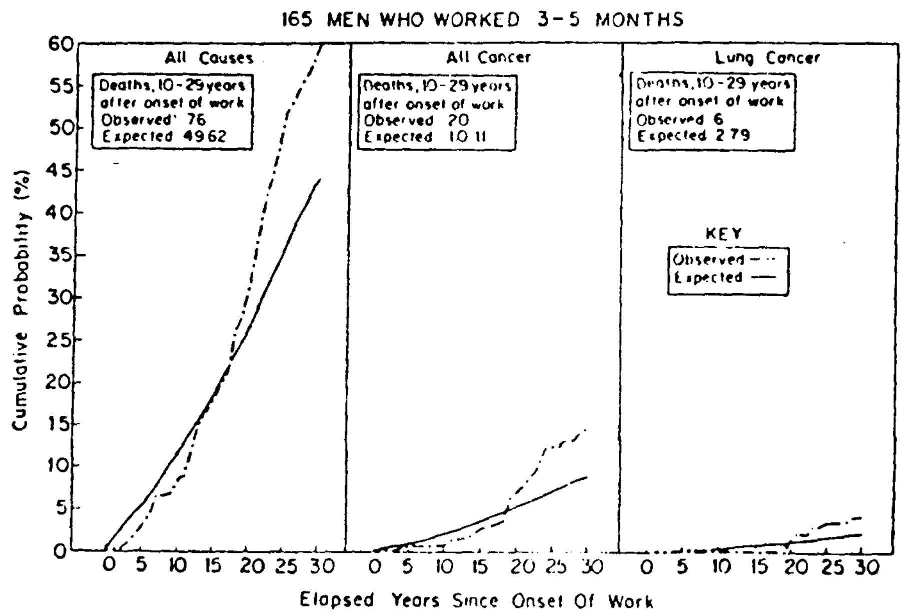

FIG. 4. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 165 men who worked 3-5 months, through 30 elapsed years since onset of work in an amosite asbestos factory, 1941-1945.

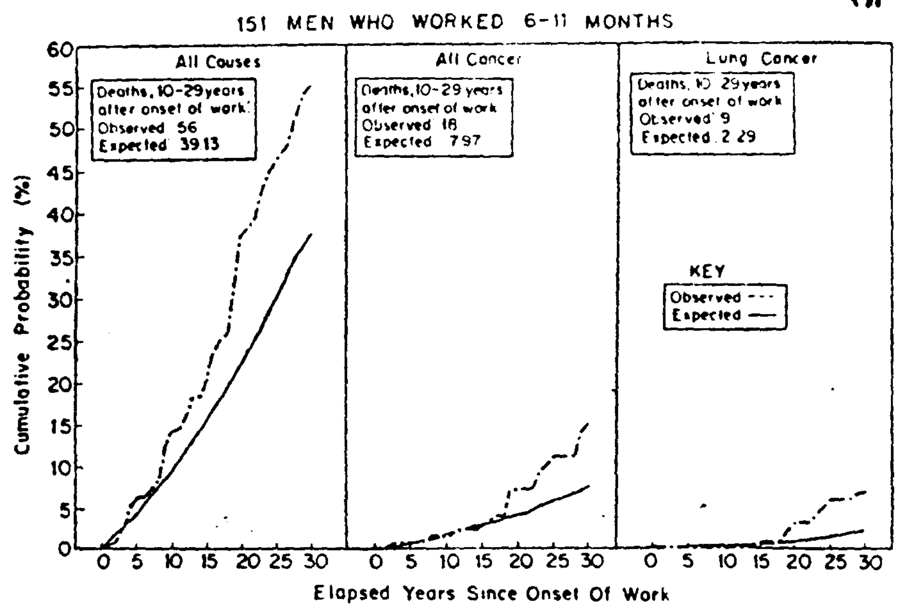

FIG. 5. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 151 men who worked 6-11 months, through 30 elapsed years since onset of work in an amosite asbestos factory, 1941-1945.

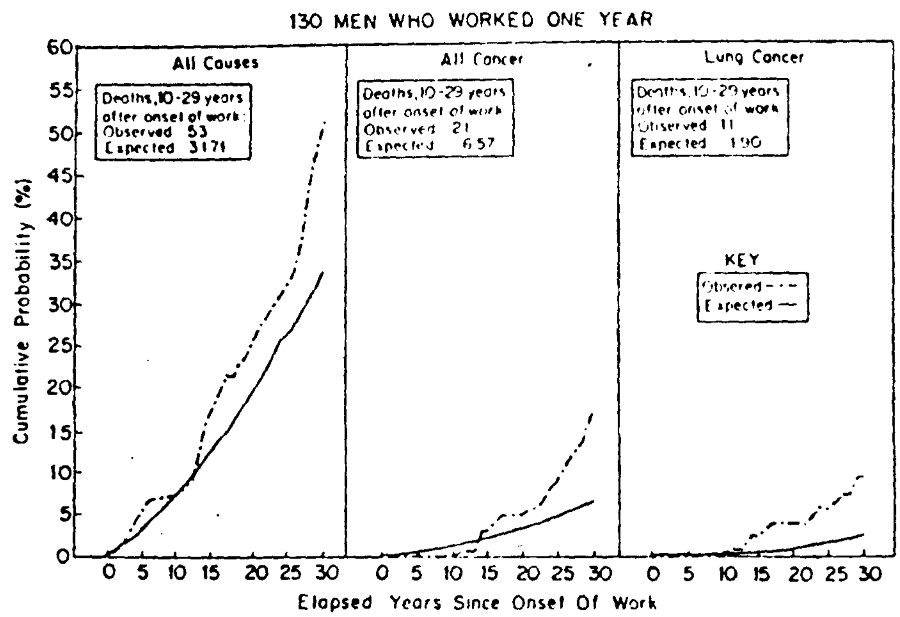

FIG. 6. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 130 men who worked 1 year, through 30 elapsed years since onset of work in an amosite asbestos factory, 1941-1945.

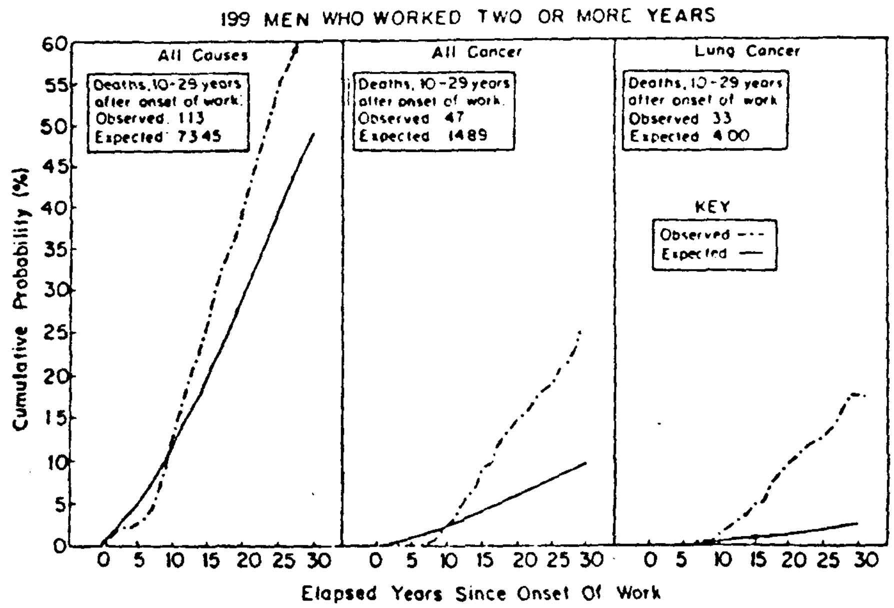

FIG. 7. Cumulative observed and expected probability of dying from all causes, all cancer, and lung cancer for 199 men who worked 2+ years, through 30 elapsed years since onset of work in an amosite asbestos factory, 1941-1945.

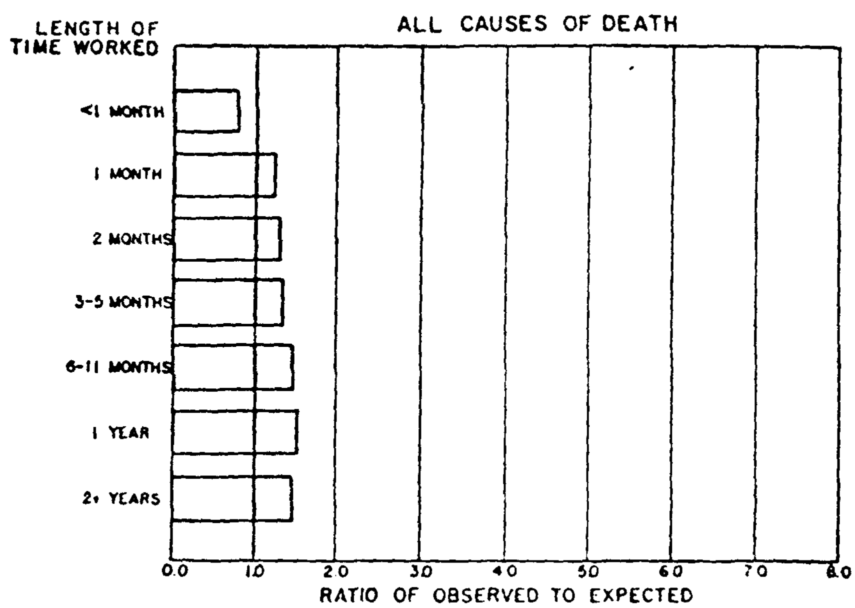

FIG. 8. Ratio of observed to expected cumulative probability of deaths at 30 elapsed years since onset of work.

ugh

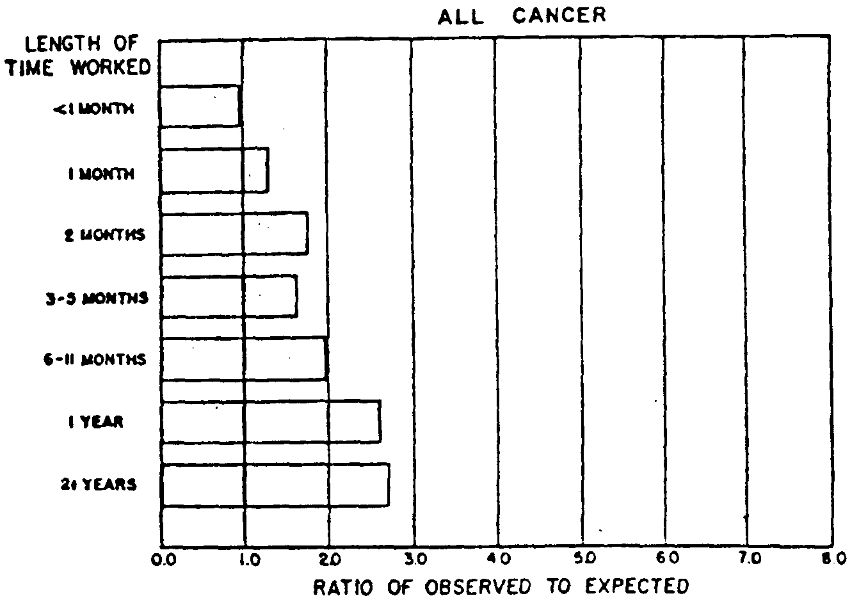

FIG. 9. Ratio of observed to expected cumulative probability of deaths at 30 elapsed years since onset of work.

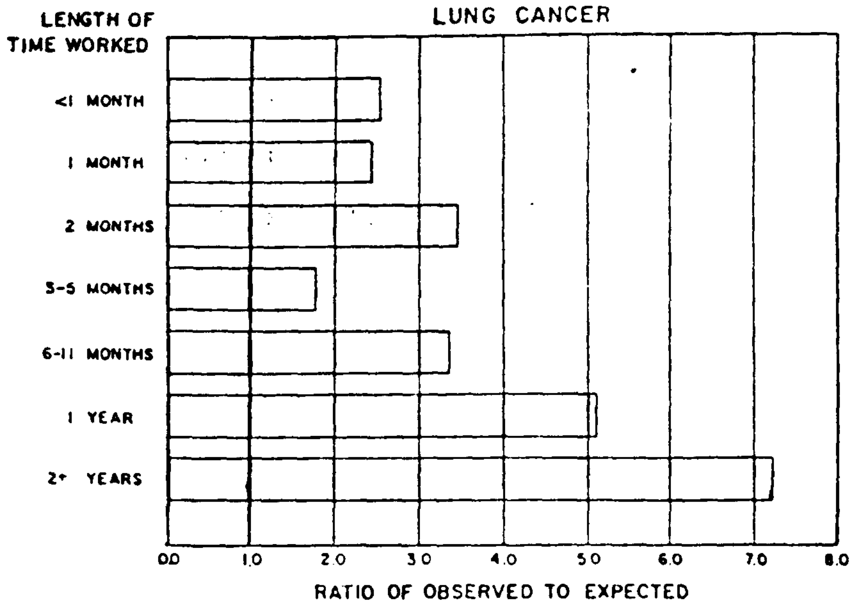

FIG. 10. Ratio of observed to expected cumulative probability of deaths at 30 elapsed years since onset of work.

The message of the Copyright Law (Title 17 USC)

References

1. Newhouse, M.L. and Thompson, H. Mesothelioma of the pleura and peritoneum following exposure to asbestos in the London area. Br. J. Industr. Med. 22: 261-269, 1965.

2. Wagner, J.C. Sleggs, C.A. and Marchand, P. Diffuse pleural mesothelioma and asbestos exposure in the N.W. Cape Province. Br. J. Industr. Med. 17: 260-271, 1960.

3. Anderson, H.A. Lilis, R. Daum, S.M. Fischbein, A.S. and Selikoff, I.J. Household - contact asbestos neoplastic risk. Ann. N.Y. Acad. Sci., 271: 311-323, 1976. In Press.

4. U. S. Federal Security Agency - Public Health Service, National Office of Vital Statistics, State and Regional Life Tables 1939-41 (New Jersey) U. S. Government Printing Office, Washington, D.C., 1948 pp. 182-185.

5. U. S. Department of Health, Education, and Welfare - Public Health Service: National Office of Vital Statistics, State Life Tables (New Jersey), 1949-51. Vital Statistics - Special Reports, 41: 265-280 (Suppl. 34), 1956.

6. U. S. Department of Health, Education, and Welfare - Public Health Service: National Vital Statistics Division. 1966. Life Tables: 1959-61, Volume 2 - No. 32, New Jersey, State Life Tables: 1959-61, Public Health Service Publication No. 1252. U. S. Government Printing Office, Washington, D.C., 1966, pp. 495-508.

7. Reed, L.J. and Merrell, M. A short method for constructing an abridged life table. Vital Statistics - Special Reports, 9: 683-712, 1949.

8. Wolfenden, H.H. Population Statistics and Their Compilation, University of Chicago Press, Chicago, 1954.

9. U. S. Public Health Service, National Vital Statistics Division: Vital Statistics of the United States, Annual 1941-1971. Government Printing Office, Washington, 1943-1975.

10. U. S. Bureau of the Census: Census of the Population: 1970, General Population Characteristics. Final Report PC(1)-B32, New Jersey. U. S. Government Printing Office, Washington, 1971.

11. Chiang, C.L. A stochastic study of the life table and its applications: III. The follow-up study with the consideration of competing risks. Biometrics, 17: 57-78, 1961.

12. Littel, A.S. Estimation of the T-year survival rate from follow-up studies over a limited period of time. Human Biology, 24: 87-116, 1952.

13. U. S. Bureau of the Census: Sixteenth Census of the United States: 1940. Population, Volume II. Characteristics of the Population. Part 4: Minnesota-New Mexico. U. S. Government Printing Office, Washington, 1943.

14. U. S. Bureau of the Census: U. S. Census of Population: 1950. Vol. II, Characteristics of the Population. Part 30, New Jersey. U. S. Government Printing Office, Washington, 1952.

15. U. S. Bureau of the Census. U. S. Census of Population: 1960. General Population Characteristics, New Jersey. Final Report PC(1)-32B. U. S. Government Printing Office, Washington, 1961.

16. U. S. Public Health Service, National Vital Statistics Division: Unpublished tabulations.

17. Selikoff, I.J. and Hammond, E.C. Lapsed Time (Editorial) Environ. Res. 4: i-ii, April 1971.