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Mortality Pattern in a Cohort of Asbestos Workers

A Study Based on Employment Experience

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IN PREVIOUS PAPERS, the basic epidemiological approaches to the study of industrial populations, demographic and cohort, were discussed, and their potential contributions and limitations cited.[1, 2, 3] Recently, we have considered several facets of long term studies, the dynamic changes of a cohort and their influence on the statistical evaluation of a cohort's progress and observation over time, and the concept of the successive cohort approach.[4, 5] In these studies, our objectives have been to improve on the methods of studying industrial populations over long periods of time and to cast some light on particular aspects of the occupational hazard for the population at risk.

The purpose of the present paper is to carry out these objectives pertaining to methodology by introducing an essential refinement—the characteristic of "duration of employment"—to the cohort studies established through the same national resource (Social Security records), and to determine what relationship exists between workers exposed to asbestos and specific causes of death

For epidemiological purposes, the question is what combination of resources and methods can be brought to bear, in the absence of company data, to establish long-term epidemiological studies of industrial populations, and to approximate environmental exposure and the degree of risk for the population under study. In the epidemiological evaluation of environmental exposures, duration of employment, length and continuity of exposure, and provision of some consistent measurement of employment exposure over the years constitute the initial broad separation of the population under study and a method of defining the population more likely to be at risk. This measure of risk—duration of employment—was not included in our earlier study[3] because such data were not available at that time. Since then, following exploratory efforts which adhered to the policy of the Social Security Administration to safeguard the confidential nature of the data, arrangements were completed to obtain information on duration of employment on a statistical basis for each member of the cohort.

The principal hypothesis being tested is

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whether the duration of cumulative employment experience among workers in the asbestos products industry is related to an increased mortality rate generally for all causes of death and particularly for specific underlying causes of death.

Wagner, in his pioneering observations of the relationship between mesothelioma and asbestos exposure, focused attention on the biological effects of asbestos, which study has served as a basis for international research and effort pertaining to experimental pathology and epidemiological studies.[6-9] The importance of duration of employment in such epidemiological studies (for evaluating the strength of association between asbestos and malignancies in longitudinal cohort studies) has been well recognized by previous investigators. Unfortunately, this type of information has been quite limited and not generally available. Consequently, there are only a few cohort reports on asbestos in the literature which include some type of reference to duration of employment. Further, in each study, official vital-statistics data of the general population of the country, state, or county were utilized for control purposes. The limitations of the use of the general population for control purposes has been recognized.[10-12]

Doll[10] defined and observed a cohort of men employed in scheduled jobs in an asbestos textile plant who had been employed for 20 years or more in the same plant. He concluded that the average lung-cancer risk was in the order of 10 times that experienced by the general population and that the risk had become progressively less as the duration of employment exposure under old dusty conditions decreased (following the institution of certain regulations and control measures at a given point in time).

These observations were further substantiated by Knox *et al* in a continuation of this basic study,[11] which revealed a decreased lung cancer risk subsequent to that point in time (1933). In this manner, the observation of the effectiveness of the environmental control measures, i.e. the decrease in asbestos exposure resulting in the decrease of lung cancer, augmented data on the previously established direct association between lung cancer and asbestos exposure.

It was also apparent from Knox and Doll's observations that the effectiveness of the environmental control measures at various periods could have an influence in testing our proposed hypothesis. It is evident that a 10-year period of employment exposure in the asbestos industry during 1920–1939 would be completely different from that of 10 years of employment in the same plant during 1940–1959. This was one of the essential reasons for using the general cohort method for testing this hypothesis.

Braun *et al*,[13] in their study of asbestos miners in Canada, established a cohort at a given point in time (1950), the members of which had 5 or more years of previous employment; the investigators observed this cohort for a period of only 6 years. The cohort composition was characterized by varying lengths of employment and they related to other factors such as smoking and weighted-exposure categories. An analysis of this study has been made,[16] citing the inherent limitations and the lack of justification for the negative conclusion derived.

Mancuso,[3] through the use of 1938-39 Social Security records, established a company cohort of asbestos workers who were observed to mid-1960. In this study, the need for data by duration and the development of more appropriate controls for industrial cohort populations were expressed and served as the basis for the present study.

Selikoff *et al*[17] utilized union records to establish a cohort of insulation workers as of 1943, in which group the elapsed time from initial exposure was the essential criterion, characterizing the cohort as those with a history of 20 years or longer since the first exposure to asbestos dust. The consistency of employment for this occupational trade group has been historically reflected in the expression "once a pipe coverer, always a pipe coverer." Consequently, the duration of employment may have been extensive.

Enterline,[18] utilizing the Social Security approach, established an industry cohort, consisting of a number of the asbestos-products plants, of workers who were employed at some time during 1948–1951 and observed to mid-1963. Cohorts were established in the same manner for cotton textile plants, which together with the specific death rates for the U.S. were utilized for comparable purposes. Enterline further cited the difficulty of interpreting findings in the absence of data on duration of employment, and the limitations of the Social Security data for this purpose. We have been able to overcome these problems in the present study.

The present study constitutes an application of the observations derived from our explorations in methodology of studying industrial populations. It differs from previous prospective

asbestos studies in the basic utilization of a generation cohort and internal controls, with gradient levels of employment as assessed through Social Security records

The problem of "adequate controls" has been a major obstacle in industrial health studies and is further accentuated in prospective longitudinal studies covering a period of many years. This problem, too, has been considered in our present study.

The primary emphasis and direction of the cohort study was to

1. Demonstrate the method of utilizing an internal control with a generation cohort, according to age and specific levels of employment experience for a company under study (as derived from Social Security data)

2. Evaluate the effects of duration of cumulative employment experience on the mortality pattern of workers exposed to asbestos, specifically in relation to malignant neoplasms, cardiovascular diseases, and asbestosis. To our knowledge, the present study is the first report to provide such essential data pertaining to all gradients of levels of duration of cumulative employment experience in an asbestos industry, and the relationship to the mortality pattern in a well-defined "total" population at risk, followed for a long period of time (24.5 years) in which a generation cohort method and internal control is used.

Method of Study

The study was conducted in the same manner as the previous asbestos study[3] in the establishment of the cohort for 1938 and 1939 through Social Security records, the method of follow-up, and the determination of the deceased and the causes of death.

Data pertaining to sex, color, year of birth, date of death, and a complete employment history in the asbestos plant (by quarters of each year) were made available to us by the Social Security Administration for the living and the deceased from 1938 and 1939 to mid-1964. The additional data made it possible to classify the population by sex, age, and cumulative employment experience during the period of 1938 to mid-1964. The dynamic changes pertaining to age, cumulative duration of employment, and years of observation in a long-term cohort study (discussed in a previous paper[4]) were considered in the computation of person years and analysis of the data.

Age

The cohort was classified in age groups of 15–24, 25–44, 45–64, and 65 and over. The date for which the age-specific death rates were calculated was the date at death; for the age at entrance generation method, the age was calculated as of 1940. The limitations and merits of the various methods of comparisons, age at death and age at entrance,[4] served as a basis for our selection and classification of the present cohort by age at 1940.

Cumulative Employment Experience

Each sex-age group was classified according to the cumulative employment experience they acquired during the period 1938 through mid-1964 into the following 5 levels:

Cumulative employment experience	*Employment experience (yr)*
I	0.1–2.0
II	2.1–7.0
III	7.1–12.0
IV	12.1–17.0
V	17.1–27.5*

Death rates for the selected underlying causes of death were calculated for each sex-age level of cumulative employment experience and for Level II through V combined.

Development of an Internal Control

In the present study, employees of the 1938 and 1939 cohort who had a cumulative employment experience of 2 years or less during the period 1938 to mid-1964 were selected as an internal control.

Average annual death rates for employees who had a cumulative employment experience of 2 years or less (Level I) were computed by sex and age group. For each sex and age group of employees having cumulative employment experience of more than 2 years (Levels II, III, etc.), the expected number of deaths was determined for the selected specific underlying cause of death by applying the average annual death rates of the employees having cumulative employment experience of 2 years or less for that age group. The standard mortality ratios (SMR) were calculated based on the observed and expected number of deaths due to underlying selected causes of death for age at death and age at 1940.

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*Maximum cumulative employment experience for an employee who was alive by mid-1964 and has a continuous employment in the asbestos plant since 1938 is 27.5 years.

TABLE 1—1930–MID-1961 FOLLOW-UP OF TOTAL (T) NUMBER OF ONE ASBESTOS COMPANY'S WORKERS (CLASSIFIED AS DESCRIBED IN TEXT) NOW LIVING (L) OR DEAD (D)*

	Level of cumulative years of employment experience																	
	Overall totals			I (0.1–9.9)			II (10.0–19.9)			III (20.0–29.9)			IV (30.0–39.9)			V (40.0 & over)		
Age at 1930	D	L	T	D	L	T	D	L	T	D	L	T	D	L	T	D	L	T
MALES																		
15–24	12	310	322	7	114	121	1	110	114	1	21	22	—	4	4	—	61	61
25–34	51	117	171	11	113	124	17	119	136	11	36	47	1	7	8	14	142	156
35–44	98	140	238	9	28	37	30	26	56	17	16	33	12	2	14	30	68	98
45–54	91	58	149	16	16	32	22	3	25	15	5	20	16	3	19	22	31	53
55–64	51	9	61	3	—	3	9	3	12	10	—	10	23	3	26	9	3	12
65 & over	21	1	22	3	1	4	6	—	6	7	—	7	4	—	4	1	—	1
All ages	330	935	1265	49	272	321	88	261	349	61	78	139	56	19	75	76	305	381
FEMALES																		
15–24	—	42	42	—	12	12	—	16	16	—	5	5	—	3	3	—	6	6
25–34	8	95	103	—	15	15	3	37	40	1	16	17	1	5	6	3	22	25
35–44	15	48	63	2	7	9	5	14	19	6	5	11	1	2	3	1	20	21
45–54	4	11	15	1	2	3	—	2	2	2	3	5	—	1	1	1	3	4
55–64	3	1	4	—	—	—	—	—	—	—	1	1	2	—	2	1	—	1
65 & over	1	—	1	—	—	—	—	—	—	—	—	—	1	—	1	—	—	—
All ages	31	197	228	3	36	39	8	69	77	9	30	39	5	11	16	6	51	57

*Excludes 6 male and 2 female deaths occurring in 1938 or 1939 to members of cohort 35–64 years of age at death. The male deaths were coded as due to endocarditis not specified as rheumatic (1), arteriosclerotic heart disease (1), asbestosis (2), accident (1), and suicide (1). The female deaths were due to malignant neoplasm of the breast (1) and asbestosis (1). Also excluded in the deaths among males are 14 due to war casualty.

TABLE 2. CAUSE OF DEATH IN 1940– MID-1964 FOLLOW-UP OF ASBESTOS-PLANT WORKERS (AS CLASSIFIED IN TEXT)

Cause of death and code	*Level of cumulative employment experience*											
	Males						*Females*					
	All levels	*I*	*II*	*III*	*IV*	*V*	*All levels*	*I*	*II*	*III*	*IV*	*V*
TOTAL	330	49	88	61	56	76	31	3	8	9	5	6
Tuberculosis, all forms (001-020)	10	3	6*	—	1	—	1	—	1	—	—	—
All neoplasms (140-239)	85	13	22	14	11	22	11	1	3	3	1	3
All malignant neoplasms (140-205)	84	13	21	14	14	22	11	1	3	3	1	3
Malignant neoplasms of digestive organs and peritoneum (150-159)	26	1	7	6	2	7	3	—	1	1		1
Malignant neoplasms of peritoneum and/or mesothelioma†	8	1	2	1	1	3	1	—	1	—	—	—
Malignant neoplasms of lung, bronchus, and trachea (162-163)	35	5	9	6	5	10	6	1	1	2	—	2
Unspecified malignant neoplasms (199)	8	—	2	—	1	2	—	—	—	—	—	—
All other neoplasms (140-149, 160-161 164-198 & 200-239)	16	1	1	2	3	3	2	—	1	—	1	—
Cardiovascular diseases (330-334 & 400-468)	112	25	30	27	26	34	8	2	2	1	2	1
Diseases of respiratory system (470-527)	43	2	9	10	11	11	5	—	1	1	1	2
Diseases of digestive system (530-587)	11	—	6	1	2	2	1	—	1	—	-	—
All other causes	39	6	15	9	2	7	2	—	—	1	1	—
Total Population L and D	1265	321	349	139	75	381	228	89	77	39	16	57

*Includes 2 individuals in whom asbestosis was reported on death certificate as secondary cause of death

†This group of malignant neoplasms is included as part of malignant neoplasms of digestive organs and peritoneum and 1 death due to mesothelioma of pleura

‡31 deaths in the males and all the deaths in the females were due to asbestosis

TABLE 3 STANDARD MORTALITY RATIO (SMR) BASED ON OBSERVED (O) AND EXPECTED (E) NUMBER OF DEATHS DUE TO SELECTED UNDERLYING CAUSE AND THE MORTALITY RATES (R) PER 100,000 POPULATION FOR AGE AT 1940 AND AGE AT DEATH AMONG ASBESTOS WORKERS STUDIED (SEE TEXT)

Cause of death and code	Factor	Age at 1940						Age at death									
		20–34		35–44		45–54		55 & over		15–24		25–44		45–64		65 & over	
		O	E	O	E	O	E	O	E	O	E	O	E	O	E	O	E
Total	No	5	8.7	132	87.1	126	39.8	18	7.1	—	0.8	32	21.3	168	65.7	81	46.5
	R	137	238	1880	528	9302	2801	14691	5825	—	168	310	206	2403	940	14056	8067
	SMR	58		150		317		252		(—)		151		256		174	
All neoplasms (140-205 & 210-239)	No	—	2.5	12	9.3	26	12.0	4	0.0	—	0.4	11	6.5	48	17.9	13	7.7
	R	—	68	598	132	1920	886	3252	—	—	84	107	63	687	256	2256	1345
	SMR	(—)		153		217		(+)		(—)		168		268		168	
Malignant neoplasms of digestive organs and peritoneum (150-159)	No	—	1.2	10	1.9	12	4.0					4	1.6	15	9.0	3	0.0
	R	—	31	142	26	886	295					39	16	215	128	521	—
	SMR	(—)		530		300						245		167		(+)	
Malignant neoplasms of peritoneum and/or mesothelioma	No			1	0.0	1	2.0							6	3.0	1	0.0
	R			57	—	221	148							86	43	174	—
	SMR			(+)		150								201		(+)	
Malignant neoplasms of lung, bronchus & trachea (162-163)	No			19	1.8	9	8.0	2	0.0			4	0.0	21	9.0	5	7.7
	R			270	26	664	590	1633	—			39	—	300	128	868	1345
	SMR			1038		113		(+)				(+)		234		65	
Malignant unspecified neoplasms (199)	No			6	0.0	1	0.0	1	0.0			1	0.0	6	0.0	1	0.0
	R			85	—	74	—	816	—			10	—	86	—	174	—
	SMR			(+)		(+)		(+)				(+)		(+)		(+)	
Other neoplasms (140-149, 160-161, 164-198, 200-239)	No	—	1.2	7	5.55	1	0.0	1	0.0	—	0.4	2	4.9	6	0.0	4	0.0
	R	—	31	100	79	295	—	816	—	—	84	19	48	86	—	694	—
	SMR	(—)		126		(+)		(+)		(—)		41		(+)		(+)	
Diseases of cardiovascular system (330-334 & 400-468)	No	1	2.5	40	16.7	66	22.0	10	7.1			4	4.9	63	38.8	50	34.9
	R	27	68	570	237	4916	1624	8163	5825			39	48	901	556	8677	6050
	SMR	40		240		300		140				82		162		143	
Diseases of respiratory system (470-527)	No	1	0.0	23	3.7	17	0.0					4	3.3	31	0.0	6	0.0
	R	27	—	327	53	1255	—					39	32	443	—	1041	—
	SMR	(+)		617		(+)						122		(+)		(+)	
Asbestosis (523.2)	No			19	0.0	12	0.0					2	0.0	26	0.0	3	0.0
	R			270	—	886	—					19	—	372	—	521	—
	SMR			(+)		(+)						(+)		(+)		(+)	
Diseases of digestive system (530-587)	No	1	0.0	4	0.0	5	0.0	1	0.0			4	0.0	2	0.0	5	0.0
	R	27	—	57	—	369	—	816	—			39	—	29	—	521	—
	SMR	(+)		(+)		(+)		(+)				(+)		(+)		(+)	
Other causes	No	2	3.71	23	7.41	12	4.0	3	0.0	—	0.4	9	6.5	24	9.0	7	3.9
	R	55	102	328	106	886	295	2449	—	—	84	87	63	343	128	1215	672
	SMR	54		310		300		(+)		(—)		138		268		181	

[1] Employment history based on data available from SSA only.
[2] All neoplasms are malignant except 1 causing death coded (237).
[3] This group of malignant neoplasms is included as part of pulmonary manifestations of disease.

Characteristics of the Cohort

The asbestos plant had only white employees in the years the cohort was selected, 1938 or 1939 (Table 1). About 85% of them were male. The age comparison showed a considerable number of young employees. Specifically, more than two-thirds of the employees in the cohort in 1938 or 1939 were in the age group 15–34 years in 1940. During the period 1938 to mid-1964, the cumulative employment experience classified by sex and age at 1940 for the cohort population is illustrated in Table 1. It was noted, for example, that about 25% of the male employees were in Level I, 28% were in Level II, and 47% were in the combined Levels III, IV, and V of cumulative employment experience in the asbestos plant.

During the period 1940 to mid-1964, there were 330 males and 31 females in the plant cohort who died, excluding 14 war casualties, death at sea, and 6 deaths during 1938-1939.

The distribution of the number of deaths by level of cumulative employment experience among the cohort population is illustrated in Table 1. For all levels of cumulative employment experience, there were 330 deaths (26.6%) in a total male population of 1265 and there were only 31 deaths (13.6%) among 228 total female employees.

Findings

In our study the cohort population represented the combined cohorts of those employed in 1938 and those whose first employment was recorded by Social Security as being in 1939. Information was not available to characterize the members of the cohort by first employment in the plant prior to 1938 and this, consequently, deferred any analysis by the successive cohort method.[5] However, in our preliminary analysis of the individual cohorts, employees of 1938 and those of 1939, we found an apparent difference. The 1939 cohort employees, representing mostly new employees, sustained a lower mortality for all causes of death and for the selected specific causes of death under study. Of the total 1265 male employees in the 1938–1939 cohort, there were 328 male employees that belonged to the 1939 cohort, of which there were 47 observed deaths due to all causes including 2 deaths caused by malignant neoplasms of lung, trachea, and bronchus, and none due to asbestosis. Of the remaining 937 male employees in the 1938 cohort, there were 283 deaths including 31 deaths due to asbestosis and 33 deaths due to malignant neoplasms of the lung, trachea, and bronchus.

In essence, the better survival for those of the 1939 cohort and the observation that none of the cases of asbestosis occurred among those whose records appeared in 1939 as recorded by Social Security when compared to those whose records appeared in 1938 could be due to the influence of previous employment prior to 1938 in the same plant among the 1938 cohort and also because of the effectiveness of the environmental changes and improvements in subsequent years. Therefore our observations on reduction of risk, although limited, are in agreement with the observations indicated by Doll and Knox *et al.*[1,2]

The subsequent findings (which follow) relate to the combined 1938-39 cohort of employees of the asbestos products plant. Table 2 characterizes the number of deaths by the underlying selected causes of death, as noted by sex and level of cumulative employment experience. Among the males there were 35 malignant tumors of the lung (42% of all malignancies), of which 3 occurred in Level I (0.1–2.0 cumulative years of employment). Of the 43 deaths due to respiratory disease, 31 deaths were due to asbestosis. For the females there were 11 deaths due to malignant neoplasms and of this group 6 (54%) were due to malignancies of the lung (one was in Level I), and all of the 8 deaths due to respiratory disease were due to asbestosis. There were 8 malignant neoplasms of the peritoneum and/or mesothelioma, identified in the 330 male deaths of all causes, 1 of which occurred in Level I. Table 2 provides the initial distribution and indication of the influence of duration of employment. As was seen in Table 1, the age group in each corresponding level varies and consequently influences the observations relative to duration of employment and specific causes of death.

Table 3 applies the average annual mortality rate by age and underlying causes of death of the internal control (Level I) to those with cumulative years of employment experience of more than 2 years (Levels II–V inclusive), and as such provides an "over view" of the mortality patterns of the cohort, without relating to specific levels of employment. It must be borne in mind that the internal control (Level I) is a subcohort of the same cohort population and differs only in being characterized by the shortest duration of cumulative years of employment ex-

perience (2 [illegible] base) in the asbestos industry during 1938 to mid-1964. In Table 3 the mortality rates are calculated by 2 methods: (1) age at entrance, the "generation cohort approach," and (2) age at death, the "usual age specific death rates."

In Table 3, the SMR calculated by age at death and age at entrance illustrated higher values as compared to the control. Most of the observed additional deaths were due to malignant neoplasms (specifically those of the lung, trachea, and bronchus, the digestive organs and peritoneum, and also "unspecified malignant neoplasms"), diseases of the cardiovascular system, diseases of the respiratory system (specifically asbestosis), and diseases of digestive system.

The SMR and average annual mortality rates for ages 25–44, classified by age at entrance, was much higher than the age 45–64 for malignant neoplasms of the digestive organs and of the lung. This difference was more marked for malignant neoplasms of the lung for age 25–44 and was 10 times that of the control group.

For the age at death, the highest rate for lung cancer occurred in the age group 45–64.

The SMR and mortality rates for lung cancer in the older age group 45–64 (as classified by both age at entrance and age at death) illustrated the effect of the "internal control" on the difference between the observed and the expected. When the experience of this age group with Level I employment experience (0.1–2 years) is applied to the corresponding age group to derive the expected rate, the expected rate would be higher by virtue of the influence of employment prior to 1935. In this respect therefore the difference observed constitutes a very conservative estimate.

Effects of Cumulative Employment Experience on the Mortality Pattern

For the purpose of assessing the relationship between the mortality pattern and the duration of employment, the rates by age at 1940 were used for the various reasons to be discussed. To examine this relationship, mortality rates were used as follows: all causes, all neoplasms, malignant neoplasms of digestive organs and peritoneum, malignant neoplasms of lung, bronchus, and trachea, cardiovascular diseases (except vascular lesions affecting the central nervous system), and asbestosis. Table 4 illustrates the observed, the expected, and the average annual mortality rates per 100,000 for selected underlying cause of death and SMR as cl[illegible] by age at 1940 and level of cumulative em[illegible] ment experience.

The main description of the results[illegible] sented in Table 4 is directed at the age gr[illegible] 25–44 age at entrance of the generation co[illegible] according to the corresponding cause of d[illegible] in order to lessen the possible influence of [illegible] vious employment.

All Causes of Death

It is noted that, with the exception of 17[illegible] and more years of level of cumulative emplo[illegible] ment experience, there is a consistent increase in the average annual mortality rates as the cumulative employment experience increases. For example, the average annual mortality rates due to all causes for age group 25–44 are 528.[illegible] for 0.1–2.0 years (control group); 1091 for 2.1–7.0 years, 2280 for 7.1–12.0 years, 6788 for 12.1–17.0 years, and 3398 for 17.1 and more years of cumulative years of employment experience. The same holds true with SMR values where, in the same age groups, there are values of 207 for 2.1–7.0, 432 for 7.1–12.0, 1287 for 12.1–17.0, and 644 for 17.1 and more years of employment experience.

All Neoplasms

Table 4 indicates an apparent increase in the average annual mortality rates for all neoplasms as the cumulative employment experience increased. For example, the average annual mortality rates for all neoplasms for the age group 25–44 are 132 for 0.1–2.0 years (control group), 348 for 2.1–7.0 years, 570 for 7.1–12.0 years, 3133 for 12.1–17.0 years, and 1081 for 17.1 and more years of cumulative employment experience. The same holds true with the SMR values where, in the same age group, SMR values are 264 for 2.1–7.0 years, 432 for 7.1–12.0 years, 2376 for 12.1–17.0, and 819 for 17.1 and more years of cumulative employment.

Malignant Neoplasms—Digestive Organs and Peritoneum

There was a total of 25 deaths in the age group 25–64 as of 1940 due to malignant neoplasms of digestive organs and peritoneum; only 3 deaths occurred in the control group (0.1–2.0 years of cumulative employment experience) and 22 deaths occurred in the higher levels. Because of the very small number of cases for each level of cumulative employment and age group, it is difficult to demonstrate a

relationship between the mortality rates from neoplasms of digestive organs and peritoneum and the cumulative employment experience. The average annual mortality rates, however, were higher for all the cumulative employment experience of any age group than for the control group. For example, the average mortality rates for employees with 7.1–12.0 years of cumulative employment experience was 12 times that of the control for the same age group 25–44 years.

Malignant Neoplasms—Lung, Bronchus, and Trachea

As is noted in Table 4, the increased mortality rates in association with the increase of cumulative employment experience is apparent for the age group 25–44 years, e.g., rates of 26 for 0.1–2.0 years, rates of 186 for 2.1–7.0 years, 163 for 7.1–12.0 years, and 1567 for 12.1–17.0 years. There was, however, a decline in the mortality rate for 17.1 and more years of cumulative employment experience. It is evident that the rate and risk for lung cancer does increase with duration of employment. The degree of risk appears highest after employment of 12 years or more. At this stage of our investigation, we cannot attach undue significance to the rate for lung cancer for Level I, since the data and specifically the Level-I employees' employment are limited to that which occurred after 1938, and we do not know what specific earlier year would represent the actual first year of employment in the company—in contrast to the year as utilized in this study for entrance into the cohort. However, Level I (0.1–2 years) for age group 25–44 can be considered a possible overestimate of the lung-cancer rate of individuals in this age group and level of employment experience. The consistency of the increase in rate, recognizing the built-in factors for successive levels of increasing employment, provides additional support to the relationship of lung cancer and asbestos exposure.

Cardiovascular Diseases

It is noted from Table 4 that there is a consistent increase in the average annual mortality rates as the cumulative employment experience increas[illegible]ample, the average annual mortality rates due to cardiovascular diseases except vascular lesions affecting central nervous system) for [illegible] age 25–44 are 211 for [illegible] 651 for 7.1–[illegible] and 849 for 17.1 and more years of cumulative employment experience. The same picture holds true with SMR values where in the same age group there are values of 132 for 2.1–7.0 years, 309 for 7.1–12.0 years, 495 for 12.1–17.0 years, and 403 for 17.1 and more years of cumulative employment experience.

Asbestosis

In Table 4, excluding the group with the level of cumulative employment experience of 17.1 and more years, the average annual mortality rates and SMR values increase with the increase of the cumulative employment experience for deaths due to asbestosis. For example, for age group 25–44, rates due to asbestosis were 0 (zero) for 0.1–2.0 years, 116 for 2.1–7.0 years, 244 for 7.1–12.0 years, 2089 for 12.1–17.0 years, and 540 for 17.1 and more years of cumulative employment experience.

It is of interest to note that among the total 41 observed deaths due to disease of respiratory system (for all age groups of employees who have worked more than 2 years in the asbestos industry) there were 31 deaths due to asbestosis, 5 deaths due to chronic interstitial pneumonia, and 1 death due to silicosis—a total of 37 deaths. Excluding these 37 deaths from the 41 observed deaths, the remainder will be 4 observed versus 3.7 expected (as was derived by applying the average annual mortality rate of internal control). This is an illustration of the fact that the excess in mortality among employees with prolonged cumulative years of employment experience is a true significant observation and not due to any bias of selection in the internal control.

Table 4 also provides rates and SMR by age group, in which the cohort is characterized as of 2.1 or more years of employment experience in comparison to Level I (1–2 years). The cohort is also characterized as "all levels," i.e., it includes Level I, which also compares the total with Level I as the internal control. These two additional characterizations of the cohort (2.1 and more, and all levels) serve to illustrate the averaging effect in the former and the dilution effect in the latter, which occurs in contrast to the rates observed for specific levels of employment experience for the corresponding age groups.

Discussion

Although we have overcome some of the limitations of our previous asbestos study[1] and

TABLE 4. STANDARD MORTALITY RATIO BASED ON OBSERVED (O) AND EXPECTED (E) NUMBER OF DEATHS DUE TO SELECTED UNDERLYING CAUSE AND MORTALITY RATES (R) PER 100,000 POPULATION AMONG COHORT DESCRIBED IN TEXT

Age level	Factor	[illegible]	[illegible]		[illegible]		12.1–17.0		17 & over		21 & more		All levels	
		O	O	E	O	E	O	E	O	E	O	E	O	E
						ALL CAUSES								
15–24	No	7	1	6.7	1	1.0	0	0.1	0	0.8	5	8.7	12	15.7
	R	238	142	238	238	238	—	238	—	238	137	238	182	238
	SMR	—	60		100		—		—		58		77	
25–44	No	20	47	22.7	28	6.5	13	1.0	44	6.8	132	37.1	152	57.1
	R	528	1091	528	2280	528	6788	528	3398	528	1680	528	1406	528
	SMR	—	207		432		1287		644		356		266	
45–64	No	19	31	11.1	25	7.9	39	8.1	31	10.7	126	39.8	145	57.0
	R	2804	7702	2804	8865	2804	13518	2804	8126	2804	9302	2804	7136	2804
	SMR	—	275		316		482		290		317		254	
65 & over	No	1	6	2.1	7	2.5	1	2.2	1	0.4	18	7.1	21	10.17
	R	5825	16667	5825	16471	5825	10667	5825	15385	5825	14694	5825	12069	5825
	SMR	—	286		283		183		264		252		207	
						ALL NEOPLASMS (140–239)								
25–44	No	5	15	5.7	7	1.6	6	0.3	14	1.7	42	9.3	47	14.3
	R	132	318	132	570	132	3133	132	1081	132	598	132	435	132
	SMR	—	264		432		2376		819		453		329	
45–64	No	6	6	3.6	6	2.5	6	2.6	8	3.4	26	12.0	32	18.0
	R	886	1491	886	2128	886	2080	886	2097	886	1920	886	1575	886
	SMR	—	168		240		235		237		217		178	
						MALIGNANT NEOPLASMS—DIGESTIVE ORGANS AND PERITONEUM (150–159)								
25–44	No	1	4	1.1	1	0.3	0	0.1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	R	26	70	26	126	26	—	26	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SMR	[illegible]	264		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	
45–64	No	—	1	1.2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	R	295	991	295	[illegible]	295	[illegible]	295	1048	295	886	[illegible]	[illegible]	[illegible]
	SMR	[illegible]	[illegible]		240		235		[illegible]		[illegible]		[illegible]	

										232	26	142	28	102	20
												355		211	
MALIGNANT NEOPLASMS—LUNG, BRONCHUS, TRACHEA (162–163)															
25–44	No.	1	8	11	2	03	3	01	6	03	19	18	20	28	
	R	26	186	26	163	26	1567	26	463	26	270	26	185	26	
	SMR	—	715		617		5939		1781		1038		712		
45–64	No.	4	1	24	3	17	1	17	4	23	9	82	13	120	
	R	590	248	590	1064	590	347	590	1048	590	664	590	640	590	
	SMR	—	42		180		59		178		109		108		
CARDIOVASCULAR DISEASES (400–468)*															
25–44	No.	8	12	91	8	26	2	04	11	27	33	148	41	228	
	R	211	279	211	651	211	1044	211	819	211	470	211	379	211	
	SMR	—	132		309		495		403		223		180		
45–64	No	9	11	53	11	37	20	38	17	51	59	180	68	270	
	R	1328	2734	1328	3901	1328	7279	1328	1456	1328	4356	1328	3346	1328	
	SMR	—	206		294		548		335		328		252		
ASBESTOSIS (5232)															
25–44	No	—	5	—	3	—	4	—	7	—	19	—	19	—	
	R	—	116	—	244	—	2089	—	540	—	270	—	176	—	
45–64	No	—	1	—	5	—	5	—	1	—	12	—	12	—	
	R	—	248	—	1773	—	1733	—	262	—	886	—	591	—	

*Except vascular lesions affecting CNS

some of the problems inherent to pre... studies in general, there still remains the ba... limitation of establishing more precisely the population at risk, as defined by department and occupation in the utilization of the Social Security approach in establishing company cohorts. The total population of a company may not be at risk. It is more likely that a smaller group of employees in specific departments and/or operations rather than those throughout the plant would be more directly exposed. Consequently, the asbestos-company cohort utilizing the Social Security approach constitutes a conservative estimate of risk because of the dilution factor of including all employees. This "dilution factor" was present also and probably was augmented in Enterline's asbestos industry study, which combined a number of asbestos companies.[1]

It must be realized that employment data prior to 1938 are not available from Social Security records and this unknown length of employment prior to 1938 could have some bearing on the interpretation of observations. It is well known that prior employment in the same or in a different plant depends on the age of the employee in 1940. Therefore, for example an employee whose age is 18 by 1940 is assumed to have no industrial employment prior to 1938 and an employee whose age is 48 by 1940 is assumed to have about 30 years of employment prior to 1938 since age 18 is considered to be the first age of active employment. The classification of the cohort by level of cumulative employment experience which is based on the employment record during 1938 to mid-1964 does not therefore represent the actual level of cumulative employment experience since the first year of employment in the asbestos plant could not be determined. This is specifically true for the older age groups, as of 1940. For each level of employment the classification for the young age group (i.e. 15–24) is considered to be the actual level of employment in the asbestos plant since this age group has no employment prior to 1938. Consequently the application of Level I as an internal control for the age group 15–24 provides the actual comparison between the various levels of cumulative employment experience. In the older age groups however, the comparative picture is different. For example in the age group 45–64, there is a period of unknown employment prior to 1938 which could average to 27 years (45 − 18 = 27). Level I for the age group 15–64 ...terized by 0.1–2.0 years of cumula... ...ment experience during the period 19... mid-1964, could actually represent a high... level of employment when the unknown em... ployment prior to 1938 is also considered.

The age group 25–44 lies between the t... age groups, 15–24 and 45–64, relative to th... employment experience prior to 1938, and... effects on the employment classification are pr... sented. Consequently, any comparison betwe... Level I and other levels for the older age grou... represent a conservative comparison. In essence... when the employment prior to 1938 is added... then the Level I for age 15–24 could be con... sidered to be the "actual" Level I, and for age... 25–44, when this prior employment is added... Level I could be a mixture of the equivalent of... Levels I, II, and III, finally, for age 45–64,... Level I could be a mixture of Levels III, IV,... and V. The mortality rates for Level I used in... the study, therefore, would for the older age... groups constitute a rate which represents that... of a level of employment that exceeds the limits... of the designated employment classification... For age group 45–64, this high rate of Level I... is carried through as the control comparison in... the development of the expected rates and SMR... in each succeeding level of employment experience and for each of the various categories of cause of death.

For these reasons, we have focused on the generation cohort utilizing the age group 25–44 at entrance as a homogeneous cohort, which provides a more representative indication of the progression and changes of rate according to various levels of employment and years of experience. Since there still remains the limitation of not knowing the employment prior to 1938, the rates derived will, in this respect, constitute a conservative estimate. In this method of establishing mortality rates, however, the use of an internal control of the same age group (age at entrance) equalizes the previous employment factor.

In the age-at-entrance method, all of the population of the specified age group will grow older by a constant number of years during the period of observation (1940 to mid-1964). This aging process, however, would not influence the results since the SMR and the expected number of deaths are derived by applying the average annual mortality rates from the internal control of the same age, which is treated and observed in the same manner.

The mean duration of employment and the

degree of environmental exposure prior to 1935 would be the same for any similar age group and different for various age groups as classified by age at 1940. Similarly, previous medical care prior to 1940 would then be the same as well as for subsequent years, but will vary with each age group. In this method, classifying the cohort by age as of 1940 and followed for 24.5 years provides a complete mortality pattern of a generation of each corresponding age group during the period of observation. The age-at-entrance (generation cohort) method provides a more precise measurement by restricting all the deaths to members of the corresponding generation at risk who have common characteristics pertaining to the year of birth, period of death, changes in environmental exposure, and previous employment exposure as well as changes in medical care and subsequent levels of employment experience. It is evident that an internal control, such as Level I, applied to the generation cohort method, does not have the limitations of age at death method and has a number of inherent advantages.[4]

In this respect, too, follow-up studies on confirmation of primary causes of death and supplementary histological examinations when applied to the cohort as a whole, include the subcohort designated as the internal control. This overcomes some of the problems previously experienced of the inability to apply the same effort of confirmation of diagnosis to the study and control groups because of size, composition, or location of the control group.

It was noted from the data presented that, with the exception of Level V of cumulative employment experience, there is a consistent increase in the average annual mortality rates as the cumulative employment experience increases. This relationship was more apparent for age 25–44 than in other age groups for the reasons explained above. Level V was an exception to the rule. In fact, the mortality rates for Level V were higher than those for Level I or Level II, but were not higher than that of Level IV. This drop of the mortality rate for Level V as compared to that in Level IV could be due to one or more of the following reasons. The employment experience for Level V differs from that of Level IV by the additional employment history during 1955–1964, which represents a period with much better environmental control; those who are classified as Level V in the cohort represent those with better [illegible] office employees or sales[illegible] mortality picture for Level V was observed for the period 1955 to mid-1964 as compared to the period of 1950 to mid-1964 for Level IV as a consequence of the dynamic changes of the cohort.[4]

The present study provides further confirmation of the high risk of cancer of selected sites in asbestos product workers and also furnishes the basis of an association of increased risk from cancer with the gradient of employment experience (Table 4). As was indicated, there was a consistent increase in the average mortality rate for all causes of death in general and specifically for malignant neoplasms, cardiovascular diseases, and asbestosis in association with more prolonged employment in asbestos industry. This increased mortality rate was evident for all cancer in general and specifically for cancer of lung, bronchus, and trachea and digestive organs. However, in evaluating malignant neoplasms by duration of employment, the problem of competing risk still holds: a person who was exposed to asbestos dust could die from asbestosis and/or cardiovascular diseases and/or malignant neoplasms.

Therefore, an important factor which influenced the extent of the observations relative to the strength of the association in this study was the question of competitive risks in the analysis of the causes of death.[17] The significance of the frequency of asbestosis as a cause of death, and its occurrence as a secondary cause of death, was noted in our earlier study. Deaths at earlier ages lessen the number of survivors, who may live long enough to meet the requirements of the latent period, to develop lung cancer or mesothelioma. Environmental exposure and dust concentrations were undoubtedly higher in the earlier years of manufacture and prior to the establishment of the cohort and chrysotile was used almost exclusively.[18,19] Consequently, more workers developed asbestosis more readily and died at an earlier age and this has lessened the extent of the findings relative to malignancy. Undoubtedly, continual long-term observation of the present cohort, with a further extension of the latent period, would be most appropriate, and in particular for the age group 15–24 and 25–44 at entrance to the generation cohort.

[illegible] present study, there was an unusually high number of malignancies specified on the death certificate as "primary site unknown." 8 [illegible] te males employed 2 or more years. [illegible] mite queries, to obtain further [illegible] histological re-

view of these cases This situation was unfortunate because the resolution of these "unknown" cases might have had some bearing on the observations pertaining to cancer of the digestive system, stomach, colon, and rectum or some other site. In our first study, such a histological review added to the number of lung cancers and detected several mesotheliomas. There were 9 cases of mesothelioma of the peritoneum and pleura, which occurred among 361 deaths of the cohort (2.5%). Hammond *et al.* observed 10 mesotheliomas (peritoneum and pleura) among 307 deaths. For malignant neoplasms of the central nervous system, there was 1 subject among the females who died in 1939 and 3 among the males who died between 1940 and mid-1964 There was 1 death due to lymphosarcoma and 4 deaths due to leukemia observed in the male group. Further interpretation of these malignant sites was deferred.

Of interest, too, was the higher mortality rate than that expected for suicides and accidents and homicides combined There were 8 deaths due to suicides and 15 deaths due to accidents and homicides in the total white male cohort. All of the suicides except 1 were employed in the asbestos industry for more than 2 years.

Useful supplementary epidemiological information relative to disease patterns can be obtained by considering the multiple causes of death and their sequence For example, in our present study, included in the 142 deaths of the cardiovascular system (330–334 and 400–468) were 11 subjects in whom asbestosis was indicated on the death certificate as a secondary cause of death and 1 with cancer of the large intestine as a secondary cause of death There were 6 cases coded primary as cor pulmonale, in 4 of which asbestosis was indicated as secondary cause of the subjects' death

We observed in the first study the contribution derived from further inquiry and how the supplementary information would have altered the sequence of coding of the cause of death as recorded on the death certificates

It was not possible in this extension of our original study to obtain further information to amplify adequately the relationships between secondary and primary causes of death

To a certain extent, the problem of multiple causes of death masked the proper interpretation of the cardiovascular problem observed in our asbestos study. Enterline[18] indicated a significantly high mortality from hypertensive heart disease among asbestos products workers as compared to that of United States and ... ers in other industries. Our findings did indi... cardiovascular diseases (excluding vascular l... sions affecting the central nervous system), w... associated with employment, as was evident... by the consistent increased mortality rate wi... more prolonged duration of employment in th... asbestos industry. The risk of dying from ca... diovascular disease was 2.5 times that of th... internal control for age 45–64 (as of 1940)... posure to asbestos dust, therefore, might affe... the cardiovascular system either directly (du... to an unknown mechanism) and/or indirectly (due to cor pulmonale and/or right heart fail... ure)

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O'Donnell,[19] a pathologist who had initially observed a high association between asbestosis and lung cancer among the employees of this plant, has now reported—based upon the admissions to only 1 of 3 main hospitals in the community area—55 cases of proved asbestosis with 28 malignant neoplasms 23 bronchogenic and 5 mesotheliomas of the peritoneum and pleura.[20] This is of particular interest to our study because of the 23 lung-cancer cases Only 12 employees could be identified as being in our 1938–1939 cohort, a significant factor when considered in light of the finding that of the 12 matched deaths of our cohort as compared with O'Donnell's lung-cancer cases, only 10 were so classified in our cohort and 2 were classified as deaths from other causes These additional 2 lung-cancer cases had accumulative employment experience of Levels II and IV, when these are added to the corresponding levels of employment experience of the cohort, the mortality rate shown in Table 4 would be raised correspondingly and the total lung cancers for the white males increased to 2... the total cohort.

This lack of identification o... one-sixth of the matched cas... evidence of the underestimati...

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This lack of identification one-sixth of the matched c evidence of the underestim

in our cohort, particularly when it is realized that the observations made on the total matched cases (related to one-fourth of the lung cancers in our asbestos cohort) constitute admissions to only one of the hospitals. O'Donnell, moreover, reported only cases of respiratory cancer that were associated with asbestosis.

Although we observed 9 cases of mesothelioma, 1 of the pleura and 8 of the peritoneum, O'Donnell reported 3 additional cases of mesothelioma in employees of the same plant (which workers were not part of our 1938–1939 cohort).

Another death due to mesothelioma of the peritoneum occurred in a former employee who was not in our cohort and was not in O'Donnell's group of cases of mesothelioma. This total of 13 cases of mesothelioma (all of employees from a single plant in a small community engaged in the manufacture of the same asbestos products) provides a very strong association for such a rare disease, in which all except 1 of the 10 mesothelioma of our study were employed for more than 2 years.

In general, the pathological confirmation by O'Donnell of lung cancers and mesothelioma among former employees of the same plant (from which plant our cohort was established, over the same period of time—1940–1965) further substantiates the relationship of malignancies and asbestos exposure, observed in our cohort study of employees classified by duration of employment.

Summary and Conclusions

A cohort study of 1265 white males and 228 white females who were employed in a plant manufacturing asbestos products in 1938–1939 was established through Social Security records and observed to mid-1964.

The cohort study represents a series of refinements in methodology pertaining to prospective epidemiological studies of industrial populations. The Social Security cohort approach has been developed to include the classification of all members of a cohort by duration of employment from 1938 in the plant under study. A method also is demonstrated of establishing a homogeneous generation cohort and an internal control according to age and specific levels of employment experience for a company under study, as derived from Social Security.

It was observed in this study that when the 1938–1939 cohort was considered as individual groups, that the 1939 one had a lower mortality experience than the 1938 one which was primarily influenced by the years of employment prior to 1938. Further, the 1939 cohort observation provided an indication of the effectiveness of environmental changes and control measures in subsequent years. For the purposes of our study, the combined cohort of 1938–1939 was utilized and the levels of accumulative employment experience from 1938 to mid-1964 and were classified as follows: Level I, 0.1–2.0 years, Level II, 2.1–7.0 years, Level III, 7.1–12.0 years, Level IV, 12.0–17.0 years; and Level V, 17.1–27.5 years.

Of employees in the 1938 and 1939 cohort that had a cumulative employment experience of 2 years or less during the period of 1938 to mid-1964, Level I was utilized as an internal control classified by age.

There was a total of 330 deaths among the white males and 31 for the females. Among the males there were 35 malignant tumors of the lung and 43 deaths due to respiratory disease, 31 of which were due to asbestosis. Among the females, of the 11 deaths due to malignancies, 6 were due to malignancy of the lung and all 8 deaths due to respiratory diseases were due to asbestosis. There were 9 malignant neoplasms of the peritoneum and/or mesothelioma, 8 in the males and 1 in the females. Among the 71 malignancies for the white males employed 2 or more years, 8 were specified on the death certificate as "primary site unknown."

The relationship of cumulative employment experience on the mortality pattern was assessed for all causes, all neoplasms, malignant neoplasms of the digestive organs and peritoneum, malignant neoplasms of lung, diseases of cardiovascular system (except vascular lesions affecting central nervous system), and asbestosis. There was a consistent increase in the average mortality rates as the cumulative employment experience increased. This was true for each of these categories with the exception of the digestive system, which involved a smaller number of cases and analysis could not be made.

The problem of "competing" risks of deaths due to asbestosis, cardiovascular disease and/or malignant neoplasms, and the relationship of primary and secondary causes of death are also discussed. It is concluded that the duration of cumulative employment experience among asbestos workers in the asbestos-products company was directly related to a general increased mortality rate for all causes of death and spe-

cifically for malignant neoplasms, lar diseases, and asbestosis.

Addendum

A few months after the close of the cohort follow-up in mid-1964, 11 deaths among the 1938–1939 cohort were reported. The causes of these 11 deaths follow: 1, lymphosarcoma of the lung, 6, cardiovascular diseases (including 1 case of cerebral embolism), 1, pulmonary fibrosis; 2, asbestosis; and 1, suicide. All of the deceased were employed in the same asbestos plant for more than 7 years since 1938.

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ORACLE OF AESCULAPIUS

Serpents were sacred to Aesculapius the healer probably because of a superstition that those animals have a faculty of renewing their youth by a change of skin. The worship of Aesculapius was introduced into Rome in a time of great sickness, and an embassy sent to the temple of Epidaurus to entreat the aid of the god Aesculapius was propitious and on the return of the ship accompanied it in the form of a serpent Arriving in the river Tiber the serpent glided from the vessel and took possession of an island in the river, and a temple was there erected to his honor

Bulfinch's Mythology, by Thomas Bulfinch Thomas Y Crowell Company, New York, 1947, p 298