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ASBESTOS-ASSOCIATED DISEASES IN A COHORT OF CIGARETTE-FILTER WORKERS

JAMES A. TALCOTT, M.D., WENDY A. THURBER, R.N., ARLENE F. KANTOR, DR.P.H.,
EDWARD A. GAENSLE, M.D., JANE F. DANAHY, B.A., KAREN H. ANTMAN, M.D., AND FREDERICK P. LI, M.D.

Abstract To estimate the effects on health of occupational exposure to crocidolite, a highly toxic form of asbestos, we studied a cohort of 33 men who worked in 1953 in a Massachusetts factory that manufactured cigarette filters containing crocidolite fibers from 1951 to 1957.

Twenty-eight of the men have died, as compared with 8.3 deaths expected. This increased mortality was attributable to asbestos-associated diseases. Fifteen deaths were caused by cancer, as compared with 1.8 expected (relative risk, 8.2; 95 percent confidence interval, 4.6 to 13.4), including eight from lung cancer, five from malignant mesothelioma, and two from other types of cancer.

THE inhalation of asbestos may result in pulmonary fibrosis (asbestosis),¹ lung cancer,² or malignant mesothelioma.³ We recently observed three cases of malignant mesothelioma among former employees of a Massachusetts company that manufactured cigarette filters containing crocidolite asbestos from 1951 to 1957.⁴ We now report a marked excess in mortality and morbidity from asbestos-related diseases in an independent cohort of 33 workers who made these filters.

METHODS

From 1951 to 1957, a subsidiary of a Massachusetts company manufactured cigarette filters according to a patented "dry" and dusty process in which asbestos, cotton, and acetate fibers were mechanically mixed, carded, and deposited on crepe paper.⁵ The parent company produced other asbestos-containing products between 1942 and 1971 by the conventional "wet" papermaking process, in which asbestos was added to a pulp. Crocidolite, a member of the amphibole family of long, straight asbestos fibers, was the primary type of asbestos used. It is strongly associated with asbestosis, lung cancer, and malignant mesothelioma,^{3,6} presumably because of its unusual resistance to degradation in the lung.⁷ Measurements at six production locations in the factory on October 27, 1952, showed an average of 80 particles of asbestos dust per milliliter of air, which was within the then-current Massachusetts standard of 175 particles per milliliter. These levels greatly exceed the current National Institute for Occupational Safety and Health standard of 0.1 asbestos fibers (not particles) per milliliter.

A list of all employees directly involved in manufacturing cigarette filters at the factory on September 22, 1953, was obtained from the records of the Massachusetts Division of Occupational Hygiene. The cohort included none of the factory workers previously described by us.⁴ The median age of these 33 white men on that date was 34 years (range, 21 to 67). The subjects were studied from that date until their death or until December 31, 1988, the closing date of

the study (the mortality analysis), or until the diagnosis of a first cancer (the morbidity analysis). There were 773 and 766 person-years of follow-up in the mortality and morbidity analyses, respectively.

We conclude that the extremely high morbidity and mortality in these workers were caused by intense exposure to crocidolite asbestos fibers. (*N Engl J Med*; 321:1220-3.)

We attempted to contact each worker, or his next of kin if the worker had died. We requested information about the worker's employment and health history and asked permission to review his medical records. For 18 workers, this information was supplemented with data gathered in an ongoing health survey of company employees begun by one of us in 1971. For 29 workers we were able to determine the total duration of employment by the company; for 23, the length of time spent manufacturing cigarette filters was known.

An experienced nosologist determined the underlying cause of death from the death certificates of all deceased workers. Medical records establishing the cause of death independently were available for 22 of the 28 deceased workers, including all those whose death was possibly related to asbestos. These included the results of a postmortem examination in 8 workers, other pathology reports for 10, and other medical records for 4. Only death-certificate diagnoses were obtained for six workers. All diagnoses of cancer were verified by a pathology report (18 workers) or radiographic and endoscopic studies (1 worker). Asbestosis was diagnosed in deceased workers on the basis of the presence of pulmonary fibrosis and asbestos bodies (in 12 workers) or clinical studies (in 3 workers). In living workers, asbestosis was diagnosed on the basis of a chest radiograph scored by one of us as 1/0 or more, according to the International Labour Office's scheme for the classification of pneumoconioses.⁸

Relative risks for mortality, or the ratio of the numbers of deaths observed to the numbers expected, were based on death rates specific to age and calendar time, according to cause, among the U.S. male population.⁹ The numbers of newly diagnosed (incident) cancers observed, other than malignant mesothelioma, were compared with those expected on the basis of incidence rates specific to age and calendar time, according to site, from the Connecticut Tumor Registry.¹⁰ More stable expected values for malignant mesothelioma, an uncommon tumor, were calculated with data from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, which provided rates in approximately 10 percent of the U.S. population for the time periods 1973 to 1976 and 1977 to 1980^{11,12} (and Connelly R; personal communication). In the calculations of significance and confidence intervals, an underlying Poisson distribution was assumed.

RESULTS

Twenty-eight (85 percent) of the 33 workers had died, and 5 were alive. The 28 deaths observed were 3.4 times the number expected (8.3 deaths) on the basis of mortality rates for the U.S. white male population.

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Supported in part by a grant (1F32CA06242) from the National Cancer Institute and by the Kellogg Foundation Program in Clinical Effectiveness. Ms. Thurber is the recipient of an Amy Potter Research Nursing Fellowship, and Dr. Gaensler has received a Research Career Award (HL1173) from the National Heart, Lung, and Blood Institute.

Table 1. Observed and Expected Numbers of Deaths among 33 Cigarette-Filter Makers, According to Cause of Death.*

CAUSE OF DEATH	NO. OF DEATHS		RELATIVE RISK (95% CI)
	OBSERVED	EXPECTED	
Cancers (ICD 140-239)	15	1.8	8.2 (4.6-13.4)
Diseases of respiratory system (ICD 460-519)	7	0.5	14.7 (5.9-30.3)
Diseases of circulatory system (ICD 390-458)	5	4.1	1.2 (0.4-2.8)
All other	1	1.9	0.5 (0.0-3.0)
Total	28	8.3	3.4 (2.2-4.9)

*CI denotes confidence interval, and ICD International Classification of Diseases.

lation (Table 1). This increased mortality was primarily attributable to asbestos-associated cancers and other respiratory diseases. Eight deaths were caused by lung cancer (relative risk, 13.1; 95 percent confidence interval, 5.6 to 27.2), five by malignant mesothelioma, and five by asbestosis. Another worker, whose death certificate listed emphysema as the cause of death, died seven months after the diagnosis of a lung adenocarcinoma.

The relative risk of death was higher during progressively later periods of follow-up: 2.1 during the first 10 years, 2.4 during the second decade, and 4.8 thereafter (17 deaths observed; 95 percent confidence interval, 2.8 to 7.7). In the most recent follow-up period, 1973 to 1988, six deaths were due to lung cancer, five to mesothelioma, three to asbestosis, and one each to rectal cancer, bladder carcinoma, and acute myocardial infarction.

Cancer developed in 19 of the 33 workers in the cohort during the period of follow-up, as compared with 3.5 cases of cancer expected (Table 2). Among the 19 were 2 living workers with lung cancer and 1 with multiple myeloma. Eleven had lung cancer and 5 had malignant mesotheliomas. Twenty-five workers (76 percent) were known to have been smokers during their lifetimes, 5 (15 percent) were nonsmokers, and for 3 (9 percent) smoking status was unknown. All 11 workers in whom lung cancers developed had been cigarette smokers. In 3 of these patients, the cancers were not diagnosed in communities near the factory, and at the time of diagnosis the medical histories obtained on hospital admission and the discharge summaries did not mention exposure to asbestos. Asbestosis was diagnosed in 19 workers, including the 5 workers who died from the disease, 10 who were diagnosed incidentally on the basis of pathology specimens, and 4 of the 5 men who were still alive.

For 23 workers whose period of cigarette-filter making could be determined, the median duration of employment was 1.7 years (range, 0.7 to 4). The median time spent at other jobs in the paper company before 1971, when the use of crocidolite ended, was 16 years (range, 0 to 25). The median intervals from the first exposure to asbestos to the diagnosis of cancer were 28

years for lung cancer (range, 17 to 40) and 34 years for malignant mesothelioma (range, 26 to 37). We were unable to find an association between either duration of filter making or total time employed by the company and asbestos-related deaths, which predominated in all exposure groups. For example, of six workers with fewer than 2.5 years of other work at the company, three died of lung cancer, one died of peritoneal mesothelioma, one died of asbestosis, and one is alive. No worker had a recognized exposure to asbestos outside the workplace. Two workers were exposed to other types of dust — one as a cotton weaver for 4 years and one (whose diagnosis at death was asbestosis) as a coal miner for 20 years.

DISCUSSION

The 3.4-fold increase in the mortality rate in our cohort of cigarette-filter makers was almost entirely attributable to the effect of 18 deaths from asbestos-associated diseases: lung cancer, malignant mesothelioma, and asbestosis. Lung cancer probably contributed to another death and has been diagnosed recently in two of the five living workers. Asbestosis developed in at least 19 of 33 workers, or 58 percent.

The relative risk of death from lung cancer in this cohort, 13.1, is similar to the highest reported rates in other industries, which range from 1.5 to 7.0.¹⁴⁻¹⁹ Since differences in analytic techniques and the composition of study and reference populations may influence relative risks,²⁰ these comparisons are only approximate. Malignant mesothelioma and asbestosis are rare causes of death, for which the population rates are less reliable than those for lung cancer. Each accounted for 5 of the 28 observed deaths in our cohort (18 percent) — a large proportion even among asbestos workers.^{19,21}

Several factors may account for such high death rates from asbestos-related diseases in our study. One is the predominant exposure to crocidolite asbestos, which has been associated with a higher risk than other asbestos fibers for malignant mesothelioma and possibly other asbestos-associated diseases.^{6,22,23} In most industrialized nations other than the United States, crocidolite is now regulated more strictly than other asbestos fibers.²⁴ The outcomes in cohorts of

Table 2. Observed and Expected Incidence of Cancer among 33 Cigarette-Filter Makers, According to Site.*

TYPE OF CANCER	NO. OF CANCERS		OBSERVED/EXPECTED (95% CI) ^b
	OBSERVED	EXPECTED	
Lung	11 ^c	0.7	15.1 (7.5-27.0)
Malignant mesothelioma ^d	5	0.01	460 (150-1080)
Other malignant cancers	3	2.7	1.1 (0.2-3.2)
All	19	3.5	5.5 (3.3-8.6)

*CI denotes confidence interval.

^bIncludes four squamous-cell tumors, two adenocarcinomas, three small-cell tumors, one large-cell tumor, and one undifferentiated tumor.

^cIn three, the primary site was not determined, and in two, the primary

manufacturing workers with a predominant exposure to crocidolite have been described previously in Britain²¹ and Canada,²⁶ but not the United States. In addition, the nature of the industrial process may have had an independent effect on outcome. McDonald and coworkers found a higher incidence of lung cancer (at comparable estimated levels of exposure to asbestos) among asbestos textile workers than among asbestos millers and miners and manufacturers of friction products. They hypothesized that the unrecognized exposure of textile workers to crocidolite or the generation of a higher proportion of respirable sizes of asbestos fiber in textile manufacturing may explain the difference.¹⁸ The dry, dusty mechanical mixing and carding of asbestos in cigarette-filter making may also have exposed our cohort to a highly respirable dust.

Difficulties in the retrospective estimation of the intensity and duration of occupational exposure to asbestos are common and were encountered in the current analysis. Other published reports suggest a dose-response relation between exposure to asbestos and asbestosis, lung cancer, and perhaps malignant mesothelioma.^{6,22} The measured levels of asbestos dust at the cigarette-filter factory we studied were much higher than the current standard, but industrial exposures of this magnitude were often permitted in industrialized nations at the time.²⁷ Moreover, the dust measurements obtained at this workplace on a single day may not be representative. Asbestos-associated diseases developed in nearly all the 33 workers in this cohort, making it difficult to identify additional factors in the work environment that modify risk. Although the duration of exposure was not known in the case of all workers, very brief exposures were associated with the subsequent development of asbestos-related disease; one man who died of asbestosis 27 years later made cigarette filters for less than nine months and had no other exposure to asbestos. Thus, even a brief exposure to this dry process apparently resulted in a high risk, a possibility that is supported by an earlier report of a worker employed part-time for nine months as a cigarette-filter maker, in whom symptomatic asbestosis developed 18 years later.²⁸ However, the latency period observed in our subjects between the first exposure to asbestos and the diagnosis of cancer was not shorter than that observed previously.²⁹ We could identify no incremental risk of asbestos-related disease that was incurred by additional employment at the parent company, despite the additional exposure to crocidolite dust. In the manufacturing of other paper products at the company, water was added to the asbestos and other fibers to produce a pulp. The wet pulp probably produced a less dusty environment during mixing and handling than did the dry process of making cigarette filters.

Cigarette smoking, a known cocarcinogen with asbestos for lung cancer, probably contributed to the

high incidence of this disease in our cohort. However, the proportion of men in our study who smoked at any time (76 percent) was within the reported range (67 to 94 percent) for industrial cohorts exposed to asbestos in Western nations.³⁰

In three workers with lung cancer, exposure to asbestos appears to have been overlooked at first as a potential cause. These omissions may reflect the fact that asbestos has a much less common contributory role than cigarette smoking in causing lung cancer. However, documenting occupational exposure to asbestos has medical and legal importance for the patient with lung cancer, which is a more common asbestos-related cause of death than malignant mesothelioma or asbestosis.³¹

These results emphasize that intense, localized occupational exposures to asbestos may have effects decades after the exposures cease and that such effects may remain unrecognized and unreported. Physicians must be alert to the appearance of asbestos-related diseases from novel sources of industrial exposure. The risk of such diseases in persons who smoked cigarettes containing this filter material is unknown.

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MECHANISMS OF DISEASE

FRANKLIN H. EPSTEIN, M.D., *Editor*

HYPERCAPNIA

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HYPERCAPNIA is a well-recognized consequence of a variety of diseases, not only those involving the lungs but also those affecting the neural, muscular, chest-wall, and circulatory components of the respiratory system. In the past 20 years, we have developed a greater appreciation of the way these components interact in the genesis of hypercapnia. The impaired elimination of carbon dioxide that results in hypercapnia reflects not merely abnormal lung function, but rather a complex interaction of abnormalities in respiratory drive, muscle function, and lung function.

In this paper, we will first consider the fundamental factors controlling the elimination of carbon dioxide and thus determining the partial pressure of arterial carbon dioxide (PaCO_2). We will then discuss the mechanisms and clinical implications of hypercapnia to establish the clinical context in which it commonly occurs. We will stress the ways that the gas

exchanger (the lungs), the mechanical system (chest wall and respiratory muscles), and the control system (respiratory centers of the central nervous system) contribute to the production of hypercapnia in disease states.

FUNDAMENTAL FACTORS DETERMINING PaCO_2

According to the standard equation, PaCO_2 is proportional to carbon dioxide production ($\dot{V}\text{CO}_2$) and inversely proportional to alveolar ventilation ($\dot{V}_A$):

$$\text{PaCO}_2 = K \frac{\dot{V}\text{CO}_2}{\dot{V}_A}$$

The constant K has the value of 0.863 mm Hg; carbon dioxide production is expressed in milliliters per minute under standard conditions (dry gas at standard temperature and pressure) and alveolar ventilation is expressed in liters per minute under conditions (saturated gas at body temperature and pressure). Alveolar ventilation represents the component of total ventilation per minute (expired minute ventilation) that reaches perfused alveoli and is therefore effective in the elimination of carbon dioxide. The portion of expired minute ventilation not reaching the alveoli, remaining in airways, is "wasted" in terms of gas exchange and is frequently referred to as dead-space ventilation.

Because dead-space ventilation does not contribute to the elimination of carbon dioxide whereas alveolar ventilation does, any change in the relative amount of dead space to alveolar ventilation will alter the volume of carbon dioxide eliminated, assuming expired minute ventilation is constant. The partitioning of each breath into a dead space and an alveolar component is commonly expressed as the ratio between the volume of dead space and the total volume per breath—the tidal volume. This ratio, normally ≤ 0.50 , is altered by varying the tidal volume, since the an

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