Interaction of Asbestos, Age, and Cigarette Smoking in Producing Radiographic Evidence of Diffuse Pulmonary Fibrosis

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The study of 3,472 chest x-rays from four populations with different levels of exposure to asbestos and with different cigarette smoking histories shows that smoking in the general population does not produce pulmonary fibrosis recognizable on chest radiography. In the general population of Michigan, the prevalence of a radiographic pattern of fibrosis was 0.5 percent in men and 0.0 percent in women. In a Long Beach, California census tract population, the prevalences were 3.7 percent for men and 0.6 percent for women. Similarly, cigarette smoking does not enhance fibrosis when the exposure to asbestos has been as light as that in households of shipyard workers. Asbestosis was recognized in 6.6 percent of 137 shipyard workers' wives who have never smoked and 7.6 percent of 132 who had ever smoked. Cigarette smoking and asbestos appear to be synergistic in those occupationally exposed to asbestos (as insulators), since 7.2 percent of 97 nonsmokers and 20.5 percent of 316 ever-smokers showed fibrosis. This apparent synergy was also found in shipyard workers up to age 70 with 31 percent of nonsmokers and 43.3 percent of ever-smokers having fibrosis. There were increases of approximately 10 percent in the prevalence of fibrosis in cigarette smokers and nonsmokers for each decade after age 40.

Diffuse pulmonary fibrosis has been recognized with increasing frequency since attention was called to this diagnosis by Hamman and Rich [1] in the 1940s. Environmental causation has been shown for asbestosis and other less frequent dust diseases. The characteristic radiographic pattern has been seen in the collagen-vascular diseases, particularly scleroderma, mixed connective tissue disease, and rheumatoid arthritis.

Assessment and quantitative analysis of chest radiographs for diffuse pulmonary fibrosis, and thus, comparison of populations have been substantially improved with widespread use of the International Labor Organization classification for radiographs for pneumoconiosis, most recently revised in 1980 [2]. Cigarette smoking, which impairs mucociliary clearance and blankets airways and alveoli with particles that can cause lung cancer, chronic bronchitis, and emphysema, has also been incriminated in diffuse pulmonary fibrosis [3]. This opinion is based on lesions seen microscopically in lungs of cigarette smokers [4,5], and on an accentuation of bronchovascular markings noted in 1.4 percent of 2,825 adult volunteers studied by 70 mm photofluorography [6]. The latter observations led to the conclusion that cigarette smoking, particularly duration of smoking, is the dominant causal factor in diffuse pulmo-

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nary fibrosis, thus, more important than age, sex, occupation, and other environmental influences [3,6]. Unfortunately, occupational histories were not included in these analyses so that the possibility that pneumoconiosis accounted for these results was not addressed.

The present analysis was made using the International Labor Organization classification for pneumoconiosis to interpret standard (14 by 17 inch) chest radiographs from 1,177 adults in a stratified random sample of Michigan residents [7], 1,347 adults in a Long Beach, California census tract [8], 419 male midwestern insulators [9], and 260 male shipyard workers and 269 wives of these workers from the Los Angeles Harbor area [7].

SUBJECTS AND METHODS

Chest radiograph findings were studied in 3,472 men and women from four populations in the United States. The first population was a stratified random sample of the state of Michigan. It included adults over the age of 18 who participated in a study to assess possible polybrominatedbiphenyl contamination of the general population of Michigan and compare it with that in residents on farms quarantined for polybrominatedbiphenyl exposure. They were studied by a team from the Environmental Sciences Laboratory of the Mount Sinai School of Medicine of the City University of New York in 1978. Standard x-rays were obtained together with pulmonary function test results and extensive questionnaire and health assessment information. The chest radiographic findings were sorted into normal and abnormal by one of us (K.H.K.). The films that showed abnormalities were interpreted for pneumoconiosis by three experienced physicians as described later.

The 1,347 members of a census tract from Long Beach, California were studied in 1976 by a team from the University of California, Los Angeles, for the purpose of assessing the health effects of air pollution [10]. Adults over 18 were examined by questionnaire, spirometry, and chest radiography. The chest x-rays were evaluated by three physicians as described later. Occupational histories were taken, although these did not include as extensive details as were obtained in the Michigan population.

The third group consisted of 419 midwestern insulators, members of the Insulators and Asbestos Workers Union, who were studied by chest radiography and spirometry to assess the presence of asbestosis and its functional effects. They were all active members of six union locals in Ohio and Michigan in 1977. Their chest x-rays were interpreted by one reader for pneumoconiosis using the International Labor Organization criteria.

The male shipyard workers and their wives were recruited from the Los Angeles Harbor area in 1981 as members of a study to determine the prevalence of asbestosis in families of shipyard workers. There were 260 white male shipyard workers and 269 wives. The workers were 20 years or more from initial shipyard employment and probable initial contact with asbestos. They were studied by questionnaires, chest radiography, and pulmonary function testing including the same information obtained from the Michigan population sample. The chest x-rays were evaluated by the same three physicians who interpreted those from the Michigan population and the Long Beach census tract.

The radiographs from shipyard workers and wives and those from the Long Beach census tract had their identification concealed and were mixed for evaluation by the aforementioned three experienced physicians. The procedure was that of the International Labor Organization 1980 revision utilizing comparison and level grading of profusion (0, 1, 2, and 3). We used arithmetic averaging of radiographic findings deemed as positive, which by the International Labor Organization classification is a profusion of irregular opacities of 1/0 or greater, by at least two interpreters. Radiographs upon which there were disagreements of greater than one full profusion grade were re-evaluated by the three physicians to reach a consensus. Evidence for pleural disease was also coded by the interpreters but was not considered in this report. The evaluations were entered into a computer and analyzed with a standard statistical package (Statistical Analysis System).

RESULTS

In the stratified random sample from the Michigan population, three of 584 men and none of the 583 women had diffuse pulmonary fibrosis equal to or greater than 1/0 profusion by International Labor Organization criteria (**Table I**). Thus, these men and women who were without known exposure to asbestos had a prevalence of diffuse pulmonary fibrosis of 0.5 percent and 0 percent, respectively, i.e., prevalence of diffuse pulmonary fibrosis in this general population was very low. The population mean age averaged 42 years for men and women, and occupational exposure to asbestos had occurred in 10 percent of men and 27 percent of women. Sixty-nine percent of these men were or had been cigarette smokers, and 50 percent of the women had ever smoked.

The Long Beach census tract population was almost a decade older with women averaging 52 years and men averaging 50 years (Table I). The women had a prevalence of diffuse pulmonary fibrosis of 0.6 percent and the men had a prevalence of 3.7 percent. Positive exposure histories on the questionnaire had permitted removal of 12 men and two women who had clear occupational exposure to asbestos, thus yielding these prevalences. A history of current or past cigarette smoking was present in 60 percent of men and 40 percent of women in this population.

The wives of shipyard workers had an average age of 58 and were divided into 137 women who had never smoked and 132 who were current or ex-cigarette smokers (Table I). Prevalence of pulmonary fibrosis was 6.6 percent in the nonsmoking group and 7.6 percent in the group who had ever smoked cigarettes. It should be understood that these women had at least 20 years of relatively low exposure only in the home to asbestos brought in by their husbands who were shipyard workers. This resulted in an overall prevalence of 7.1 percent of

typical lung changes of asbestosis (diffuse pulmonary fibrosis). Approximately 4 percent of both cigarette smokers and nonsmokers had pleural thickening or plaques, in addition to diffuse fibrosis. There was no significant difference between the prevalence of diffuse pulmonary fibrosis in those who had smoked cigarettes versus nonsmokers.

In **Table II,** the prevalence of diffuse irregular opacities or pulmonary fibrosis for the midwestern insulators is shown for the three smoking categories. Seven of 97 or 7.2 percent of nonsmokers with a mean age of 40 years had signs of asbestosis. In contrast, 22.1 percent of exsmokers with a mean age of 44 years had diffuse pulmonary fibrosis and 19.4 percent of the current smokers with an average age of 48.2 years had such changes. Thus, at the exposure levels considerably above those for shipyard workers' wives, the nonsmoking midwestern insulators had a very similar prevalence of asbestosis, but they showed these changes 14 years earlier. The prevalence of asbestosis in smokers and exsmokers was increased more than twofold above that in nonsmokers. Because exsmokers were four years older and current smokers 8.2 years older than nonsmokers, and therefore had more years from onset of exposure, these risk ratios should be interpreted with caution.

The prevalence of diffuse pulmonary fibrosis for 260 male shipyard workers was 31 percent in nonsmokers and 40.5 percent in workers who had ever smoked (**Table III**). This difference was significant ($p < 0.05$). Analysis of asbestosis in these persons by their decades of birth showed that in those born before 1910, 71.4 percent of nonsmokers and 60 percent of those who had ever smoked had diffuse pulmonary fibrosis. In the 1911 to 1920 and 1921 to 1930 decades, there was a clear difference of 1.6 to 1 between the ever-smokers' prevalence of irregular opacities and that of men who had never smoked. In the group born between 1931 and 1940, which had the lowest prevalence of diffuse pulmonary fibrosis, the ratio increased to 2.2 to 1. Smoking seems to enhance the appearance of asbestos-related diffuse pulmonary fibrosis. In these workers, lengthening the interval from initial exposure (coupled with the accumulation of exposure years) increased the prevalence of asbestosis by about 10 percent per decade in both smoking categories. Why did the group born in 1899 to 1910 have a "reversed ratio" of 0.84? Perhaps lapse of time with aging permitted the nonsmokers to catch up with the smokers. More likely it reflects the study of survivors who have not died from cancer and heart disease.

COMMENTS

These data show first that smoking did not produce diffuse pulmonary fibrosis in the general population as it was sampled in Michigan. Second, men showed an increased prevalence of pulmonary fibrosis in a local census tract

TABLE I **Diffuse Interstitial Pulmonary Fibrosis of Profusion of 1/0 or More (International Labor Organization Criteria) in Three Groups**

	Men	Women
Stratified Random Sample of Michigan Population, 1978		
Mean age (years)	41.9	43
Number with diffuse pulmonary fibrosis/number in population	3/594	0/583
Percent	0.5	0
Long Beach Census Tract Population, 1976		
Mean age (years)	50	52
Number with diffuse pulmonary fibrosis/number in population	25/673	4/674
Percent	3.7	0.6
Wives of Shipyard Workers, 1981		
Mean age (years)		58
Nonsmokers		
Number with diffuse pulmonary fibrosis/number in population		9/137
Percent		6.6
Smokers		
Number with diffuse pulmonary fibrosis/number in population		10/132
Percent		7.6

TABLE II **Pulmonary Parenchymal Asbestosis of Profusion 1/0 or More (International Labor Organization Criteria in 419 Midwestern Insulators by History of Cigarette Smoking**

Smoking Category	Mean Age (years)	Number with Asbestosis/Number in Population	Percent	Risk Ratio
Nonsmokers	40	7/97	7.2	
Exsmokers	44	29/131	22.1	3.1
Current smokers	48.2	37/191	19.4	2.7

TABLE III **Proportion of Parenchymal Asbestosis of Profusion 1/0 or More (International Labor Organization Criteria) in Shipyard Workers Who Had Ever Smoked and Never Smoked, Arranged by Decade of Birth**

	Never Smoked		Ever Smoked		
Decade	Number with Asbestosis/ Number in Population	Percent	Number with Asbestosis/ Number in Population	Percent	Risk Ratio (ever smoked/ never smoked)
1896–1910	5/7	71.4	15/25	60.0	0.84
1911–1920	4/13	30.8	42/86	48.8	1.6
1921–1930	4/17	23.5	28/75	37.3	1.6
1931–1940	1/8	12.5	8/29	27.6	2.2
Totals	14/45	31.0	93/215	43.3	1.4

population from Long Beach, California, a sample that probably included shipyard, industrial, and oil refinery workers. Third, at the levels of asbestos exposure that occur in the homes of shipyard workers, 7 percent of their wives, after a minimum of 20 years from initial home exposure, had asbestosis. However, in this group, cigarette smoking did not enhance the prevalence of diffuse pulmonary fibrosis due to asbestos exposure.

Fourth, insulators who were on the average 15 years from initial occupational exposure to asbestos, which almost certainly was at higher concentrations than in the homes of shipyard workers, showed a more than twofold increased prevalence of diffuse interstitial fibrosis among current and exsmokers compared with nonsmokers.

Fifth, when male shipyard workers were divided into nonsmokers and those who had ever smoked, the smokers had more fibrosis than did nonsmokers for every age group until the very oldest. The higher prevalence of asbestosis in nonsmokers in the oldest decade may be attributable to chance because of small numbers. However, there may be a greater likelihood for nonsmokers to survive into this age cohort or possibly a catching-up of the fibrotic process as additional years of survival increase the duration since initial exposure to asbestos.

Diffuse interstitial pulmonary fibrosis in those who are susceptible presumably reflects an interaction of the burden of the causal agent, the susceptibility of the host, and elapsed time for accumulation of effect. This susceptibility includes the interaction of host factors that are not fully understood, but are probably multiple and are not, at present, accessible to modification. There is no reason to believe that they vary in any dependent fashion with cigarette smoking behavior. Age is one measure of accumulation of one or more specific fibrogenic agents such as asbestos and of elapsed time since initial exposure. This is certainly reflected in the data presented, showing that as the mean age of the population group increases in either the insulators or the shipyard workers, the prevalence of diffuse interstitial pulmonary fibrosis rises. The evidence, although inadequate to prove the hypothesis, suggests that a greater lapse of time may permit the nonsmoker to have as high a prevalence of asbestosis, i.e., diffuse pulmonary fibrosis, as does the cigarette smoker. This possibility should be examined by further exploration of populations with asbestosis.

The alveolar burden of particles is the net result of deposition and of clearance. Clearance includes physical removal via the mucociliary system or by transport to lymph nodes and other organs, and by chemical action including solubility and digestion. It is well known that mucociliary clearance is reduced by exposure to air pollutants, particularly cigarette smoke [11]. In the normal human lung, cigarette smoke decreases clearance temporarily during waking hours but there is recovery overnight [12]. However, cigarette smoke damages small airways [13]; although deposition may be changed, clearance is certainly impaired from the damaged airways. This decrease in clearance would enhance asbestos fiber burdens in those lung units and increase the propensity for fibrosis. It is also well appreciated that cigarette smoke causes pulmonary emphysema [14]. In the absence of other exposures, such as to asbestos or silica, which produce fibrosis, the net effect of smoking is a larger lung that loses its alveolar partitions to produce emphysema. However, with exposure to asbestos, this latter effect may be counteracted by simultaneous fibrosis that would modify or reduce emphysema. This is clearly not provable from the evidence presented and needs physiologic study, ideally a prospective study of a larger population, one portion that has been exposed to asbestos alone and the other to asbestos plus cigarette smoke.

The need for more research should not detract from the clarity of these data concerning the effects of asbestos, cigarette smoking, and age on diffuse pulmonary fibrosis as assessed by chest radiography. The conclusions are: (1) Cigarette smoking does not by itself in a general population produce detectable diffuse pulmonary fibrosis. (2) When exposure to asbestos is relatively light, as in worker households, cigarette smoking does not enhance diffuse pulmonary fibrosis. (3) Cigarette-smoking workers exposed to asbestos in the insulating trade show more diffuse pulmonary fibrosis than nonsmoking insulators. (4) The additive effect of cigarette smoking and asbestos seen in insulators is also demonstrated in shipyard workers. This interaction appears to apply to many modern occupational exposures with an age-accelerating effect. (5) Increasing age permits greater accumulation of agents (asbestos, other inorganic particles, and cigarette smoke materials). Also, aging lengthens the time available for interactions in the lung between processes such as bronchial obliteration, fibrosis, and emphysema, which cause radiographic changes.

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