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# An Industry-wide Pulmonary Study of Men and Women Manufacturing Refractory Ceramic Fibers

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An industry-wide pulmonary morbidity study was undertaken to evaluate the respiratory health of employees manufacturing refractory ceramic fibers at five US sites between 1987 and 1989. Refractory ceramic fibers are man-made vitreous fibers used for high temperature insulation. Of the 753 eligible current employees, 742 provided occupational histories and also completed the American Thoracic Society respiratory symptom questionnaire; 736 also performed pulmonary function tests. Exposure to refractory ceramic fibers was characterized by classifying workers as production or nonproduction employees and calculating the duration of time spent in production employment. The risk of working in the production of refractory ceramic fibers and having one or more respiratory symptoms was estimated by adjusted odds ratios and found to be 2.9 (95 percent confidence interval 1.4–6.2) for men and 2.4 (95 percent confidence interval 1.1–5.3) for women. The effect of exposure to refractory ceramic fibers on forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), the ratio of the two ($FEV_1$/FVC), and forced expiratory flow (liters/second) between 25 percent and 75 percent of the FVC curve ($FEF_{25-75}$) was evaluated by multiple regression analysis using transformed values adjusted for height, by dividing by the square of each individual's height. For men, there was a significant decline in FVC for current and past smokers of 165.4 ml ($p < 0.01$) and 155.5 ml ($p = 0.04$), respectively, per 10 years of work in the production of refractory ceramic fibers. For $FEV_1$, the decline was significant ($p < 0.01$) only for current smokers at 134.9 ml. For women, the decline was greater and significant for FVC among nonsmokers, who showed a decrease of 350.3 ml ($p = 0.05$) per 10 years of employment in the production of refractory ceramic fibers. These findings indicate that there may be important sex differences in response to occupational and/or environmental exposure. *Am J Epidemiol* 1998;148:910–19.

occupational exposure; occupations; respiratory function tests; sex; spirometry

Man-made vitreous fibers are a class of insulating materials composed of inorganic substances that include glass fibers (glasswool, special purpose glass fibers, and continuous glass filament), mineral wool (rock and slag wool), and refractory ceramic fibers. Refractory ceramic fibers are amorphous silicates developed in the 1950s and used in industrial processes requiring high temperature speciality insulation beyond the capacity of glass fibers and mineral wool. Raw materials include kaolin clay, alumina/silica, or alumina/silica/zirconium, which are melted and fiberized through a wheel centrifuge or steam jet fiberization process. Production of these fibers sharply increased in the 1970s with the declining use of asbestos in the United States. Refractory ceramic fibers constitute 1–2 percent of the man-made vitreous fibers produced in the United States; the bulk fiber may be manufactured into products such as blankets, boards, paper, and textiles (1).

Current knowledge of the biologic activity of fibers is derived from in vitro, animal, and epidemiologic studies of man-made vitreous fibers and naturally occurring fibers (2–6). The primary determinants of fiber toxicity are dose delivered to the target organ and include biologic durability, fiber composition, and fiber dimension (7). Refractory ceramic fibers have high durability and fall within the respirable size range, that is, less than 3.5 $\mu$m in aerodynamic diameter and less than 200 $\mu$m in length (7). Animal inhalation studies

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Abbreviations: CI, confidence Interval; $FEF_{25-75}$, forced expiratory flow (liters/second) between 25 percent and 75 percent of the FVC curve; $FEV_1$, forced expiratory volume in 1 second (the volume in liters of air that can be forcibly expired during the first second of expiration); $FEV_1$/FVC, forced expiratory volume in 1 second expressed as a percentage of the forced vital capacity; FVC, forced vital capacity (the maximal volume in liters of air expired with a maximally forced effort from a position of maximal inspiration); OR, odds ratio.

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in rats and hamsters have demonstrated mesothelioma, lung cancer, and pulmonary fibrosis (8–11).

The International Agency for Research on Cancer in 1987 designated ceramic fiber as "possibly carcinogenic to humans" on the basis of animal data (12, p. 152). Because of the unknown human health impact, a morbidity study was initiated to determine if exposure to refractory ceramic fibers was associated with pulmonary health risk in the manufacturing sector. Previously published results demonstrated that latency and duration of employment in a production job involving refractory ceramic fibers were associated with developing pleural plaques but no pulmonary fibrosis (13). It was shown that 20.7 percent of workers with greater than 20 years of duration in the manufacturing of refractory ceramic fibers had pleural plaques on posteroanterior chest radiographs (odds ratio (OR) = 8.8, 95 percent confidence interval (CI) 2.6–30.1). An additional analysis of posteroanterior and oblique films and a nested case-control study of this cohort confirmed the initial findings (14). It was also confirmed that asbestos exposure did not account for the observed association, and no increase in the prevalence of interstitial fibrosis was noted (14). The respiratory symptoms and pulmonary function results in this cohort of men and women are reported here.

## MATERIALS AND METHODS

### Study subjects

Study subjects included male and female active employees of four manufacturers of refractory ceramic fibers at five locations in New York, Indiana, Tennessee, Georgia, and Oklahoma, who participated in occupational history interviews between 1987 and 1989. Hourly, salaried, and temporary employees were included. At one site, workers transferred between the production of refractory ceramic fibers and other manufacturing processes. Workers at this site were included if they had spent a minimum of 1 year in refractory ceramic fibers' operations or were actively working in these processes at the time of interview. Each active employee received a letter describing the study and signed an informed consent form. The American Thoracic Society respiratory symptom questionnaire, an occupational history questionnaire, and pulmonary function tests were administered on-site by the research team.

### Exposure evaluation

The occupational history questionnaire elicited information about job activities at the facilities that manufactured refractory ceramic fibers. Information also was collected concerning all previous jobs held for 4 months or longer, including the dates and details of specific tasks. Data were reviewed for completeness, and responses to all open-ended questions were standardized, double entered, and compared. Additionally, a 10 percent check of all computerized questionnaire records was made using the written survey instruments for verification.

Operations at each manufacturing plant were reviewed by industrial hygienists from the University of Cincinnati. To estimate current levels of exposure to refractory ceramic fibers at the five manufacturing locations, we selected at random persons who worked with raw materials to wear personal air-monitoring samplers (15). Plant personnel were instructed by the University staff to conduct full shift monitoring. Results represent 484 fiber count samples across the five plant locations. The median time-weighted average exposure estimate was 0.01–1.04 fibers/cm$^3$ for the blanket line, 0.03–0.61 fibers/cm$^3$ for dry fabrication, 0.01–0.27 fibers/cm$^3$ for wet fabrication, 0.01–0.47 fibers/cm$^3$ for furnace operations, and 0.02–0.62 fibers/cm$^3$ for maintenance (15). Thus, current fiber levels generally remained below 1 fiber/cm$^3$.

Interviews of long-term employees were gathered on the tasks associated with each job activity in order to understand historical job operations. Office and research and development personnel were provided a self-administered form to document the time spent in production areas. If the time spent in production areas was 4 or more hours per week (10 percent of work time), the job was classified as "production." Participants were defined as having one or more production jobs or never participating in production operations involving refractory ceramic fibers. Data collected using these instruments defined the following exposure variables: production (exposed) and nonproduction (no to minimal exposure) and duration of time (years) in production employment.

### Symptom evaluation

The American Thoracic Society questionnaire was modified slightly to include additional questions on smoking and to add questions concerning pleuritic chest pain (16). Subjects were considered to have *chronic cough* if occurrence was 4–6 times a day, 4 or more days a week, for 3 months, for 2 consecutive years or more. *Chronic phlegm* was phlegm production at least two times a day, 4 or more days a week, for 3 months, for 2 or more years. A positive response to *pleuritic chest pain* was defined as sharp, shooting pain located in the chest or in the chest and shoulder, lasting more than 6 hours, worse with deep breath, evaluated by a physician, with onset after age 18, and not caused by physical injury. *Dyspnea grade 1* included all grades of shortness of breath upon exertion. *Dyspnea grade 2* included all grades of shortness of breath upon exertion, excluding shortness of breath when hurrying on the level or walking up a slight hill. *Wheezing* that occurred "most days or nights" for 2 years or more and *asthma* that was confirmed by a physician with onset after age 18 were considered positive symptom responses.

Each positive response to pleuritic chest pain was reviewed individually by the investigator pulmonologist (J. E. L.) who was unaware of the respondent's exposure status. Subjects were excluded from the pleuritic chest pain analysis if the pain antedated exposure to refractory ceramic fibers ($n = 1$) or was clearly related to a medical condition ($n = 6$) unlikely to have a relation with fiber exposure (e.g., pulmonary embolus).

Having smoked was defined as consumption of 20 or more packs of cigarettes in a lifetime or at least one cigarette per day for a year. The smoking history provided pack-year information and allowed categorization of participants as current smokers, that is, smoking cigarettes as of 1 month ago, past smokers, or never smokers at the time of interview.

### Pulmonary function testing

Spirometric values for forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), the ratio of the two ($FEV_1$/FVC), and the maximum midexpiratory flow rate ($FEF_{25-75}$) were obtained. Testing technicians (D. M. P., D. J. F.) completed a National Institute for Occupational Safety and Health-approved spirometry training program and conducted tests according to American Thoracic Society criteria (17). Using the Ohio Medical 822 spirometer coupled to a Spirotech 300 microprocessor (Graseby Anderson, Smyrna, Georgia), technicians were directed to obtain a minimum of five acceptable tracings with at least three meeting American Thoracic Society criteria. Height was measured to the nearest quarter inch, and weight was measured to the nearest pound. At the time of analysis, these were converted to meters and kilograms, respectively. Each test was performed in the standing position unless a medical condition precluded this, with nose clips and loosening of tight-fitting clothing. The technician demonstrated the breathing technique and aggressively coached each subject to achieve maximal effort. Testing usually continued until the highest and second highest FVC and $FEV_1$ values were within 5 percent of each other. Further, if the highest valid FVC or $FEV_1$ value occurred on the last trial, another was performed to ensure maximal effort. Tubing and the spirometers were always tested for leaks, and spirometers were checked for accuracy before and after each half day of testing for volume and time.

### Statistical analyses

Prevalence rates of seven symptoms plus a combined symptom outcome (at least one symptom vs. none) were obtained for male and female production and nonproduction employees. Inferences regarding differences between nonproduction and production employees were based on odds ratios adjusted for age, pack-years, smoking categories (current, past, and never), and years of possible asbestos exposure in a logistic regression model.

Tests of normality of the distributions of the spirometric data were performed using the SAS Proc univariate procedure (18), and optimal transformations of $FEV_1$/FVC and $FEF_{25-75}$ values were made using the Box-Cox method (19). Values of FVC and $FEV_1$ did not require transformation. Results of FVC and $FEV_1$ are presented on the original scale.

The effects of duration of production employment in the manufacture of refractory ceramic fibers on FVC, $FEV_1$, $FEV_1$/FVC, and $FEF_{25-75}$ were investigated using multiple linear regression. First, FVC, $FEV_1$, and $FEF_{25-75}$ values were transformed to adjust for body size, by dividing by the square of each individual's height. This transformation was chosen because it has been shown to eliminate the effect of height and to permit the linear decline in lung function with age and age-squared, and because it has been found to be superior to other methods of adjusting for height (20, 21). Dockery et al. (20) compared the height-squared adjustment approach with those that divided by other powers of height and with inclusion of a linear height term in the model in samples of 1,904 women and 647 men (white, asymptomatic, nonsmokers). The distributions of FVC/height$^2$ and $FEV_1$/height$^2$ were found to be approximately normal with constant variance at each age, supporting assumptions of regression modeling. The normality of residuals of FVC/height$^2$ and $FEV_1$/height$^2$ was examined separately for men and women, and the assumptions were found to hold. For ease of interpretation, height-transformed results were expressed in volume units after multiplying by 1.73 m$^2$ for males and 1.65 m$^2$ for females, the respective heights of the average male and female study subject. $FEV_1$/FVC outcomes were analyzed without height correction by assuming a model that included linear height to allow for a residual height effect.

Variables, possibly related to pulmonary outcome, were added and removed from the models and were tested for contribution to model fit by comparison of $R^2$ values. Transformations of age and pack-years were performed, including quadratic and categorical determinations; results were compared with models in which these were modeled linearly. A surrogate measure of exposure to refractory ceramic fibers, number of years in production employment, was modeled linearly as well as categorically, and models were compared. The possible difference in the effect of years in production employment across smoking categories was investigated by modeling the interaction between smoking category and production years. Similarly, the possible difference in pack-years between current and former smokers was investigated by including interaction terms between these two smoking categories and pack-years. Collinearity of time-dependent variables was checked by the methods of Belsley et al. (22). The final model was chosen based on significance testing, assessment of model simplicity, plots of residuals, model fit, and appropriateness for addressing study goals. The variables included in the final model were age, age-squared (females only), weight, race (Caucasian vs. other races), categorical smoking (current, past, never), categorical plant location, categorical smoking interaction with number of years in production employment, and categorical smoking (current, past) interaction with pack-years. The categorical variable, plant location, was included in the model to adjust for possible geographic, socioeconomic, and demographic differences as well as exposure or process differences that might alter pulmonary function. This analysis of covariance design was implemented using the SAS PROC GLM procedure (18).

Estimates of the effect of refractory ceramic fibers by smoking category should help to control for a possible artifactual synergism between dust/fiber exposure and smoking that has been reported by others (23). In addition, analyses of predicted percentages using the reference values of Crapo et al. (24–28) were performed and were similar. Therefore, analyses of the height-adjusted values are presented, since these are not derived from groups outside the study populations that can introduce biases and reduce the reliability of the findings.

### Reliability and validity

The reliability and validity of the findings are influenced by the accuracy of the self-reported information and the quality and consistency of the pulmonary function testing procedures. In order to address these issues, we selected a 10 percent random sample of the subjects for reevaluation within 48 hours of the original evaluation. Seventy-four percent of the reinterviewed subjects agreed exactly on the number of jobs with refractory ceramic fibers, and 90 percent agreed on their year of hire within 1 year. All questions regarding respiratory symptoms and smoking status were found to have moderate-to-excellent reproducibility in regard to agreement (29); kappa statistics ranged from 0.47 (95 percent CI 0.03–0.91) for pleuritic chest pain to 0.97 (95 percent CI 0.91–1.03) for ever smoking (yes/no). Company records were available at two sites and were evaluated for the validity of recall of hire date provided at interview. The proportion of agreement on hire date was high. The agreement rate was approximately 92 percent (±1 year) with employee-reported and company-recorded hire date.

Ten percent of the subjects also were compared on FVC and $FEV_1$ test-retest values. There were no cases where the "best test" parameter values on retest were more than 5 percent higher than those found on the initial test values. For FVC and $FEV_1$ measurements, 95 percent were within 176 ml (standard deviation = 90 ml) and 148 ml (standard deviation = 76 ml), respectively, on retest. In addition, a 5 percent random sample of pulmonary function test results was separately evaluated (R. T. M.) for testing technique and the technician's decision to accept or reject individual tracings. An exceptionally high quality of testing was verified by this separate evaluation based on results of the technician's ability to obtain the following: 1) an adequate number of valid starts (97.6 percent), 2) acquiring an adequate plateau, defined as a volume change not greater than 40 ml over the last 2 seconds of expiration (100 percent), 3) obtaining variability of less than 5 percent (or 100 ml) between the two highest acceptable trials for FVC (100 percent) and $FEV_1$ (97.6 percent), and 4) not having the best FVC or $FEV_1$ occur on the last trial (≤1 percent). In summary, these study findings were shown to have excellent reliability and quality control measures.

## RESULTS

Of the 753 eligible active workers at five manufacturing sites, 742 (98.5 percent) completed the American Thoracic Society questionnaire, and 736 (97.7 percent) completed both the American Thoracic Society and pulmonary function tests. Characteristics of the cohort by nonproduction ($n$ =139) and production ($n$ = 603) worker categories showed similarity in age, 38.3 and 39.3 years. Other characteristics differed, however, including mean education, 15 versus 12 years; mean pack-years of smoking, 8.6 versus 13.7 pack-years; percent Caucasian, 98.6 versus 74.3 percent Caucasian; and percent male, 57.6 versus 85.7 percent male, respectively. Values for male and female employees also differed. The mean age among men was 39.7 years compared with 36.8 years for women. The mean number of pack-years of smoking was higher in men, 13.7, compared with 8.7 for women. The median number of years in the production employment of refractory ceramic fibers for the 517 men was 8.5 years, with a range of 0.25–37.4 years. For the 86 production female employees, the duration was much lower, with a median of 4.0 years and a range from 0.8 to 14.8 years.

### Respiratory symptoms

Except for dyspnea 1, the male nonproduction group had a higher prevalence of respiratory symptoms than did the female nonproduction group. This finding is in contrast to the production employees where the opposite was true except for wheezing (table 1). The adjusted odds ratios for respiratory symptoms in male production versus nonproduction employees ranged from 1.0 to 7.3, and for females they ranged from 1.3 to 5.4. The prevalence rates for all symptoms were higher in production versus nonproduction workers except for asthma in males. The most frequently reported symptom for men in production was dyspnea 1, at 15.7 percent versus 2.5 percent for those in nonproduction, followed by wheezing, 10.3 percent versus 3.8 percent, respectively. In males, the odds ratios for dyspnea 1 and 2 were statistically significant. For dyspnea 1, an odds ratio equal to 7.3 was obtained (95 percent CI 1.7–30.5). For dyspnea 2, the probability of obtaining a result as extreme or "more so" than that observed, when the prevalence rates are truly the same, was equal to $p = 0.03$, based on Fisher's exact test. The odds ratio comparing prevalence rates of having one or more symptoms was significant (OR = 2.9, 95 percent CI 1.4–6.2) at 29.6 and 11.3 percent in the male production versus nonproduction groups, respectively.

Dyspnea 1 and 2 were the most prevalent symptoms in the female production group followed by chronic cough and phlegm. Women in production were twice as likely to report one or more respiratory symptoms, 40.7 percent compared with 20.3 percent for the women in nonproduction (OR = 2.4, 95 percent CI 1.1–5.3), respectively. For men only, pack-years of smoking were significantly associated with having chronic cough, chronic phlegm, and wheezing and having at least one respiratory symptom.

### Spirometry

There were no statistically significant findings for $FEV_1/FVC$ or $FEF_{25-75}$ for either sex. FVC for men demonstrated a statistically significant decrement in lung function associated with the duration of employment in the production of refractory ceramic fibers for those who were either a current or past smoker. The effect for 10 years of employment in the production of refractory ceramic fibers and for being male and either a current or past smoker was associated with FVC reductions of 165.4 ml and 155.5 ml, respectively, as compared with 40.6 ml for never smokers (table 2). In addition, weight, age, and non-Caucasian racial status were significant predictors of lowered FVC. Results persisted when the duration of employment in the production of refractory ceramic fibers was measured categorically as nonproduction, production employment of 8 years or less, or greater (the median).

For $FEV_1$, 10 years' duration of employment in the production of refractory ceramic fibers for current male smokers showed a significant estimated 134.9-ml decline (table 3). Also, each 10 pack-years of smoking for male current and past smokers were significantly related to a 55.0-ml and a 51.7-ml reduction in $FEV_1$ for those respective groups. Age and race also were significant predictors for lowered $FEV_1$. For the men, plant differences were significant with respect to both outcomes, but quadratic age effects were not. Additional post hoc analysis showed that the effect of duration of employment in the production of refractory

**TABLE 1. Prevalence of respiratory symptoms in 597 male and 145 female refractory ceramic fiber workers and adjusted odds ratios* comparing nonproduction and production workers in five US states, 1987–1989**

| Symptom | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Prevalence (%) | | Adjusted odds ratio | 95% confidence interval | p value† | Prevalence (%) | | Adjusted odds ratio | 95% confidence interval | p value |
| | Nonproduction (n = 80) | Production (n = 517) | | | | Nonproduction (n = 59) | Production (n = 86) | | | |
| Chronic cough | 5.0 | 7.4 | 1.0 | 0.3–3.0 | | 1.7 | 9.3 | 5.4 | 0.6–46.9 | |
| Chronic phlegm | 3.8 | 5.8 | 1.2 | 0.4–4.6 | | 1.7 | 9.3 | 3.8 | 0.4–33.5 | |
| Pleuritic chest pain | 0.0 | 1.6 | | | 0.31 | 0.0 | 3.5 | | | 0.21 |
| Dyspnea 1 | 2.5 | 15.7 | 7.3 | 1.7–30.5 | | 18.6 | 25.6 | 1.3 | 0.6–3.2 | |
| Dyspnea 2 | 0.0 | 4.8 | | | 0.03 | 0.0 | 10.5 | | | 0.001 |
| Wheezing | 3.8 | 10.3 | 2.5 | 0.8–8.5 | | 1.7 | 7.0 | 3.9 | 0.4–38.8 | |
| Asthma | 2.5 | 2.3 | 1.0 | 0.2–4.7 | | 0.0 | 3.5 | | | 0.21 |
| One or more symptoms | 11.3 | 29.6 | 2.9 | 1.4–6.2 | | 20.3 | 40.7 | 2.4 | 1.1–5.3 | |

* Adjusted for age, pack-years, smoking categories, and years of possible asbestos exposure in a logistic regression model.
† One-tailed probability level using Fisher's exact test.

**TABLE 2. Regression coefficients of height-adjusted forced vital capacity (FVC) (ml) determined by analysis of covariance* for three smoking categories of 736 refractory ceramic fiber production and nonproduction employees in five US states, 1987–1989**

| FVC | Males ($n$ = 592)† | | | Females ($n$ = 144)† | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | 95% confidence interval | $p$ value | Regression coefficient | 95% confidence interval | $p$ value |
| Intercept | 6,507.2 | 6,080.9 to 6,933.5 | <0.001 | 3,842.5 | 2,701.2 to 4,983.8 | <0.001 |
| Current smokers ($n$ = 245 males, $n$ = 56 females) | 11.0 | −172.7 to 194.7 | NS‡ | −164.7 | −417.5 to 88.1 | NS |
| Past smokers ($n$ = 174 males, $n$ = 20 females) | 140.9 | −60.2 to 342.0 | NS | −239.7 | −528.5 to 49.2 | NS |
| Duration of ceramic fiber employment, 10 production years for | | | | | | |
| Current smokers | −165.4 | −279.8 to −51.0 | <0.01 | −110.8 | −411.5 to 190.0 | NS |
| Past smokers | −155.5 | −301.9 to −9.1 | 0.04 | −330.5 | −872.1 to 211.1 | NS |
| Never smokers | −40.6 | −175.1 to 193.8 | NS | −350.3 | −692.0 to −8.7 | 0.05 |
| Weight, 10 kg | −34.6 | −65.2 to −4.1 | 0.03 | −59.0 | −114.7 to −3.2 | 0.04 |
| Race§ | −557.7 | −711.4 to −404.0 | <0.001 | −270.4 | −662.7 to 121.9 | NS |
| 10 pack-years for | | | | | | |
| Current smokers | −33.8 | −81.2 to 13.6 | NS | 10.9 | −74.9 to 96.7 | NS |
| Past smokers | −34.7 | −84.7 to 15.3 | NS | 162.1 | −31.1 to 355.3 | 0.10 |
| Age, 10 years | −248.1 | −305.4 to −192.0 | <0.001 | 456.7 | −0.1 to 913.6 | 0.05 |
| Age-squared, 100 years² | | Not modeled | | −84.4 | −141.8 to −26.9 | <0.01 |

* Model allows coefficients of duration of ceramic fiber employment and pack-years to differ among smoking categories. The coefficients include the main effects of duration of ceramic fiber employment and pack-years and the effects of their interaction with smoking categories. The plant variable, 4 df, was significant for males only, $p < 0.01$.

† $R^2 = 0.46$.

‡ NS, not statistically significant at the 10% level.

§ Caucasian at baseline.

**TABLE 3. Regression coefficients of height-adjusted forced expiratory volume in 1 second ($FEV_1$) (ml) determined by analysis of covariance* for three smoking categories of 736 refractory ceramic fiber production and nonproduction employees in five US states, 1987–1989**

| $FEV_1$ | Males ($n$ = 592)† | | | Females ($n$ = 144)‡ | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | 95% confidence interval | $p$ value | Regression coefficient | 95% confidence interval | $p$ value |
| Intercept | 5,395.4 | 5,036.1 to 5,754.8 | <0.001 | 3,941.1 | 3,058.5 to 4,823.8 | <0.001 |
| Current smokers ($n$ = 245 males, $n$ = 56 females) | −42.8 | −197.6 to 112.0 | NS§ | −263.3 | −458.9 to −67.8 | 0.01 |
| Past smokers ($n$ = 174 males, $n$ = 20 females) | 107.8 | −61.7 to 277.3 | NS | −73.0 | −296.4 to 150.4 | NS |
| Duration of ceramic fiber employment, 10 production years for | | | | | | |
| Current smokers | −134.9 | −231.3 to −38.5 | <0.01 | 13.9 | −218.7 to 246.5 | NS |
| Past smokers | −72.5 | −195.9 to 50.9 | NS | −321.4 | −740.2 to 97.4 | NS |
| Never smokers | −20.4 | −133.7 to 92.9 | NS | −223.5 | −487.7 to 40.7 | 0.10 |
| Weight, 10 kg | −24.9 | −50.6 to 0.9 | 0.06 | −54.5 | −97.6 to −11.4 | 0.01 |
| Race¶ | −356.4 | −485.9 to −226.8 | <0.001 | −325.2 | −628.6 to −21.8 | 0.04 |
| 10 pack-years for | | | | | | |
| Current smokers | −55.0 | −95.0 to −15.1 | <0.01 | 7.2 | −59.1 to 73.6 | NS |
| Past smokers | −51.7 | −93.8 to −9.5 | 0.02 | −4.1 | −153.5 to 145.3 | NS |
| Age, 10 years | −304.3 | −351.9 to −256.7 | <0.001 | 146.7 | −206.7 to 500.0 | NS |
| Age-squared, 100 years² | | Not modeled | | −52.9 | −97.3 to −8.4 | 0.02 |

* Model allows coefficients of duration of ceramic fiber employment and pack-years to differ among smoking categories. The coefficients include the main effects of duration of ceramic fiber employment and pack-years and the effects of their interaction with smoking categories. Plant variable, 4 df, was significant for males only, $p < 0.01$.

† $R^2 = 0.52$.

‡ $R^2 = 0.61$.

§ NS, not statistically significant at the 10% level.

¶ Caucasian as baseline.

ceramic fibers by smoking status persisted after excluding one male whose $FEV_1$ value was identified as an outlier using Cook's [Adair] statistic (30).

The regression model for females included the above factors plus a quadratic age term that was significant for both FVC and $FEV_1$. The magnitude of the effect of 10 years of production of refractory ceramic fibers on FVC was significant and greatest among never smokers (−350.3 ml), slightly less but nonsignificant for past smokers (−330.5 ml), and smallest and nonsignificant for current smokers (−110.8 ml) (table 2). The effect of 10 years of production of refractory ceramic fibers on FVC was equal to −346.0 ml ($p$ = 0.04). For $FEV_1$, the effect of 10 years of production of refractory ceramic fibers was greatest, but nonsignificant, among past smokers (−321.4 ml). Because of potential large variability due to small sample sizes, the analysis of $FEV_1$ was repeated with past ($n$ = 20) and never smokers ($n$ = 68) combined. The effect of 10 years of production of refractory ceramic fibers on $FEV_1$ was equal to −244.7 ml ($p$ = 0.05) in this combined nonsmoking group.

High collinearity was found only between age and age-squared in the model for females. As with the males, additional explanatory post hoc analyses were performed for females. Results persisted when the duration of employment in the production of refractory ceramic fibers was measured categorically as nonproduction and as production employment of 4 years or less and more than 4 years (the median). For never smokers in the 4-year or longer production category, the decrement in FVC and $FEV_1$ was 302.9 ml and 197.7 ml, respectively. After the exclusion of three females whose values were outliers, the effects of the duration of production of refractory ceramic fibers in past and never smokers still showed a 10-year decline of 242.4 ml and 210.1 ml for FVC and 270.2 ml and 151.4 ml for $FEV_1$, respectively. Thus, after these additional analyses, the trends reported in tables 2 and 3 remained.

## DISCUSSION

In general, the prevalence of respiratory symptoms here is similar to that reported in other dust-exposed populations (31, 32). Overall, there was a two- to fivefold increase of symptoms in the production workers exposed to refractory ceramic fibers compared with the increase in those in nonproduction jobs. Refractory ceramic fibers' workers had generally lower rates compared with those found in a dust- and nondust-exposed blue collar worker force (32), for which a less stringent criterion for symptom definition was used. Trethowan et al. (33) studied workers involved in the manufacturing of refractory ceramic fibers at seven European plants. The mean fiber concentrations ranged from 0.2 to 0.88 fibers/$cm^3$ and 0.49 to 1.36 fibers/$cm^3$ for primary and secondary production workers, respectively, and the mean duration of employment was 10.2 years. Similar to our findings, breathlessness and wheezing were associated with increasing exposure.

The importance of stratifying the analysis by sex is apparent, as the reporting of symptoms and pulmonary function tests results was decidedly different. Except for dyspnea grade 1, nonproduction males generally reported higher rates of individual symptoms than did nonproduction females. One explanation for these differences could be related to possible higher rates of smoking in men. Though the percentage of nonproduction women who were current smokers was slightly higher at 25.4 percent compared with 22.5 percent for men, the average pack-year smoking history was lower at 7.2 years compared with 9.7 years, respectively. Thus, the longer smoking history may be more important than current smoking status.

This sex difference was reversed in the production employees, with women reporting more symptoms even though they had about half the duration of employment in the production of refractory ceramic fibers as did the men. Both female and male subjects in production compared with nonproduction jobs had double the rate of current smokers at 48.8 percent and 44.3 percent, respectively. Their pack-year smoking histories were 9.7 years and 14.3 years, respectively. Thus, there were similarities in the rates of current smokers, and women had two-thirds the smoking history as men as measured in pack-years but half the duration of possible dust exposure. One interpretation of these symptom findings is that differences may exist in the intensity of exposures between the sexes. Certainly the women in production jobs had less tenure than did the men, which may be associated with less desirable, dustier jobs. Another interpretation may be that females are a more susceptible subgroup to the combined exposures of smoking and dust, since the reporting of one or more symptoms was higher for females working in production at 40.7 percent, compared with men at 29.6 percent. A third interpretation is that these sex differences are related to over- or underreporting, as noted on the overall test-retest reliability of the pleuritic chest pain symptom's having a kappa of 0.47, indicating only moderate agreement.

Pulmonary function results revealed a general pattern of reduction for both FVC and $FEV_1$ with increased years of production employment for male smokers. This pattern persisted in past smokers for FVC but not for $FEV_1$. For men, there was no significant decline in pulmonary function in nonsmokers associated with employment in the production of refractory ceramic fibers. Thus, for men there was a significant interaction effect between fiber production employment and smoking. The yearly reduction for current male smokers after adjusting for pack-years, age, race, and weight was 16.5 ml and 13.5 ml for FVC and $FEV_1$, respectively. In a longitudinal study of a subset ($n$ = 361) of the male employees producing refractory ceramic fibers, additional yearly loss in lung function was not observed (34). This finding of no continual pulmonary decline may be a reflection of recent reductions in fiber and dust exposures since 1987 compared with historical levels, or it could be associated with inherent differences in the two cohorts

(35). The European study of refractory ceramic fiber manufacturing plants found a significant association between the decrement in $FEV_1$ and cumulative exposure in past smokers and a nonsignificant trend in cumulative exposure and decrement in FVC for current and past smokers (33). An additive or synergistic effect of smoking and dust exposure manifested by a decrease in pulmonary function has been observed in other studies (36–38). Hnizdo et al. (38) demonstrated an interaction between smoking and silica dust exposure in South African gold miners with marked airway obstruction. Others have demonstrated no interaction between smoking and coal dust exposure (39).

In the current study of male employees who manufactured refractory ceramic fibers, there was no effect on FVC or $FEV_1$ values in never smokers; the yearly decline was 4.1 ml and 2.0 ml, respectively. There was, however, a significant yearly reduction in FVC values of 35.0 ml for females who never smoked that exceeded the reduction in current smokers of 11.1 ml. This trend persisted after excluding three possible outliers. Other studies of male nonsmokers exposed to asbestos have demonstrated spirometric findings consistent with reduction in air flow as measured by $FEV_1$ (40). Similar findings have been demonstrated for fibrous wollastonite in regard to the $FEV_1$/FVC ratio (41). Exposure to nonfibrous dusts, such as coal and/or silica, has been linked to airflow obstruction in nonsmoking male miners. Overall, the population with the greatest dust exposures at an early age may sustain the greatest loss in airflow (38, 39, 42, 43). Therefore, it was not surprising that effects were observed in nonsmokers.

What was curious, however, is that the *largest* effect for FVC was seen in women in production work who were nonsmokers, but this effect was not observed for nonsmoking males in production work. One explanation for the findings of duration of employment in the production of refractory ceramic fibers and pulmonary function effects in the never smoking group could be associated with differences by sex in health status. This hypothesis was evaluated by examining the symptom data. The female production never smoker group had a higher percentage (71.9 percent) reporting one or more respiratory symptoms than did the production smokers (53.7 percent). The reverse would have been predicted. The comparison group of female nonproduction never smokers, however, also had a high rate of symptom reporting at 77.8 percent. Another explanation for this finding in female never smokers was that the results may be due to a confounder associated with weight. The effect of obesity and weight gain on lung function has been shown by others (38, 44, 45). To test this hypothesis, women with a body mass index of 30.0 kg/m$^2$ or greater ($n$ = 18) were excluded (46). The effect of 10 years' duration of employment in the production of refractory ceramic fibers in past and never smokers was attenuated. For FVC, the current, past, and never smokers had a yearly decline of 12.3 ml, 40.9 ml, and 40.3 ml, respectively. For $FEV_1$, the decline was 34.5 ml and 23.9 ml for past and never smokers. For current smokers, there was a slight yearly increase at 1.3 ml. Thus, weight was not considered the explanation for the finding in never smokers.

It is also possible that there is a basic sex difference. For women, smoking may "mask" a more subtle effect of refractory ceramic fibers, which is only detectable in a group without another overriding, intense exposure. Thus, the effect of refractory ceramic fibers becomes more apparent in the nonsmokers. Others have showed that adult females have greater bronchial responsiveness than do males after adjusting for baseline lung function (47–51). Females demonstrate a higher degree of bronchial responsiveness than do males for all age groups after puberty (51). This finding may be related to hormonal changes that occur in females at puberty. Hormonal variation during the menstrual cycle also seems to impact airway responsiveness in asthmatic women (52). Females show a higher susceptibility to nonspecific stimuli than do males. Cigarette smoke was shown to clearly affect the methacholine response regardless of the initial lung function in females. In this study, it was only in women that there was a statistically significant relation between current smoking status and a decrement in $FEV_1$.

Another explanation for the differences seen in the male and female never-smoker production workers may be a reflection of the difference in length of production for each group and the healthy worker effect. The median duration of production of refractory ceramic fibers was 8 years and 4 years for males and females, respectively. The females who have experienced significant reductions in FVC and/or $FEV_1$ values may not have had time to leave the work force, resulting in a residual "unhealthy" worker effect. The results may also be a reflection of unstable parameter estimates due to smaller numbers in the female group.

In summary, the best statistical models demonstrated an increase in respiratory symptoms in production versus nonproduction workers and a decline in FVC and $FEV_1$ values with employment in the production of refractory ceramic fibers in excess of that attributed to smoking, age, and other factors. The significant FVC decline associated with employment in the production of refractory ceramic fibers was limited to current and past smokers for men and nonsmokers for women. The two surrogate measures of past fiber and dust exposure, duration of employment and categorical duration of employment status, provide strength as to an exposure effect relation. Future analysis of the longitudinal data on female refractory ceramic fibers' employees in this ongoing study will help to clarify these findings. This study provides estimates of lung function among a cohort of men and women exposed to refractory ceramic fibers. In a computerized search of published studies from 1980 to 1997 that examined occupational exposure and pulmonary health for women, only one study was identified (53). This study evaluated both men ($n$ = 301) and women ($n$ = 88) exposed to silica in the pottery industry and demonstrated a significant reduction in FVC and $FEV_1$ for both sexes after adjustment for age, height, and smoking habits. Another study was identified through cross-referencing articles, and it showed a decrease in lung function for female never smokers exposed to asbestos (54). Therefore, these findings are among the first to demonstrate an occupational exposure and effect on lung function in women employees as well as sex-specific differences. As more women enter and remain in exposure-intensive jobs, it will be important to determine if the effect of dust or fibers on women from an occupational setting differs from what historically has been demonstrated to occur in males.


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## REFERENCES


1. Lockey JE, Ross CS. Health effects of man made fibres. In: Steelman JM, ed. Encyclopaedia of occupational health and safety. 4th ed. Vol I. Geneva, Switzerland: International Labour Office, 1998:10.74–8.
2. Stanton MF, Layand M, Tegeris A, et al. Carcinogenicity of fibrous glass: pleural response in the rat in relating to fiber dimension. J Natl Cancer Inst 1977;58:587–603.
3. Harington JS. Fiber carcinogenesis: epidemiological observations and the Stanton hypothesis. J Natl Cancer Inst 1981;67: 977–89.
4. Leineweber JP. Dust chemistry and physics: mineral and vitreous fibres. IARC Sci Publ 1980;30:881–900.
5. Leineweber JP. Fiber toxicology. J Occup Med 1981;23: 431–4.
6. Suzuki Y, Kohyama N. Malignant mesothelioma induced by asbestos and zeolite in the mouse peritoneal cavity. Environ Res 1984;35:277–92.
7. Lippmann M. Man-made mineral fibers (MMMF): human exposures and health risk assessment. Toxicol Ind Health 1990;6:225–46.
8. Davis JMG, Addison J, Bolton RE, et al. The pathogenic effects of fibrous, ceramic aluminum silicate glass administered to rats by inhalation or peritoneal injection. In: Biological effects of man-made mineral fibres: proceedings of a WHO/IARC conference in association with JEMRB and TIMA: Copenhagen, 20–22 April 1982. Vol 2. Copenhagen: World Health Organization, 1984:303–23.
9. Smith DM, Ortiz LW, Archuleta RF, et al. Health effects in Osborne-Mendel rats and Syrian golden hamsters chronically exposed to man-made vitreous fibers. Ann Occup Hyg 1987; 31:731–54.
10. Bunn WB, Bender JR, Hesterberg TW, et al. Recent studies of man-made vitreous fibers. J Occup Med 1993;35:101–13.
11. Mast RW, McConnell EE, Hesterberg TW, et al. Multiple-dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer rats. Inhal Toxicol 1995;7:469–502.
12. IARC. Man-made mineral fibres and radon. IARC Monogr Eval Carcinog Risks Hum 1988;43:152.
13. Lemasters G, Lockey J, Rice C, et al. Radiographic changes among workers manufacturing refractory ceramic fibre and products. Ann Occup Hyg 1994;38(suppl 1):745–51.
14. Lockey J, Lemasters G, Rice C, et al. Refractory ceramic fiber exposure and pleural plaques. Am J Respir Crit Care Med 1996;154:1405–10.
15. Rice C, Lockey J, Lemasters G, et al. Assessment of current fibre and silica exposure in the U.S. refractory ceramic fibre manufacturing industry. Ann Occup Hyg 1994;38(suppl 1): 739–44.
16. Ferris BC. Epidemiology standardization project (American Thoracic Society). Am Rev Respir Dis 1978;118:1–120.
17. American Thoracic Society. Standardization of spirometry: 1987 update. Am Rev Respir Dis 1989;136:1285–98.
18. SAS Institute, Inc. SAS/STAT user's guide, version 6.0. 4th ed. Cary, NC: SAS Institute, Inc, 1990.
19. Box GEP, Cox DR. An analysis of transformations. J R Stat Soc 1964;B26:211–52.
20. Dockery DW, Ware JH, Ferris BGJ, et al. Distribution of forced expiratory volume in one second and forced vital capacity in healthy white, adult never-smokers in six US cities. Am Rev Respir Dis 1985;131:511–20.
21. Dockery DW, Speizer FE, Ferris BG, et al. Cumulative and reversible effects of lifetime smoking on simple tests of lung function in adults. Am Rev Respir Dis 1988;137:286–92.
22. Belsley DA, Kuh E, Welsch RE. Regression diagnostics. New York: John Wiley & Sons, Inc, 1980.
23. Rossiter CE, Weill H. Synergism between dust exposure and smoking: an artefact in the statistical analysis of lung function. Bull Physiopathol Respir (Nancy) 1974;10:717–25.
24. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 1981;123:659–64.
25. Crapo RO, Lockey J, Aldrich V, et al. Normal spirometric values in healthy American Indians. J Occup Med 1988;30: 556–60.
26. Crapo RO, Jensen RL, Lockey JE, et al. Normal spirometric values in healthy Hispanic Americans. Chest 1990;98:1435–9.
27. OSHA (Dept of Labor). Occupational exposure to cotton dust: final mandatory occupational safety and health standards. Federal Register June 23, 1978. Part III.
28. American Thoracic Society. Lung function testing: selection of reference values and interpretive strategies. Am Rev Respir Dis 1991;144:1202–18.
29. Landis JR, Koch GG. The measure of observer agreement for categorical data. Biometrics 1977;33:159–74.

30. Cook RD. Detection of influential observations in linear regression. Technometrics 1977;19:15–18.
31. Lockey JE, Brooks SM, Jarabek AM, et al. Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis 1984;129:952–8.
32. Petersen M, Castellan R. Prevalence of chest symptoms in nonexposed blue-collar workers. J Occup Med 1984;26: 367–74.
33. Trethowan WN, Bunge PS, Rossiter CE, et al. Study of the respiratory health of employees in seven European plants that manufacture ceramic fibers. Occup Environ Med 1995;52: 97–104.
34. Lockey JE, Levin LS, Lemasters GK, et al. Longitudinal estimates of pulmonary function in refractory ceramic fiber manufacturing workers. Am J Respir Crit Care Med 1998;157: 1226–33.
35. Rice CH, Lockey JE, Lemasters GK, et al. Estimation of historical and current employee exposure to refractory ceramic fibers during manufacturing and related operations. Appl Occup Environ Hyg 1997;12:54–61.
36. Fairman RP, O'Brien RJ, Swecker S, et al. Respiratory status of surface coal miners in the United States. Arch Environ Health 1997;32:211–15.
37. Holman CDJ, Psaila-Savona P, Roberts M, et al. Determinants of chronic bronchitis and lung dysfunction in Western Australian gold miners. Br J Ind Med 1987;44:810–18.
38. Hnizdo E, Baskind E, Sluis-Cremer GK. Combined effect of silica dust exposure and tobacco smoking on the prevalence of respiratory impairments among gold miners. Scand J Work Environ Health 1990;16:411–22.
39. Marine WM, Gurr D, Jacobsen M. Clinically important respiratory effects of dust exposure and smoking in British coal miners. Am Rev Respir Dis 1988;137:106–12.
40. Kilburn KH, Warshaw RH, Einstein K, et al. Airway disease in non-smoking asbestos workers. Arch Environ Health 1985; 40:293–5.
41. Hanke W, Sepulveda M-J, Watson A, et al. Respiratory morbidity in wollastonite workers. Br J Ind Med 1984;41:474–9.
42. Seixas NS, Robins TG, Attfield MD, et al. Exposure-response relationships for coal mine dust and obstructive lung disease following enactment of the federal coal mine health and safety act of 1969. Am J Ind Med 1992;21:715–34.
43. Seixas NS, Robins TG, Attfield MD, et al. Longitudinal and cross sectional analyses of exposure to coal mine dust and pulmonary function in new miners. Br J Ind Med 1993;509: 929–37.
44. Enright PL, Kronmal A, Higgins M, et al. Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular Health Study. Am Rev Respir Dis 1993;147: 125–33.
45. Wang M-L, McCabe I, Hankinson JL, et al. Longitudinal and cross-sectional analyses of lung function in steelworkers. Am J Respir Crit Care Med 1996;153:1907–13.
46. American Society for Clinical Nutrition (ASCN). Energy, obesity, and body weight standards (panel screening statement). Am J Clin Nutr 1987;45:1035–47.
47. Cerveri I, Bruschi C, Zoia MC, et al. Distribution of bronchial nonspecific reactivity in the general population. Chest 1988; 93:26–30.
48. Baake PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. Am Rev Respir Dis 1991;143: 317–22.
49. Peat JK, Salome CM, Berry G, et al. Relation of dose-response slope to respiratory symptoms and lung function in a population of adults living in Busselton, Western Australia. Am Rev Respir Dis 1992;146:860–5.
50. Tashkin DP, Altose MD, Bleecker ER, et al. The Lung Health Study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. Am Rev Respir Dis 1992;145:301–10.
51. Paoletti P, Carrozzi L, Viegi G, et al. Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. Am J Respir Crit Care Med 1995;151:1770–7.
52. Juniper EF, Kline PA, Roberts RS, et al. Airway responsiveness to methacholine during the natural menstrual cycle and the effect of oral contraceptives. Am Rev Respir Dis 1987; 135:1039–42.
53. Neukirch F, Cooreman J, Korobaeff M, et al. Silica exposure and chronic airflow limitation in pottery workers. Arch Environ Health 1994;49:459–64.
54. Rodriguez-Roisin R, Picaclo C, Roau J, et al. Early lung function changes after short heavy exposure to chrysolite asbestos in nonsmoking women. Bull Eur Physiopathol Respir 1986;22:225–9.