A Longitudinal Study on the Effects of Cigarette Smoking on Rate of Decline in Spirometric Measurements in Male Japanese Workers

Toshio Nakadate and Toshihiko Satoh

To estimate the effect of cigarette smoking on decline of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) with aging in the Japanese population, 461 male workers were longitudinally followed for over seven years. Analyses were conducted on 336 of them who were 30 years old or more, had not changed their smoking habits, were effectively followed up for at least three years, and had acceptable spirometric results in three or more surveys. The annual decline in the indices for each subject was estimated in the form of the slope of a simple regression after correction for height. Significant acceleration of the decline in FEV1 was observed as a result of cigarette smoking, and the magnitude of the effect appeared to be well within the range reported previously for white populations in Europe and North America. The magnitude of the decline in FEV1 of non-smokers, however, appeared smaller than in previous reports. These findings suggest that the susceptibility of Japanese people to cigarette smoke is similar to that of white populations in terms of acceleration of FEV1 decline, although there may be a racial difference in the magnitude of the decline in the ordinal aging process in Japanese and white populations.

The rate of decline in forced expiratory volume in one second (FEV1) is widely accepted as the best index for describing and predicting the status of COPD. Many longitudinal studies have shown a significant effect of smoking in accelerating the FEV1 decline in Western populations. To our knowledge, however, there have been no relevant studies in Japanese populations.

The purpose of this study was to assess the effect of smoking on the decline of FEV1 in Japanese occupational cohorts and to compare the results with those reported in Western countries.

SUBJECTS AND METHODS

Subjects: The subjects were selected from three occupational cohorts. They consisted of 461 men who had been working in three factories for three years or more as of 1991. Two cohorts were comprised of all employees at two asbestos factories of the same company (n=351), and the other consisted of welders at a machinery factory (n=110). The first survey was conducted in the two cohorts in

Chronic obstructive pulmonary disease (COPD) has been one of the major causes of disability and premature death in Western industrialized countries. The incidence and mortality of COPD is generally lower in Japan than in Western countries, but the factors responsible for the differences are not understood. In 1989, for example, the age-specific mortality rates for COPD per 100,000 males in Japan were 11.2, 61.0, 252.0, and 589.7 for ages 55-64 years, 65-74 years, 75-84 years, and 85 years or more, respectively. These figures are several times smaller than their counterparts in countries in Europe and North America in the mid-1980s.

Smoking is a well-known extrinsic causal factor for COPD. At least in males, however, smoking has been even more common in Japan than in most Western countries, and in the 1980s more than 60% were smokers in Japan versus 30-40% in most developed Western countries. Thus, it is suspected that the differences in COPD mortality or morbidity between Western countries and Japan may be ascribable to lower susceptibility of the pulmonary system of Japanese to cigarette smoke.
asbestos factories in the spring of 1985 and in the cohort of welders in the autumn of 1984. Follow-up examinations have been carried out annually in the asbestos factory employees except in 1987, and every two years in the welders. During each examination, spirometric measurements were made by the same methods, and a self-administered questionnaire was utilized to ascertain symptoms, past history, smoking, and other background factors.

Spirometry: The spirometric procedures have been described in detail elsewhere\(^{18}\). Briefly, spirograms were measured with a dry rolling seal spirometer (CHESTAC 65, CHEST Co. Ltd., Tokyo). Subjects were asked to repeat a forced expiration maneuver in the standing position at maximum seven times. Routine BTPS (Body temperature pressure saturated) correction and back-extrapolation correction were carried out. The acceptability of each maneuver was evaluated according to the following criteria: starting without hesitation, apparent maximal effort, and smooth continuous exhalation without cough. Reproducibility was judged by the criteria of the American Thoracic Society\(^{20}\) based on the measured values and on the shapes of flow-volume and flow-time curves. In each survey, subjects with at least two reproducible spirograms were considered acceptable. The FEV\(_1\) and forced vital capacity (FVC) values were derived from a maneuver producing the largest sum of FVC and FEV\(_1\). A single examiner carried out each measurement using the same spirometer throughout the surveys. Percent predicted FVC (%FVC) values based on reference equations reported by Yokoyama and Mitsufuji\(^{21}\) and forced expiratory volume in one second as a percentage of FVC (FEV\(_1\)% FVC) were calculated.

Calculation of annual change: After preliminary testing of several models to adjust for height, the height-squared model was found to be most appropriate. We thus used the height-squared proportional values of FEV\(_1\) and FVC (FEV\(_1\)/HT\(^2\) and FVC/HT\(^2\), respectively) in this analysis. Annual change in FEV\(_1\)/HT\(^2\) and FVC/HT\(^2\) was calculated for each subject as a slope of a linear regression of FEV\(_1\)/HT\(^2\) or FVC/HT\(^2\) to age.

Occupational exposure: Among the possible harmful sources of occupational exposure were asbestos fibers/dust and the gas and fumes accompanying welding. Although the concentrations of the possibly harmful substances had been well controlled below the permissible levels of occupational exposure set in Japan\(^{22}\), subjects were categorized into three groups: workers handling asbestos in their routine work, welders, and others for whom no harmful exposure was recognized.

Questionnaire survey: The standardized questionnaire of the American Thoracic Society (ATS-DLD-78-A)\(^{20}\) was used to determine smoking status, respiratory symptoms and past medical history, with slight modification and translation into Japanese. Mean cigarette consumption during the follow-up period was calculated for each smoking subject as the number of cigarettes smoked per day. It was used as an index of smoking dose in those who continued smoking throughout the follow-up term (continuing smokers). Cigarette consumption was defined as zero for never smokers who had never smoked cigarettes regularly for more than one year and for former smokers who had smoked cigarettes regularly for more than one year but quit prior to the first survey. Those who changed their smoking habits during the follow-up period were excluded from this analysis.

Statistical analysis: The effect of smoking on the decline in height-adjusted pulmonary function was evaluated by analysis of covariance in which adjustment was made for age and occupational status. Daily cigarette consumption was treated as a 3-level categorical variable: 0 cigarettes (non-smokers), 1-19 cigarettes daily (light smokers), and 20 or more cigarettes daily (heavy smokers). To compare the effect of smoking in this study with those of previous studies, daily cigarette consumption was treated as a continuous variable, and its effect was estimated as a partial regression coefficient per 20 cigarettes consumed daily.

All statistical tests and estimations were performed at the Tokyo University Computer Center using the SAS statistical packages.

RESULTS

Spirometry data at three or more different points in time were available for 410 of the 461 cohort members (89%). The mean follow-up period was 5.2 years, and the mean

Figure 1. Distribution of decline in forced expiratory volume in one second divided by height squared (FEV\(_1\)/HT\(^2\), ml/m\(^2\)) plotted against age. Second-order polynomial regression line is also shown.
number of spirometry measurements was 4.7 times. Twenty-seven men who had changed their smoking status during follow-up were excluded.

Those below 30 years of age showed little decline in FEV1, as shown in Figure 1. Since their relationship was not linear, a second-order polynomial regression line is also shown in the figure to explain the relationship. Student's t-test revealed that the mean annual decline in FEV1/HT2 was significantly different between those below the age of 30 and older subjects. The mean ± SD of the change was -5.2 ± 10.7 ml/m²/year for the former and -9.8 ± 11.2 ml/m²/year for the latter \( t=2.66, p=0.008 \). Since a steady decline in FEV1/HT2 appeared to occur after 30 years of age, we limited the following analysis to the 336 middle-aged subjects who were 30 years of age or older.

Table 1 shows the background of the 336 subjects according to their smoking habits during the follow-up period. Analysis of variance (ANOVA) revealed a significant difference in age distribution among those in the three smoking categories, i.e., heavy smokers were younger than light smokers and non-smokers. The mean values for height, %FVC, FEV1%, and job category distribution were comparable in all three smoking categories. Twenty-one subjects had reduced spirometry values (defined as either mean FEV1% less than 70% or mean %FVC less than 80% during follow-up). They displayed insignificantly faster annual declines in FEV1/HT2 and FVC/HT2 than the others (-11.8 ± 15.8 vs. -9.6 ± 10.9 ml/m²/year for FEV1/HT2, \( p=0.55 \), and -10.3 ± 16.4 vs. -6.3 ± 13.0 ml/m²/year for FVC/HT2, \( p=0.19 \)). The frequency of men with reduced spirometric values differed slightly according

| Number of cigarettes smoked per day | 0 (n=118) | 1-19 (n=109) | 20+ (n=109) | Total (n=336) | P |
|------------------------------------|-----------|--------------|-------------|---------------|---|
| Age (yrs)                          | 45.1 (6.0) | 44.5 (7.1)   | 41.9 (5.8)  | 43.9 (6.5)    | <.001 |
| Height (m)                         | 1.65 (.05) | 1.66 (.06)   | 1.65 (.05)  | 1.65 (.05)    | .06  |
| %FVC (%)                           | 98.7 (12.2)| 96.7 (13.2)  | 98.9 (11.8) | 98.1 (12.4)   | .35  |
| FEV1% (%)                          | 84.1 (5.6) | 83.5 (5.8)   | 84.4 (5.4)  | 84.0 (5.6)    | .50  |
| Cigarettes per day*                | 0 (0)      | 14.5 (3.4)   | 22.9 (4.5)  | 18.7 (5.8)*   | <.001 |
| Pack-years in lifetime*            | 5.6 (8.3)  | 17.7 (6.6)   | 23.6 (7.1)  | 20.6 (7.5)*   | <.001 |
| Job                                | No exposure| 50 (42)      | 34 (31)     | 36 (33)       | 120 (36) |
|                                   | Asbestos   | 44 (37)      | 54 (50)     | 50 (46)       | 148 (44) |
|                                   | Welder     | 24 (20)      | 21 (19)     | 23 (21)       | 68 (20)  |
| Low function*                     | No         | 112 (95)     | 97 (89)     | 106 (97)      | 315 (94) |
|                                   | Yes        | 6 (5)        | 12 (11)     | 3 (3)         | 21 (6)   |

*Each figure is a mean (SD), and statistical test was performed by one-way analysis of variance.
†Each figure represents frequency (%), and the statistical test was based on the chi-square test or Fisher's exact test.
‡Among continuing smokers only.
§FEV1<70 or %FVC<80 (21).

Table 2. Mean (standard error) of annual changes in FEV1/HT2 and FVC/HT2 according to smoking status during the follow-up period.

| Smoking† n | Unadjusted | Annual change (ml/m²/year) | Adjusted* |
|------------|------------|-----------------------------|-----------|
|            | FEV1/HT2   | FVC/HT2                     | FEV1/HT2  | FVC/HT2 |
|            | Mean (SE)  | p†                          | Mean (SE) | p†       | Mean (SE) | p† |
| 0 118      | -7.9 (0.9) | -5.9 (1.1)                  | -7.9 (1.1)| -6.0 (1.2)| -7.9 (1.1)| -6.0 (1.2)|
| 1-19 109   | -10.4 (1.2)| -7.1 (1.4)                  | -10.5 (1.1)| 0.08     | -7.3 (1.3)| 0.46    |
| 20+ 109    | -11.2 (1.0)| -6.8 (1.3)                  | -11.6 (1.1)| 0.02     | -7.8 (1.3)| 0.32    |
| Total 336  | -9.9 (0.6) | -6.6 (0.7)                  |            |          |            |        |

*Adjusted for age and job category.
†Number of cigarettes smoked per day.
‡p-values as compared with non-smokers.
Table 3. Independent effects of smoking and age on FEV1 and FVC decline adjusted for job category in those with normal spirometry after excluding ex-smokers (N=267).

|                | FEV1/HT² | FVC/HT² |
|----------------|----------|---------|
| Smoking¹       | Age²     | Smoking¹ | Age²    |
| -3.08 (1.44)   | -1.55 (1.08) | -1.09 (1.77) | -3.34 (1.33) |

*Each figure is a mean (SE).

¹Per 20 cigarettes a day.
²Per 10 years.

to smoking habit (p=0.03).

Table 2 compares annual changes in FEV1/HT² and FVC/HT² according to the amount of cigarette consumption during the follow-up period. Non-smokers exhibited an about 8 ml/m² loss in FEV1/HT² annually. No significant differences were observed between never-smokers (n=66) and former-smokers (n=52) in either FEV1/HT² decline or FVC/HT² decline (−7.8±9.0 vs. −8.2±11.2 ml/m²/year for the FEV1/HT², p=0.84, and −6.3±11.5 vs. −5.3±12.4 ml/m²/year for the FVC/HT², p=0.66). A much faster decline in FEV1/HT², but not in FVC/HT², was observed in smokers than in non-smokers. After adjustment for age and job category, a dose-related decline in FEV1/HT² was found according to smoking, when mean cigarette consumption in each smoking category was taken into consideration. A similar
Table 4. Comparison of declines in FEV1 in non-smokers and effects of smoking in the present study with results of other studies reported previously.

| Age range | Decline in non-smokers | Effect of smoking (daily dose*) |
|-----------|------------------------|---------------------------------|
| Tashkin (7) 40-45 (mean) | -48.5 | -32.7 (all smokers) |
| Fletcher (8) 30-39 | -36 | -8 (<15) -13 (15 ≤) |
| Camilli (9) 35-50 | -9 | -9 (all smokers, mean ≥20) |
| 50-70 | -19 | -21 (all smokers, mean ≥20) |
| Xu (10) 35-44 | -25 | -12.6 (/20, all ages) |
| 45-54 | -42 | |
| Jaakkola (11) 15-40 | | -8.4 (/20) |
| Peat (12) 40-49 | -32 | -9 (<20) -11 (20 ≤) |
| 50-59 | -37 | -11 (<20) -11 (20 ≤) |
| Lange (13) 20-55 | -21 | 7 (mean = 8) -14 (mean = 22) |
| Beaty (14) 40s (mean) | -30 | - |
| Kiżywanowski (15) 40s (mean) | -47 | -11 (20 ≤) |
| Bosse (16) 40s (mean) | -61 | -17 (all smokers, mean = 24) |
| Kauffmann (17) 30-54 | -40 | -6 (<15 g) -11 (15 g ≤) |
| Present study 30-59 | -23 | -9 (/20) |

*Definition or mean dose of each category in terms of daily cigarette consumption. Point estimate per unit dose is indicated by “/”.
(8) without obstruction only
(11) including females
(14) multiple regression adjustment
(17) adjusted for pulmonary function

DISCUSSION

Considerable evidence has been shown that a significant acceleration of decline in FEV1 occurs if one smokes at least 15 or 20 cigarettes or more daily, and an age-dependent acceleration of FEV1 decline has been also observed7-17. The present study confirmed a similar effect of smoking in middle-aged Japanese workers.

In this study, age-dependent acceleration of FEV1 decline was not obvious in subjects 30 years of age or older. We therefore examined the effect of smoking on FEV1 decline in middle-aged subjects as a whole. Although our sample consisted of three different occupational categories, a similar pattern of difference in FEV1 decline was observed between non-smokers and continuing smokers. Smoking did not make a significant contribution to FVC/HT2 decline, and age instead was found to significantly accelerate FVC loss.

In order to assess the learning effect with respect to spirometric maneuvers in terms of annual change estimates, we compared the two estimates of FEV1/HT2 decline based on all successive data and excluding the data for the first examination (Figure 3). The solid line in the figure indicates points at which the two estimates are equal. There was no tendency for one to be systematically larger or smaller than the other. A pairwise comparison did not reveal a statistically significant difference (p=0.13). The repeated analysis for FVC/HT2 yielded similar results (p=0.45).
annual FEV1 decline, and an additional FEV1 annual decline in the 10 to 15 ml range is expected if they smoke at least 15 or 20 cigarettes or more per day. Our results suggest a smaller decline with aging in non-smokers but a similar effect of smoking.

The effect of smoking may have been slightly underestimated in this study. According to previous studies, the effect of smoking seems dose-dependent, and a marked influence was chiefly observed in heavy smokers. A significant effect has not always been observed in light smokers. For example, when only those without airway obstruction were analyzed, Fletcher and Peto found an acceleration of FEV1 decline in smokers consuming 15 or more cigarettes daily, but not in those consuming less than 15 daily. Xu and co-workers reported a marked effect of smoking on FEV1 decline in males consuming 25 or more cigarettes daily. In our sample, mean cigarette consumption by heavy smokers was 22.9 cigarettes a day, somewhat less than in previous studies, probably because the subjects, especially asbestos workers and welders, were strongly urged to reduce their cigarette consumption. In this case, the assessment of the smoking effect may have been underestimated to some extent in comparison with settings in which heavy smokers smoke more frequently. Based on these results, acceleration of the FEV1 decline due to smoking in Japanese may well be within the range reported previously for whites.

Non-smokers during the follow-up period in this study showed an average -7.9 ml/m2/year FEV1/HT2 decline, corresponding to about a 23 ml/year decline in FEV1 in a 170-cm tall subject. Previous studies generally showed a faster decline in FEV1 in non-smokers than was shown in this study. In some cases, as shown in Table 4, the difference was more than two-fold, even when values for similar age ranges were considered. Among the studies in which a smaller annual FEV1 decline than ours was reported in non-smokers, the result obtained by Lange and co-workers was based on subjects including those younger than 30 years old whose FEV1 would plateau or continue to increase. Xu and co-workers also found an FEV1 decline similar to ours in 35-45 year old non-smokers, but reported further acceleration for those older than 45 years of age. Of course it is quite difficult to directly compare absolute values obtained in different settings or studies, however, the results of this study in comparison with those of previous studies, suggest that the difference in FEV1 decline between whites and the Japanese middle-aged population, if any, may be an overall change associated with aging itself, rather than acceleration by cigarette smoking. In this context, it is interesting that slightly smaller age-related differences in FEV1 were reported in Japanese-Americans in Honolulu than in whites, although the study was cross-sectional.

The effect of smoking on FVC decline is unclear. Although some previous studies have reported a significant effect of smoking on FVC decline, the degree was less than in the case of FEV1 decline. We cannot explain the reason for the insensitivity of our FVC decline to smoking, but it would not be very surprising for smokers not to show an accelerated decline in FVC if asymptomatic or in the sub-clinical stage of an obstructive disorder; FVC is more susceptible to restrictive changes in the respiratory system than obstructive changes.

One important source of bias was the so-called “healthy worker effect”. The proportion of those with reduced spirometry values was only 6.3% (21 out of 336) in this study. If the subjects in this study were healthier and less susceptible to cigarette smoke than the general population, then the magnitude of decline in FEV1 associated with smoking would be underestimated. However, the mean FVC of the subjects during follow-up was 98% of that predicted by the reference formula based on the healthy Japanese population, and mean FEV1% was 84% and also within the range of reference values for Japanese.

In conclusion, a significant acceleration of the decline in FEV1 by cigarette smoking was observed in the longitudinal spirometry data of middle-aged Japanese workers. The magnitude of the effect appeared to be well within the range reported in previous studies for white populations in Europe and North America. In contrast, middle-aged subjects who did not smoke in this study seemed to have a smaller annual FEV1 decline than non-smoking white populations. Since COPD incidence and mortality markedly increase after 60 years of age, that is, beyond the range of this study population, further assessment will be needed, especially in a more elderly Japanese population.

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