

Analysis of a follow-up study

An example from asbestos-exposed insulation workers

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CAMPBELL MJ, LANGLANDS JHM. Analysis of a follow-up study: An example from asbestos-exposed insulation workers. *Scand j work environ health* 8 (1982): suppl 1, 43-47. An 11-a follow-up study was carried out on a working population of asbestos insulation workers to investigate the possible progression of symptoms and signs. A total of 166 men had repeat radiology, and the 43 men who had progressed in radiographic category of profusion of small irregular opacities (as determined by the ILO U/C International Classification of Radiographs of Pneumoconioses, 1980) comprised 37 (32%) of the 117 smokers, 3 (17%) of the 18 exsmokers, and 3 (10%) of the 31 nonsmokers. For 148 men over 20 a of age at the time of the original study, and with lung function measured in both surveys, smoking was associated with a significantly reduced transfer factor (T_{LCO}). For smokers in category 0 at first survey, a low T_{LCO} was associated with subsequent progression to higher radiographic categories.

Key terms: asbestos workers, smoking, small opacities, transfer factor, progression, follow-up studies, analysis of covariance.

A survey was carried out in 1965-1966 and has been described by Langlands et al (7). The target population was all male insulation workers in Belfast, including men temporarily unemployed, but not men who had left the trade or who were not working in Belfast. This population consisted of 271 men, of whom 255 (95%) were interviewed. The follow-up study was conducted between 1975-1978 and in that time 35 (14%) of the men had died and 47 (18%) could not be traced. Exposure to asbestos had virtually ceased by 1970.

Methods

Data collection

Forced expiratory volume in 1 s ($FEV_{1.0}$) and forced vital capacity (FVC) were mea-

sured by spirometry, and the average of the last three of five attempts was taken. Residual volume (RV) and total lung capacity (TLC) were measured by closed circuit helium dilution, and the transfer factor (T_{LCO}) by a single breath-holding technique using a carbon monoxide/helium/air mixture. The alveolar volume was estimated from the ratio of inspired and expired helium concentrations. In the first survey the equipment consisted of a Gaesler water-filled spirometer and an early prototype of the present Morgan "Resparameter" used for both static lung volume and transfer factor measurements. In the second survey a Vitalograph dry spirometer was used, together with a Godart closed-circuit spirometer for static lung volumes and a Pk Morgan "Resparameter" for T_{LCO} . Volumes were converted to BTPS (temperature of 37°C, ambient pressure, saturated with water vapor at 37°C). At each survey a postero-anterior radiograph was taken of each subject. After the second survey these were read separately in randomized order by three readers according to the ILO U/C International Classification of Radiographs of Pneumoconioses (6). In particular a combined profusion

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score was read for small rounded and irregular opacities. Fifty-one radiographs were reintroduced into the reading session and read again to provide evidence on the consistency of the readers. The small opacities were all found to be predominantly irregular. The median profusion score used to classify the radiographs was similar to that used by Rossiter & Harries (11). In the present study we have restricted our attention to small parenchymal opacities. An analysis of the other changes will be reported elsewhere. The subjects were classified as those having never smoked (nonsmokers), exsmokers, current smokers, and smokers having quit between surveys. For the lung function analysis, we excluded subjects who grew between the two surveys. A total of 148 subjects with technically satisfactory lung function measurements were included in the analysis.

Statistical analysis

In this study we have usually used multiple regression/analysis of covariance as outlined, eg, by Anderson et al (1). We then expressed the results corrected to a particular age and height (usually the overall mean age and height). Cole (3) has shown how to correct FEV_{1.0} and FVC for height, but this procedure may not apply to the other lung function measurements. Anderson et al (1, p 148) have outlined the assumptions underlying the analysis of covariance. In cases where smoking materially affects the level of lung function, it is important to include smoking as a covariate. With multiple regression, age, height, and smoking terms, possibly with a smoking-age interaction term, are first fit, and then a check is made of whether the addition of a term corresponding to the factor of interest significantly reduces the residual sum of squares. An alternative method is to correct the observed values and look at the corrected values in relation to the factor of interest. If b_1 and b_2 are the regression coefficients for age and height (allowing for smoking), respectively, then, if y_{obs} and y_{corr} are the observed and corrected values, respectively, for the lung function measurement, in order to correct to age 45 a and height 1.7 m, we put

$$y_{\text{corr}} = y_{\text{obs}} + b_1 (45 - \text{age}) + b_2 (1.7 - \text{height}).$$

In comparisons between corrected values it is important to reduce the degree of freedom associated with the pooled sum of squares by the number of estimated parameters. It follows from the preceding equation that a further assumption is that the lung function is linearly dependent on age and height. Cole (3) has investigated this possibility for FEV_{1.0} and FVC and shown that the relationship with height is not necessarily linear.

We have applied his method, as well as the analysis of covariance, to these variables, but with no material difference in the results. In follow-up studies, the rate of decline of lung function between surveys is of interest. Unfortunately, as shown by Berry (2) and also by Higgins & Oldham (5), this measurement usually has a larger standard error than the age coefficient in a multiple regression of a cross-sectional study. It is subject to potentially large biases, especially if different equipment or operators are used in the follow-up. If the observer errors are substantially different in the two surveys, an artificial correlation between the rate of decline and the average of the observations in the two surveys will be generated. Thus, it can be difficult to make useful inferences from these measurements.

Results

Table 1 shows how the radiographs were divided by major profusion category of the ILO (International Labour Organization) classification. It can be seen that, of those who were not traced in the second survey, 87 % belonged to category 0 in the first survey, whereas, of those who died, 58 % had some degree of profusion in the first survey. Subjects who were seen on both occasions had an average increase in profusion of about 0.8 of a category, over an average of 11 a. In table 2 it can be seen that, of those seen on both occasions, 32 % of the smokers showed increased profusion compared with 12 % of non- or exsmokers. The smokers were slightly younger than the nonsmokers, and, because profusion category tends to increase naturally with age, we stratified the results from table 3 into 10-a age groups and used the Mantel-Haenszel estimator of the odds ratio to test whether smokers and nonsmokers were

equally likely to progress. This procedure gave an odds ratio of 6 : 1, which was found to reject the null hypothesis that smokers progress at the same rate as nonsmokers with an approximate normal statistic of 3.1 ($p < 0.001$). The odds ratio for smokers and exsmokers was 2 : 1, but this value was not significant at the 5 % level.

The effect of smoking on lung function is shown in table 3 for values corrected to age 45 a and height 1.70 m. It is clear that the smokers had a large deficit in T_{LCO} ,

and they also appeared to have a larger RV/TLC % than nonsmokers. There were no significant differences in lung function between subjects who smoked at the time of both surveys and subjects who claimed to have given up smoking between the surveys. Since smoking was so strongly correlated with progression, we decided to restrict attention to smokers and see if the lung function in the first survey could tell us about future changes in the radiographic category. Table 4 shows the average

Table 1. Change in profusion category between surveys.

First survey category	Second survey category						Total
	0	1	2	3	Dead	Missing	
0	84	34	3	0	15	41	177
1	2	33	6	0	15	6	62
2	0	1	2	0	5	0	8
3	0	0	0	1	1	0	2
Missing ^a	1	3	1	0	0	1	6
Total	87	71	12	1	36	48	255

^a At the second survey six radiographs from the first survey had been lost.

Table 2. Change in profusion category by smoking habit at first survey.

	Increase	No change	Decrease	Total
Nonsmokers	3	28	0	31
Exsmokers	3	15	0	18
Smokers	37	77	3	117
Total	43	120	3	166

Table 3. Lung function in first survey corrected to age 45 a and height 1.7 m.

	Nonsmokers (N = 26)		Smokers in both surveys (N = 82)		Smokers in first survey only (N = 40)	
	Mean	Standard error	Mean	Standard error	Mean	Standard error
Forced expiratory volume in 1 s (l)	3.09	0.103	3.02	0.052	2.87	0.084
Forced vital capacity (l)	4.13	0.104	4.14	0.066	4.02	0.085
Residual volume (RV) (l)	1.49	0.111	1.85	0.110	1.81	0.154
Total lung capacity (TLC) (l)	5.44	0.174	5.83	0.132	5.62	0.175
RV/TLC %	25.9	1.55	30.2 *	1.33	31.1	1.81
Transfer factor (mmol · min ⁻¹ kPa ⁻¹)	7.43	0.298	6.34 **	0.169	6.84	0.325

* $p < 0.05$, ** $p < 0.01$ (significantly different from nonsmokers).

standardized lung function of smokers in the first survey, classified by whether the subject progressed in radiographic category. The group that progressed from category 0 appeared to have a deficit in T_{LCO} of about $0.9 \text{ mmol} \times \text{min}^{-1} \text{ kPa}^{-1}$. It is not clear that a t-test is valid under

these circumstances, since we would need to assume that those originally in category 0 formed a mixture of two normal distributions, the progressors and the non-progressors, and this assumption goes against the idea of radiographic progression as one of gradual change, some subjects changing much more than others. A Wilcoxon Rank Sum Test was carried out on the two groups; it yielded a significant result ($p < 0.02$). Another possibility (discussed in the statistical methods) is that T_{LCO} is not linearly dependent on age and that perhaps the covariance analysis is "overcorrecting" the younger nonprogressors. We therefore age-matched the two groups, with a tolerance of 2 a. An exact match was found for eight pairs and an approximate match for another eight. The T_{LCO} was adjusted for height by the covariance analysis, and a paired t-test for the difference in the two groups gave a highly significant result ($t = 4.36$, $df = 14$, $p < 0.005$). A discriminant analysis was carried out to determine whether a combination of lung function indices could predict progression. Besides T_{LCO} the next best discriminator was TLC, and these two

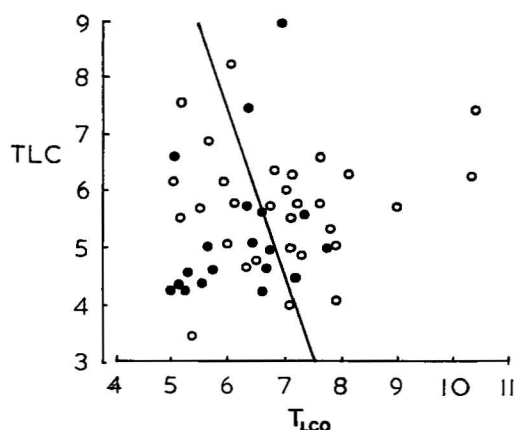


Fig 1. Discriminant function for progressors (●) and nonprogressors (○) at first survey. [TLC = total lung capacity (l), T_{LCO} = transfer factor ($\text{mmol} \cdot \text{min}^{-1} \text{ kPa}^{-1}$)]

Table 4. Lung function of smokers in first survey corrected to age 45 a and height 1.7 m.

	Category change (first survey-second survey)			
	0-0 (N = 33)		0-1, 0-2 or 0-3 (N = 18)	
	Mean	Standard error	Mean	Standard error
Forced expiratory volume in 1 s (l)	3.05	0.086	3.15	0.108
Forced vital capacity (l)	4.26	0.108	4.23	0.143
Residual volume (RV) (l)	1.87	0.173	1.84	0.292
Total lung capacity (TLC) (l)	5.99	0.177	5.45	0.290
RV/TLC (%)	30.4	1.74	28.9	3.08
Transfer factor ($\text{mmol} \cdot \text{min}^{-1} \text{ kPa}^{-1}$)	6.60	0.228	5.69 *	0.214

* $p < 0.02$ (significantly different from category 0).

Table 5. Transfer factor of progressors and nonprogressors classified by the extended ILO classification.

	First survey category					
	0/0			0/1		
	Mean	Standard error	N	Mean	Standard error	N
Nonprogressors	6.50	0.264	27	7.04	0.389	6
Progressors	6.03	0.400	7	5.47	0.200	11

are plotted for progressors and nonprogressors in fig 1. The discriminant function was

$$T_{\text{LCO}} + 0.35 \text{ TLC} = 8.59,$$

and it misclassified 5 progressors and 17 nonprogressors, a success rate of about 67 %. We found that the main error was the classifying of people with low T_{LCO} as progressors. It is possible that the progressors are subjects already classified as category 0/1 in the extended ILO classification. The results are shown in table 5. Progressors do in fact contain a higher proportion of subjects in category 0/1, but within each subcategory progressors are still associated with a lower T_{LCO} .

Discussion

The fact that, of people exposed to asbestos, smokers are much more likely to develop small opacities is in agreement with the findings of Rossiter & Berry (10) and Weiss (12). It would also appear that giving up smoking (ie, exsmokers in the first survey) reduces the probability of progression. McMillan et al (8) have shown in a 9-a follow-up survey that smokers exposed to asbestos are more likely to develop pulmonary or pleural lesions than nonsmokers. The concept of "progressors" and "nonprogressors" is rather artificial, since profusion is really a continuous process and even nonprogressors may be expected to have progressed, but not to have actually crossed a category boundary. More research is needed to tackle this problem properly. Regan et al (9) have shown that a deficit in T_{LCO} was the best index for measuring the severity of both asbestosis and obstructive airways disease. Gaensler et al (4) described several cases of subjects with a normal radiograph, but with low diffusing capacity and whose lung biopsy showed interstitial fibrosis. Thus we have some confirmation that subjects may suffer a deficit in lung function before disease becomes apparent in radiographs.

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