

## Restricted cohort study designs

by David Oakes, PhD, J Corbett McDonald, MD<sup>1</sup>

OAKES D, MC DONALD JC. Restricted cohort study designs. *Scand j work environ health* 8 (1982): suppl 1, 30-33. Practical constraints may limit both cohort selection and the degree of follow-up in longitudinal studies of occupational mortality. For example, it may be possible to study only those men employed on a certain date or to trace (through pension fund records) only men employed at or close to normal retirement age or to follow men only for a very limited period after they have left employment. In an examination of the effects of such restrictions, advantage was taken of the availability of detailed work histories and the full follow-up of a large birth cohort of chrysotile asbestos workers. Age-matched case-referent analyses were performed under each type of restriction. All three analyses revealed the clear exposure-response relationship between cumulative dust exposure and lung cancer that was found in the full analysis. Most other findings were also not inconsistent with the earlier results. Such restricted cohort studies, with case-referent approaches to analysis, can be justified in logic. The findings provide some empirical support for these methodological variants and suggest that they may be useful when complete follow-up of an entire birth cohort is not feasible.

**Key terms:** case-referent analysis, chrysotile asbestos, exposure-response relationship, occupational mortality study, restricted follow-up.

The problem of estimating exposure-response relationships from cohort studies of occupational mortality has led to scrutiny of available study designs and methods of analysis. For example, a case-referent analysis of a cohort study combines the simplicity of the former with the validity of the latter at only a modest cost in statistical efficiency (7, 8). Even so, this approach requires the determination of the vital status of every member of the cohort, with dates and cause of death — a difficult and expensive exercise. The impracticability of such studies for every suspected industrial hazard indicates the need for quicker and cheaper methods. Many companies now have good personnel records,

covering current employees and those eligible for pension funds. Work histories can be abstracted and estimates made of occupational exposure. However, these records are of little help in tracing workers who have left the company. It would be easier if cohorts could be confined to persons close to retirement age or to those working on a certain date or if follow-up could be limited to a very short period after workers leave employment.

We have studied the effect of these three types of restriction using data from a large cohort of Quebec chrysotile miners and millers comprising all 11,379 persons born between 1891 and 1920 who had worked for 28 d or more in this industry (9). It was assumed *first* that deaths could be identified only if they occurred in the same calendar year as the termination of employment; *second* that only men employed at age 60 could be traced; and *third* that the cohort was limited to men aged 36 to 65 and employed during 1956. The first restriction was on follow-up, whereas the second and third were on cohort membership but not on follow-up.

<sup>1</sup> TUC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, University of London, London, England.

Reprint requests to: Dr D Oakes, TUC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, University of London, Keppel Street (Gower Street), London WC1E 7HT, England.

## Methods

Only deaths from pneumoconiosis and malignant disease of the respiratory and digestive tracts among males were studied. In the first analysis, for each death a pool of eligible referents was selected, born in the same year and employed throughout the calendar year of the death of the case. A small number of cases with fewer than six eligible referents were omitted. In the second and third analyses, membership in the constricted cohorts was required. From each pool of potential referents a sample of six was selected strictly at random.

The exposure histories of the cases and referents were compared with the methods described by McDonald et al (9). Cumulative dust exposure in terms of millions of particles per cubic foot-years ( $\text{mpcf} \cdot \text{y}$ )<sup>2</sup> was calculated for cases and referents up to 9 a before the year of death of the case. The same broad groupings of exposure were used as by McDonald et al (9), and the risks relative to the lowest exposure category were calculated with the method of Doll (5). Chi-squares with one degree of freedom for linear trend were calculated as by Armitage (1).

## Results

Table 1 shows the results of the three restricted analyses, preceded by the case-referent analysis of the full cohort [adapted from table 10 of McDonald et al (9)], in which there were 4,463 male deaths.

### *Follow-up restricted to year of employment termination*

As work histories were recorded only to the end of 1966, later deaths could not be included, and the total number of deaths was therefore reduced to 530 in the first restricted analysis. Despite this reduction the same clear trend in the relative risk of lung cancer with increasing exposure was apparent, as in the full analysis. The somewhat less consistent findings for the gastrointestinal cancers were also congruent with the full results, but the ab-

sence of any trend for pneumoconiosis was not.

### *Men employed at age 60*

In all, 929 men in the cohort fulfilled the requirement of the second analysis of being employed at age 60, and of these 480 had died. As the cohort was set up in 1966, it was not possible to include men born after 1906. Strong trends for pneumoconiosis and lung cancer were revealed. Little relationship with exposure was indicated for malignant disease of the gastrointestinal tract.

### *Men aged 36–65 and employed in 1956*

The cohort included 3,424 men aged 36–65 and employed in 1956, and of these 1,363 subsequently died. Again in this third analysis the trends for both pneumoconiosis and lung cancer were evident. There was also a suggestion of a trend for cancers of the upper gastrointestinal tract, but not for other sites.

## Discussion

Three factors affect the results of any occupational mortality study, namely, selection for employment, survival at work, and susceptibility to the effects of exposure. The first two have been discussed frequently in recent years (6) and are often referred to as the healthy worker effect. They imply that workers entering an industry, or those who have been employed in the industry for some time, are likely, in the absence of any appreciable occupational risk, to have a different standard of health, usually though not invariably better, than an external reference population which includes the unemployed or those who frequently change jobs.

The biasing effects of selection and survival on estimated exposure-response relationships are possibly reduced with the use of internal comparisons within the study cohort. Case-referent analyses of the type used in this paper provide one approach (7). An a priori technique, based on the stratification of person-years of follow-up, but which does not use an external reference population, was used by Darby

<sup>2</sup> 1  $\text{mpcf} \cdot \text{y}$  = 35.31 millions of particles/ $\text{m}^3 \cdot \text{a}$ .

**Table 1.** Relative risk established in the case-referent analyses. (Number of cases:referents in parentheses)

|                                                     | Dust exposure (mpcf • y) accumulated<br>up to 9 a before death of case <sup>a</sup> |               |               |              | $\chi^2_1$ |
|-----------------------------------------------------|-------------------------------------------------------------------------------------|---------------|---------------|--------------|------------|
|                                                     | < 30                                                                                | 30—300        | 300—1,000     | ≥ 1,000      |            |
| <i>Full cohort</i>                                  |                                                                                     |               |               |              |            |
| Pneumoconiosis                                      | 1 (7: 63)                                                                           | 1.65 (9: 49)  | 5.57 (13: 21) | 30.6 (17: 5) | 40.2       |
| Lung cancer                                         | 1 (89:333)                                                                          | 1.12 (73:243) | 1.65 (56:127) | 3.16 (27:32) | 17.0       |
| Cancer of esophagus<br>and stomach                  | 1 (74:143)                                                                          | 0.75 (41:105) | 0.80 (22: 53) | 4.69 (17: 7) | 2.17       |
| Cancer of colon<br>and rectum                       | 1 (39: 88)                                                                          | 0.93 (29: 70) | 1.96 (13: 15) | 5.26 (7: 3)  | 5.40       |
| Other abdominal<br>cancers                          | 1 (43: 83)                                                                          | 1.05 (25: 46) | 0.52 (7: 26)  | 1.93 (5: 5)  | 0.07       |
| <i>Deaths in the year of employment termination</i> |                                                                                     |               |               |              |            |
| Pneumoconiosis                                      | 1 (1: 3)                                                                            | 0.13 (1: 23)  | 1.20 (4: 10)  | 0.50 (1: 6)  | 0.59       |
| Lung cancer                                         | 1 (2: 17)                                                                           | 1.24 (8: 55)  | 1.33 (5: 32)  | 3.40 (4:10)  | 1.67       |
| Cancer of esophagus<br>and stomach                  | 1 (2: 28)                                                                           | 1.50 (3: 28)  | 5.44 (7: 18)  | 2.80 (2:10)  | 3.25       |
| Cancer of colon<br>and rectum                       | 1 (3: 7)                                                                            | 0 (0: 12)     | 0.47 (1: 5)   | — (0: 0)     | 1.08       |
| Other abdominal<br>cancers                          | 1 (1: 14)                                                                           | 8.40 (3: 5)   | 0 (0: 5)      | 2.33 (1: 6)  | 0.03       |
| <i>Men employed at age 60</i>                       |                                                                                     |               |               |              |            |
| Pneumoconiosis                                      | — (0: 6)                                                                            | 1 (3: 41)     | 2.28 (4: 24)  | 7.36 (7:13)  | 9.13       |
| Lung cancer                                         | 1 (1: 17)                                                                           | 2.24 (17:129) | 2.56 (14: 93) | 5.93 (15:43) | 6.70       |
| Cancer of esophagus<br>and stomach                  | 1 (3: 6)                                                                            | 0.17 (5: 60)  | 0.37 (7: 38)  | 0.55 (6:22)  | 0.61       |
| Cancer of colon<br>and rectum                       | 1 (3: 5)                                                                            | 0.15 (2: 23)  | 0.22 (4: 31)  | 0.48 (2: 7)  | 0.32       |
| Other abdominal<br>cancers                          | 1 (1: 6)                                                                            | 0.55 (2: 22)  | 1.64 (3: 11)  | 1.33 (2: 9)  | 0.56       |
| <i>Men employed in 1956</i>                         |                                                                                     |               |               |              |            |
| Pneumoconiosis                                      | — (0: 28)                                                                           | 1 (8: 81)     | 1.88 (10: 54) | 7.15 (12:17) | 20.8       |
| Lung cancer                                         | 1 (9: 80)                                                                           | 0.96 (31:288) | 2.00 (40:178) | 2.96 (22:66) | 15.3       |
| Cancer of esophagus<br>and stomach                  | 1 (5: 22)                                                                           | 0.44 (11:110) | 0.83 (11: 58) | 1.38 (10:32) | 2.58       |
| Cancer of colon<br>and rectum                       | 1 (2: 6)                                                                            | 0.33 (7: 64)  | 0.62 (6: 29)  | 0.80 (4:15)  | 0.69       |
| Other abdominal<br>cancers                          | 1 (3: 14)                                                                           | 0.73 (8: 51)  | 0.58 (4: 32)  | 1.27 (3:11)  | 0.01       |

<sup>a</sup> 1 mpcf • y = 35.31 millions of particles/m<sup>3</sup> • a. (mpcf • y: millions of particles per cubic foot-years)

& Reissland (3) in a reanalysis of the Hanford study of workers exposed to ionizing radiation.

Differences in individuals' susceptibility to exposure pose a more complex problem. Susceptible persons may begin to experience adverse health effects after a short period of exposure and therefore move to jobs with less exposure or even

leave the industry altogether. The consequence in statistical terms would be a three-way interaction between past exposure, current job status, and future mortality, in contrast to the two-way interaction between current job status and future mortality implicit in the so-called healthy worker effect. Ashford & Wearing (2) have recently proposed a mathematical

model incorporating these points. However, the appropriate general formulation of the problem is not immediately clear, and it is possible that the parameters of such a model would not be statistically identifiable, as happens in certain similar, though simpler, problems related to competing risks (4, 10). However, it is evident that detailed studies of persons with short exposure might provide useful information.

The study designs considered in this paper all tend to exclude men with short service. The most radical departure from orthodox design is the exclusion, in our first analysis, of follow-up after the year of employment termination. The justification for this approach is that a limited study may be preferable to none at all and certainly better than a patchy or incomplete follow-up. Viewed as a case-referent study of men in employment, the proposed design is valid in logic, and better than most case-referent studies in that both the cases and referents satisfy the same strict criteria for inclusion.

For the susceptibility effect, as we have defined it, to be important, the exposure-response relationships calculated from men who remain at work should prove less steep than for the entire cohort. Table 1 shows no such effect for any form of cancer although the results for pneumoconiosis might conceivably be explained in this way. In general, slowly progressive and very disabling diseases, such as the pneumoconioses, are unlikely to cause death at or soon after a person leaves work. This is a serious drawback for method 1. The other two restricted cohort designs yielded no surprises. The trends for pneumoconiosis and lung cancer were clear both for those employed at age 60 and for those employed in 1956.

## Conclusion

Our findings provide empirical support for the validity of certain restricted cohort

study designs, with case-referent analysis. Since they would be useful when complete follow-up of an entire birth cohort is not feasible, further tests need to be made on other large sets of occupational mortality data.

## Acknowledgment

This study was supported by a grant from the Institute of Occupational and Environmental Health of the Quebec Asbestos Mining Association.

## References

1. Armitage P. Statistical methods in medical research. Blackwell, Oxford 1971.
2. Ashford JR, Wearing A. The assessment of industrial health hazards on the basis of observational data — Some statistical pitfalls. *Bull appl stat* 8 (1981) 62—81.
3. Darby SC, Reissland JA. Low levels of ionising radiation and cancer — Are we underestimating the risk? *J r stat soc A* (in press).
4. David HA, Moeschberger ML. The theory of competing risks. Griffin, London 1978.
5. Doll R. Retrospective and prospective studies. In: Witts LP, ed. Medical surveys and clinical trials. Oxford University Press, London 1964, pp 64—90.
6. Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. *Br j prev soc med* 30 (1976) 225—230.
7. Liddell FDK, McDonald JC, Thomas DC. Methods of cohort analysis: Appraisal by application to asbestos mining. *J r stat soc A* 140 (1977) 469—491.
8. Mantel N. Synthetic retrospective studies and related topics. *Biometrics* 24 (1973) 479—486.
9. McDonald JC, Liddell FDK, Gibbs GW, Eyssen G, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910—75. *Br j ind med* 37 (1980) 11—24.
10. Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure time data in the presence of competing risks. *Biometrics* 34 (1978) 541—554.