Lung cancer

Asbestos, smoking, and lung cancer: interaction and attribution

B W CaseCommentary on the paper by Reid *et al* (see page 509)

Lung cancer is almost as dramatic a disease as is mesothelioma in its clinical course and prognosis. It has been a “rule of thumb” that there may be two asbestos related lung cancers for every mesothelioma, with a ratio of up to 10:1 in some heavily exposed occupational cohorts. Even in the United Kingdom, where mesothelioma deaths have risen so high they may have surpassed asbestos related lung cancer deaths,¹ the latter remains estimated at 2–3% of all lung cancer. Due to disease time course, the potential effects of smoking cessation, and possibly improved screening of at-risk populations, lung cancer seems more amenable to early detection or prevention. Yet lung cancer receives far less attention, both scientifically and in the popular press.

The problem is partly one of ease of attribution. For compensation boards and others charged with this task, this has proved more difficult for lung cancer. For mesothelioma, most—80% generally, and perhaps over 90% in the UK—are currently due to one factor. The potent associated influences of asbestos fibre type and of time from first exposure make deconstruction of the cause of individual cases of mesothelioma a straightforward matter given adequate information.²

Lung cancer has always presented less simple dilemmas. Approximately the same proportion of cases are also due to one factor—smoking. Richard Doll’s seminal lung cancer discoveries for both smoking and asbestos were separated by only a few years. Ever since, by sheer numbers, the smoking related lung cancer has always been pre-eminent. The very high exposures and frequent finding of asbestosis in the past also led to a mistaken idea that clinical asbestosis was a “necessary precondition” for lung cancer, a proposition now generally thought due to collinearity of the dose-response relationships in the two diseases. The loss of this factor as a scientifically reliable marker of attribution adds to the difficulty. Published evidence regarding histological type or

site within the lung has been contradictory and has also failed in the long term in reliably assigning cause to asbestos (or to smoking).

Through the years, evidence for “synergy” between smoking and asbestos exposure has varied from as little as none at all—a simple addition of the two risk factors—to a multiplication of the two risks, or more. It has only been in this century, with the maturing of the two most studied occupational cohorts in the history of asbestos research—the chrysotile miners and millers of Quebec and the mainly shorter term crocidolite miners and millers at Wittenoom that the picture has become clearer.

In this issue, the paper by Reid *et al* demonstrates in the latter group—as had been shown in the former, with help from one of Reid’s co-authors, Geoffrey Berry—the true mathematical nature of the interaction.³ It is less than a “multiplication of risks”, but clearly synergistic—more than additive. The authors provide a concise explanation of how the “relative asbestos effect”—the ratio of risks (odds ratios) in non-smokers and (20-year or more) ex-smokers to that in current smokers—operates to prove this point. This difficult concept is amplified in their own work and that of Liddell *et al*, which they reference. A biological interaction is also implied, although there has been little work on how this happens. Increased polycyclic aromatic hydrocarbon uptake from benzo(a)pyrene coated asbestos fibres has been demonstrated *in vitro*;⁴ and DNA strand breakage has been shown in rat respiratory tract epithelial cells after co-exposure to asbestos and cigarette smoke *in vivo*,⁵ but we remain far from understanding the mechanisms.

The Australian studies and the corresponding Quebec 1891–1920 birth cohort studies led by Corbett and Alison McDonald remind us of the importance of the occupational cohort study which is mature—that is, in which most of the members have been followed unto death—and in which

there is individual exposure assessment available. Exposure assessment in both cohorts has been criticised, principally for the use of available measurements “of the day”—such as koniometric particulate measurements. Yet as John Gilson observed when such measures were first being debated, “Everybody is unwilling to start using...a particular instrument because they say we do not know whether it is the one that is the best...Surely, the way to start is to choose a method at some time”.⁶ The proof is in the pudding: the two groups of authors have published over 100 papers arising from these two cohorts which substantially increased our knowledge of almost every aspect of asbestos exposure and disease. Cohort studies of textile and other asbestos workers added the dimension of differing slopes of lung cancer risk for different types of industrial exposure, mediated at least in part by greater fibre length in those occupations at greatest risk.⁷

There remain serious practical problems in translating into attribution what we know about smoking interaction, dose, and type of exposure. This is true both for the individual case and for risk assessment. Even if we are confident in our estimates of past smoking and asbestos exposure, there remain the problems of how great the asbestos dose needed to be, and where the particular exposure fits on the varying risk slopes.⁸ Dose reconstructions are often attempted in individual cases but the associated uncertainty is high unless they worked in one well-characterised industry all their lives. Good overall risk assessments have been produced,^{8,9} but applying them to specific locations or at-risk groups is still difficult.

Some compensation boards advocate the construction of algorithms to distribute attribution proportionally to smoking and asbestos exposure. With the increased knowledge of the shape of the smoking interaction this may be more feasible, but the lowest dose at which lung cancer is even in part caused by asbestos exposure (with or without smoking) remains controversial. A practical, case-by-case approach, supplemented by common-sense rules concerning (for example) length and type of employment seems best, but our improved knowledge of the nature of smoking interaction will be of considerable help. We should also not forget that while asbestos is the best understood and most researched lung co-carcinogen in the occupational environment it is not the only one: similar work regarding the smoking effect is needed not only for the other well known occupational lung carcinogens, but also for environmental

causes including particulates and other elements of air pollution.

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