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Accessibility
Comment on ‘The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)’: the effect of left censoring

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Sir,

We read with extreme interest the article by Frost on mesothelioma latency period among asbestos workers (Frost, 2013). Despite the main aim of the study being to investigate ‘the determinants of mesothelioma latency among a cohort of asbestos workers, paying particular attention to indicators of latency’ (Frost, 2013), the reported lack of evidence of an association between duration of exposure and latency attracted some attention. Commenters argued that right censoring occurring in the underlying cohort could have biased an analysis restricted to cases (Consonni et al., 2014; Mirabelli and Zugna, 2014).

We would like to highlight a different pitfall of Frost’s analysis. She observed huge differences in median latency periods across categories of year of first exposure to asbestos. Indeed, the median latency for deaths among workers exposed to asbestos before 1940 was 48 years, whereas a median latency of only 11 years characterised cases exposed not earlier than 1980. This difference translated in a dramatic decrease of time ratios with increasing year of first exposure. However, it is surprising that the author interpreted these data without considering the limited follow-up window (1978–2005). On the one hand, all the cases exposed before 1940 entered the analysis with a latency of at least 38 years, as all deaths that occurred before 1978 were left censored. On the other hand, the maximum latency observable for subjects exposed after 1980 was just 25 years as events potentially occurring after 2005 were right censored. To describe how left and right censoring can affect the estimates presented by Frost, we conducted a simple simulation study. We assumed a true latency period constant across categories of the year of first exposure to asbestos based on a gamma distribution (shape parameter 11, scale parameter 3). This distribution has a median of 32 years, in line with the median latency for deaths among workers exposed to asbestos before 1940 presented by Frost in the discussion section of her paper (Lanphear and Buncher, 1992).

In our simulation, we considered six categories for the year of first exposure to asbestos (as in Frost’s article) and we assumed 300 mesothelioma deaths within each category (Table 3). Indeed, all the estimates for variables putatively correlated with the year of first exposure (e.g. main occupation, as the proportion of subjects employed in manufacturing and removal has changed over time) could be biased by the improper adjustment for a covariate associated with the outcome. Furthermore, left censoring could also spuriously associate the year of the first exposure and mesothelioma latency with a median of 32 years, in line with the median latency for deaths among workers exposed to asbestos before 1940 reported for occupational mesothelioma and presented in Table 3 of Frost’s manuscript and this fact suggests that a strong bias might affect her findings. Remarkably, a spurious association between the year of the first exposure and mesothelioma latency might bias all the multivariate time ratios presented in Figure 1. Indeed, all the estimates for variables putatively correlated with the year of first exposure (e.g. main occupation, as the proportion of subjects employed in manufacturing and removal has changed over time) could be biased by the improper adjustment for a covariate spuriously associated with the outcome. Furthermore, left censoring could also spuriously bias the estimates for other time variables. Compared to the latter cohorts, the group of workers exposed for the first time to asbestos before 1950 is likely to have a longer average duration of exposure as well as a spuriously longer average latency. This fact could contribute to explain the

Figure 1. Simulation study of mesothelioma latency after occupational exposure to asbestos. Analysis of latency periods by categories of first year of exposure. Latency periods were simulated assuming a gamma distribution (shape parameter: 11; scale parameter: 3). Time ratios were estimated by fitting accelerated-time failure models based on a gamma distribution of the events.

Table 1. Simulation study of mesothelioma latency after asbestos exposure

| Year of First Exposure | Observed Deaths | Median Latency | Time Ratio |
|------------------------|-----------------|----------------|------------|
| 1925                   | 300             | 31.7 years     | 1.00 (Ref) |
| 1935                   | 300             | 31.2 years     | 0.99       |
| 1945                   | 300             | 32.3 years     | 1.02       |
| 1955                   | 300             | 31.5 years     | 1.01       |
| 1965                   | 300             | 31.2 years     | 0.97       |
| 1975                   | 300             | 32.7 years     | 1.01       |
| 1985                   | 300             | 31.7 years     | 1.00 (Ref) |

Table 2. Simulation study of mesothelioma latency after asbestos exposure

| Year of First Exposure | Observed Deaths | Median Latency | Time Ratio |
|------------------------|-----------------|----------------|------------|
| 1925                   | 49              | 47.8 years     | 0.70       |
| 1935                   | 122             | 39.9 years     | 0.84       |
| 1945                   | 238             | 33.2 years     | 0.70       |
| 1955                   | 238             | 29.0 years     | 0.60       |
| 1965                   | 149             | 25.4 years     | 0.50       |
| 1975                   | 38              | 18.8 years     | 0.37       |
| 1985                   | 49              | 47.8 years     | 0.70       |

Table 3. Simulation study of mesothelioma latency after asbestos exposure

| Year of First Exposure | Observed Deaths | Median Latency | Time Ratio |
|------------------------|-----------------|----------------|------------|
| 1925                   | 49              | 47.8 years     | 0.70       |
| 1935                   | 122             | 39.9 years     | 0.84       |
| 1945                   | 238             | 33.2 years     | 0.70       |
| 1955                   | 238             | 29.0 years     | 0.60       |
| 1965                   | 149             | 25.4 years     | 0.50       |
| 1975                   | 38              | 18.8 years     | 0.37       |
| 1985                   | 49              | 47.8 years     | 0.70       |
increase in time ratios observed across categories of duration at the univariate analysis (Table 2).

Noteworthy, as the information on asbestos was available only from 1978, Frost restricted the follow-up window even though information on mesothelioma deaths was available from 1972. This choice determined both a larger number of cases and an exacerbation of the bias due to left censoring. Remarkably, asbestos was only weakly associated with the outcome; hence, this variable is not likely to induce substantial confounding. Thus, Frost should have considered the entire follow-up period to study the other variables. Estimates restricted to 1978 and 2005 and adjusted by asbestosis could have served as a sensitivity analysis.

With a view to perform a simple and quick reanalysis. She should (i) include only cases exposed for the first time between 1950 and 1969 to limit left and right censoring (she would still retain 56% of the cases); (ii) analyse the entire follow-up period (1972–2005) to limit left censoring and increase the number of cases; (iii) avoid adjustment for the year of first exposure. If confounding by the latter is a strong concern, Frost could conduct stratum-specific analysis.

REFERENCES

Consonni D, Barone-Adesi F, Mensi C (2014) Comment on ‘The latency period of mesothelioma among a cohort of British asbestos workers (1978-2005)’: methodological problems with case-only survival analysis. Br J Cancer 111: 1674.

Frost G (2013) The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005). Br J Cancer.

Lanphear BP, Buncher CR (1992) Latent period for malignant mesothelioma of occupational origin. J Occup Med 34: 718–721.

Mirabelli D, Zugna D (2014) Comment on ‘The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)’. Br J Cancer 111: 1675.

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Response to comment on ‘The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)’

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Sir,

I read with interest the comments by Farioli et al (2014) on the recent publication investigating the latency period of mesothelioma (Frost, 2013). They raised important points regarding the decisions made during analysis—in particular, adjusting for year of first exposure, and restricting follow-up to 1978 onwards—and their potential effects on the results. These were touched on in the paper, but perhaps not to the detail that was warranted. Farioli et al (2014) requested additional analysis, which has been completed and is presented here.

Table 1 shows the results of a multivariable generalised gamma accelerated failure-time model that includes only cases first exposed to asbestos between 1950 and 1969 to limit left and right censoring, and analysing the entire follow-up period (1971–2005) rather than restricting it to post 1978. In addition, results are also presented for the same multivariable model but avoiding adjustment for the year of first exposure, as requested by Farioli et al (2014). Unfortunately, it was not possible to undertake the stratum-specific analysis as suggested by Farioli et al (2014), owing to the relatively small number of cases in each stratum.

Only including cases exposed for the first time between 1950 and 1969, and analysing the entire follow-up period (1971–2005) did not greatly influence the results in comparison to those presented in the original paper (Table 1). However, avoiding adjustment for the year of first exposure resulted in three notable differences: the latency period for women was no longer statistically significantly longer than that for men; asbestos removal workers now observed a statistically significantly shorter latency period than insulation workers; and there was now a statistically significant association between duration of exposure and latency, with latency tending to increase with duration (Table 1). As touched upon in the original paper and in the comment by Farioli et al (2014), this is not unexpected given what we know about latency—for example, in order to have experienced > 30 years of exposure to asbestos, an individual could not have died with mesothelioma within 30 years of their first exposure to asbestos. Table 2 shows the results of a multivariable generalised gamma accelerated failure-time model with a reasonable number of covariates. We believe that this model is closely related, and so adjusting for time since first exposure removed this spurious association between duration and latency (Table 1).

Finally, Farioli et al (2014) commented on the choice to restrict follow-up to when information on asbestos was available (from 1978 onwards), rather than including the full follow-up period. This choice was made because having asbestos is an important indicator of the intensity of exposure to asbestos and so was of interest in its own right, rather than being included purely to adjust for potential confounding. A sensitivity analysis conducted at the time, and now the results presented here, confirmed that including all follow-up rather than restricting this to 1978 onwards made little difference to the results. Hence I presented the results using the restricted follow-up and including death with asbestosis, with an analysis of the full follow-up time serving as a sensitivity analysis.

There were three main indicators of intensity of asbestos exposure specified in the original paper that were used to judge the strength of support for the intensity hypothesis: sex, presence of asbestosis and occupation. The additional analysis presented here did not allow presence of asbestosis to be included, and so the judgement here relies on sex and occupation. The difference in mesothelioma latency with sex was in the direction expected if the intensity hypothesis was true, but it was not statistically significant when not adjusted for year of first exposure. In addition, the difference in latency between insulation workers and removal workers was in the opposite direction to that expected if the hypothesis was true. Hence my conclusion from the original paper remains unchanged; this study found no evidence that greater intensity asbestos exposure would lead to shorter mesothelioma latencies.

I would also like to take this opportunity to remark on the comment mentioned by Farioli et al (2014) and made by Consonni et al (2014) and Mirabelli and Zugna (2014), that the analysis should have included all individuals in the cohort and not just those who died with mesothelioma. This is a point that was considered before undertaking the analysis, but a number of problems arise if all individuals are included. First, <1% of individuals in the cohort died from mesothelioma during follow-up. Therefore, if individuals who died from other causes or were alive at the end of follow-up were treated as censored observations, then the median latency would not be estimable using classical methods. In addition, any median latency predicted from survival analysis would be longer than the life expectancy of individuals in the cohort—the predicted median latency from an empty generalised gamma accelerated failure-time model using data from the full cohort was 115 years.