

## Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)'

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Sir,

In a paper published on the October 1 issue, Frost (2013) analysed mortality from mesothelioma among members of the Great Britain Asbestos Survey (GBAS), to test whether higher asbestos exposure shortened mesothelioma latency. The author applied accelerated failure time models to estimate time ratios and concluded that there was not sufficient evidence that greater intensity of exposure to asbestos led to shorter latencies. We are concerned that this analysis may have been inappropriate and the conclusions unwarranted.

As from Frost's Table 1, out of 94 960 workers entering GBAS between 1978 and 2005—start and, respectively, end of observation—614 died from mesothelioma and 14 009 from other causes: the large majority (85%) were alive at follow-up and mesothelioma deaths represented 4.4% of all deaths. In this framework, both (right) censoring and important competitive mortality were present.

As only cohort members dying with mesothelioma—a reasonable proxy for incident cases of mesothelioma—were included, the analysis was limited to the subset of individuals who developed the outcome of interest. Such an approach is at variance with the risk-set sampling designs traditionally used to analyse data from cohort studies (Langholz and Richardson, 2010).

In a competitive risk framework, two key quantities are of interest: the cause-specific hazard function  $\lambda_l(t)$ , which can be interpreted approximately as the instantaneous risk per time unit of failure at time  $t$  from cause  $l$  conditional on survival until just before  $t$ ; and the cumulative incidence function  $I_l(t)$ , which is the probability to fail from cause  $l$  before  $t$ . As  $I_l(t)$  depends on both the hazard function for cause  $l$ ,  $\lambda_l(t)$ , and the hazard functions for other competitive causes, there is no one-to-one correspondence between  $\lambda_l(t)$  and  $I_l(t)$ , that is, the relationships between the explanatory variables and  $\lambda_l(t)$  may not reflect the relationships between explanatory variables and  $I_l(t)$  (Andersen *et al.*, 2012).

For simplicity, let  $0 < t_1 < t_2 < \dots < t_N$  be the ordered distinct time points at which failures of any cause occur. In a non-parametric setting,  $I_l(t)$  can be estimated as follows:

$$I_l(t) = \sum_{j:t_j \leq t} S(t_{j-1}) \lambda_l(t_j) = \sum_{j:t_j \leq t} \left[ \prod_{j':t_{j'} \leq t} \left( 1 - \sum_{l=1}^k \frac{d_{lj'}}{n_{j'}} \right) \right] \frac{d_{lj}}{n_j} \quad (1)$$

where  $S(t_{j-1})$  is the survival function at time  $t_{j-1}$ ,  $d_{lj}$  is the number of subjects failed from cause  $l$  at  $t_j$ ,  $n_j$  is the number of subjects at risk at  $t_j$ , that is, subjects still in follow-up and not failed from any causes at time  $t_j$ , and  $l = 1, \dots, k$  are the competitive causes.

From expression (1), it is clear that restricting the analysis to individuals failing from the cause of interest  $l$  will affect both the set risk over time—that is,  $n_j$  at each time  $t_j$ —and the complement to one of the survival function,  $\sum_{l=1}^k \frac{d_{lj}}{n_j}$ , as much as the censoring and the competitive causes are large. Hence estimates of  $\lambda_l(t)$  and  $I_l(t)$  will be biased. Again from Frost's Table 1, out of more than 1.6 million person-years of observation in the full cohort, mesothelioma decedents contributed only 9280 person-years.

We want to recall here the scenario depicted by Pike and Doll (1965), who used exposure and mortality data from the British doctors study to argue that

practical conditions of human exposure to cigarette smoking, which included consideration of both amount and duration of smoke and competitive mortality, would not lead to significant differences in average age at death from lung cancer between 'heavy' and 'light' smokers. Only much higher exposures, that cannot be encountered in practice, could do the opposite. They concluded that the lack of anticipation in the age of occurrence of lung cancer (as represented by age at death) could not be considered evidence of lack of effect from tobacco smoking: it could at most be interpreted as showing that smoking is not a 'strong' carcinogen—in the meaning used in experimental carcinogenesis. This was their warning against the use of 'life-span', as they called it, or cohort, as we might say, average age at death.

However, their paper included a stronger, introductory remark against the use of another type of average: 'period' average. If the observation period during which cases are enrolled in a study is fixed by the observer, when cases of the disease of interest are split into groups according to some 'exposure', their differences in time-dependent variables such as age at death, age at onset and latency since some event (start of exposure, for instance) will not depend on any biological property of the exposure, but solely or predominantly on historical factors: the period when an industry entailing that exposure was developed or phased out is just an example. We think that this second caution applies to GBAS in general, and in particular to Frost's analysis, as it has both left truncation (for cohort members first exposed before 1978) and a closing date at which about 85% of cohort members were alive. Further, the two main comparison groups, that is, asbestos insulators and asbestos removers, had rather distinct secular trends: basically, when the former occupation started to disappear, the latter started to develop.

We believe that the above remarks are relevant not only for naive statistics, like average time to events such as death or incidence, but also extend properly to the distributions of times to event and therefore to relative times, that can be defined as: 'ratios of times that a given percentage of individuals with different exposures take to develop the event' (Cox *et al.*, 2007). The analysis carried out by Frost did not find evidence of consistent deviations of time ratios from unity because there was no chance for such deviations to occur consistently in the GBAS observational setting—as, indeed, in most if not all other cohort studies.

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## Neoadjuvant chemotherapy in pancreatic cancer: innovative, but still difficult

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Sir,

We read with great interest the recent article by Alvarez and co-workers reporting the effects of nab-paclitaxel on tumour stroma in

pancreatic cancer (Alvarez *et al.*, 2013). The authors should be congratulated on their interesting findings from a translational study that investigated the biological effects of neoadjuvant gemcitabine and