LETTER TO THE EDITOR

‘Environment’ in cancer causation and etiological fraction: limitations and ambiguities

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Boffetta et al. (1) discussed in depth ‘the main “errors” that produce over-estimates’ in the attributable fraction of environmental cancer, because they are ‘less widely appreciated’ than those producing the opposite effect. We would like to focus on the risk of mesothelioma following environmental exposures to asbestos, the first environmental carcinogen taken into account by the authors in their paper and in a previous article (2), because we think that, on the contrary, it has often been overlooked.

A relative risk (RR) of 3.5, with 95% confidence interval (95% CI) 1.8–7.0, is quoted by Boffetta et al. as deriving from the meta-analysis of the 10 studies in their Table 1. In an earlier review, a meta-analytical RR of 7.0 (95% CI 4.7–11) after neighborhood exposure to asbestos had been reported (3). A value of 3.5 was presented for the first time in a subsequent paper (2), where the following RRs from 11 studies were quoted: 8.7, 1.3, 7.6, 6.6, 14.6, 11.5, 5.4, 6.6, 182, 40.9 and 6.7. No details on data analysis were given, so the reasons of the shift from the first meta-analytical estimate of 7.0 to the new value of 3.5 are not clear. After excluding the RR of 40.9, derived from a study regarding exposures mainly due to peculiar household exposures, and the RR of 182, as the number of cases was not reported, a simple weighted average (weight: the number of cases) of the RRs can be computed, corresponding to 8.1.

Furthermore, when several RRs are reported in a paper, as in the case–control study in Casale Monferrato (Italy), which one should be retained in a meta-analysis? The one presented in Table 1 of the 2003 review and not in the original text (RR retained in a meta-analysis? The one presented in Table 1 of the 2003 case–control study in Casale Monferrato (Italy), which one should be up to 500 m from the factory (RR computed, corresponding to 8.1.

No details on data analysis were given, so the reasons of the shift from the first meta-analytical estimate of 7.0 to the new value of 3.5 are not clear. After excluding the RR of 40.9, derived from a study regarding exposures mainly due to peculiar household exposures, and the RR of 182, as the number of cases was not reported, a simple weighted average (weight: the number of cases) of the RRs can be computed, corresponding to 8.1.

Moreover, when several RRs are reported in a paper, as in the case–control study in Casale Monferrato (Italy), which one should be retained in a meta-analysis? The one presented in Table 1 of the 2003 review and not in the original text (RR = 14.6), the RR for residence up to 500 m from the factory (RR = 27.7), that from 500 to 1499 m (RR = 22) or that from 1500 to 2500 m (RR = 21), which, by the way, included all the town (4)?

The absence of the study on Wittenoom residents (5) in the 2000 review, and of its update (6) in the 2007 review, is unfortunate. In this setting, a quantitative assessment of environmental exposures has been possible, offering the opportunity to investigate the dose–response relationship at low cumulative doses. Thus, extrapolation from doses outside the range of observed data, a possible cause of overestimation of the attributable fraction (1), was avoided. In addition, as this is a cohort study, it is not expected to suffer the shortcomings that might hamper the quantitative assessment of the exposure–response relation in population-based case–control studies (7). A French case–control study on mesothelioma, showing an increase in risk at low cumulative exposures (8), had been the target of specific criticism from this point of view. However, the Wittenoom residents cohort and the French case–control study gave consistent results. Exposure to Wittenoom crocidolite seems to increase mesothelioma incidence after exposure to <7 fibre/ml-years and to double the background risk of mesothelioma at a cumulative level of 0.015 fibre/ml-years (5.9). Iwatsubo et al. (8) found that at 0.5–0.99 fibre/ml-years, the odds ratio for mesothelioma was 4. Thus, the evidence of a substantial increase in risk at these levels in independent studies is strong and the possibility that these findings were severely biased can be ruled out.

Mesothelioma registries have been established in several countries, especially in the European Union, and are another source of information on environmental mesotheliomas. In Italy, among the 3552 mesotheliomas occurring in 1993–2001 whose exposure could be assessed, ~10% were due to non-occupational, residential and household, exposures to asbestos (10). This is a direct observation, avoiding the difficulties of obtaining consistent estimates of the RR and of exposure frequency, and it shows that the burden of mesotheliomas due to environmental exposures to asbestos may be substantial in populations where the industrial use of asbestos has been relevant.

Estimates of ~200 mesothelioma cases per year in Great Britain (1), or 500 in the European Union (2), compared with a current yearly incidence of ~1000 cases in Italy (10), represent a huge toll for the general population, completely unaware of the exposures it was (and sometimes it still is) experiencing. Furthermore, should an RR estimate of 8.1, instead of 3.5, be applied, these figures would of course be more than doubled, so that the number of environmental cases in the European Union might approximately equal the overall mesothelioma incidence in a country like Italy. Lastly, the occurrence of environmental cases of mesothelioma is not evenly distributed. It rather interests subgroups of the general population and reflects the environmental distribution of (mainly) past sources of asbestos pollution. In these communities, one paradigm of which may be Casale Monferrato (4), mesothelioma incidence may remain remarkably high even after cases related with occupational exposures have been taken into account.

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References


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