

The Interaction of Asbestos and Smoking in Lung Cancer: A Modified Measure of Effect

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Objectives: The ratio of the relative risk of lung cancer due to asbestos exposure in non-smokers to that in smokers has been termed the relative asbestos effect (RAE). In a review, Liddell [Liddell FDK (2001) *Ann Occup Hyg*; 45: 341–56] estimated that the RAE was ~2. This measure is satisfactory when there is an appreciable relative risk due to asbestos but does not generalize to lower levels of exposure. A modified measure is proposed to overcome this difficulty. The modified measure, RAE_m, is defined as the ratio of the excess relative risk (RR – 1) in non-smokers to that in smokers.

Methods: The cohort studies combined in Liddell's 2001 analysis have been used to give a combined estimate of the modified measure.

Results: The combined value of RAE_m is 3.19 with 95% confidence interval 1.67–6.13.

Conclusion: The excess relative risk of lung cancer from asbestos exposure is about three times higher in non-smokers than in smokers. The modified measure has been placed within a more versatile model of interaction. If interaction is present the relative risk from asbestos exposure changes only slightly between light and heavy smokers, but is higher in very light smokers and non-smokers. The relative risk estimated from epidemiological studies of a mixed population of non-smokers and smokers applies to smokers.

Keywords: asbestos exposure; cigarette smoking; lung cancer; interaction; multiplicativeness

INTRODUCTION

Liddell (2001) reported on a review of studies in which the relative risk of lung cancer associated with exposure to asbestos could be determined separately for smokers and non-smokers. Liddell worked with a measure of interaction, the relative asbestos effect (RAE), originally put forward by Berry *et al.* (1985), defined as the ratio of the relative risk for lung cancer due to asbestos exposure in non-smokers to that in smokers. His conclusion was that 'the relative risk of lung cancer from asbestos exposure is about twice as high in non-smokers as in smokers; the best estimate of RAE is 2.04, with 95% confidence interval 1.28–3.25'. This conclusion was in conflict with the multiplicative hypothesis under which the RAE would be equal to 1. This conclusion was not without controversy, since in another review Lee (2001) had

concluded that 'asbestos exposure multiplies risk of lung cancer by a similar factor in non-smokers and smokers'. The main reason for the contrary conclusions reached by Liddell and Lee is whether it is appropriate to include case-referent studies as well as cohort studies. The issues were discussed by Liddell (2002) and Lee (2002). It is not the purpose of this paper to enter this debate but rather to propose a modified measure of the interaction, which is illustrated by application to the cohort studies included in the review of Liddell (2001).

Most of the studies reviewed by Liddell had an appreciable risk of lung cancer due to asbestos exposure. The overall relative risk from Table 3 of Liddell was 2.1. However, if there is interaction, so that the relative risk associated with asbestos exposure is higher for non-smokers than smokers, then using the ratio of the two relative risks as a measure of the interactive effect does not generalize to low levels of asbestos exposure. For example, suppose that the asbestos exposure gave a relative risk in smokers of 1.1, then it would seem unreason-

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able that the relative risk in non-smokers would be double this, i.e. 2.2. Extending this argument to an even lower level of exposure, doubling a relative risk in smokers of 1.01 to 2.02 is clearly unrealistic. Rather, it would be expected that a factor representing an increased risk due to asbestos exposure for non-smokers compared with smokers would apply to the excess risk above the base of 1. If this factor were 2, then a risk of 1.1 for smokers would give a value of 1.2 for non-smokers, and 1.01 would give 1.02. This argument is the rationale for a proposed modified measure of relative effect (RAE_m) defined as the ratio of the excess relative risk ($RR - 1$) due to asbestos exposure in non-smokers to that in smokers. The value of RAE_m would not be the same as that of RAE, but would be higher.

MATERIALS AND METHODS

The relative asbestos effect is defined as:

$$RAE = RR(NS)/RR(S)$$

where $RR(NS)$ and $RR(S)$ are the relative risks due to asbestos exposure for non-smokers and smokers, respectively. The modified measure is defined as

$$RAE_m = [RR(NS) - 1]/[RR(S) - 1].$$

Liddell's main review (summary from Group A, p. 351) was of seven cohort studies which he referred to as [r] (Acheson *et al.*, 1984), [o] (Berry *et al.*, 1985; results for 1960–1970), [p] (Berry *et al.*, 1985; results for 1971–1980), [m+h] (Selikoff *et al.*, 1968; Hammond *et al.*, 1979), [q] (Selikoff *et al.*, 1980), [e] (McDonald *et al.*, 1993) and [d] (Liddell *et al.*, 1984). For further details see Liddell (2001).

Details of the method of calculating confidence intervals for RAE were given by Liddell. For five of the studies it was possible to produce these directly since the limits for a ratio of SMRs can be obtained using the F distribution. This method does not apply

to the ratio in the modified measure and the sampling variability has to be obtained from the variances of the two relative risks. The confidence limits for a SMR may be obtained directly from the χ^2 distribution. For studies [e] and [d] the variances of the two SMRs were calculated as in Liddell.

Using this method for RAE gives:

$$\text{var}[\ln(RAE)] = \text{var}\{\ln[RR(NS)]\} + \text{var}\{\ln[RR(S)]\}$$

and

$$\begin{aligned} \text{var}[\ln(RAE_m)] = & \left\{ \frac{RR(NS)}{[1 - RR(NS)]} \right\}^2 \text{var}\{\ln[RR(NS)]\} \\ & + \left\{ \frac{RR(S)}{[1 - RR(S)]} \right\}^2 \text{var}\{\ln[RR(S)]\} \end{aligned}$$

Studies were combined using the meta-analytic method of DerSimonian and Laird (1986).

RESULTS

Using the above method for calculating the variance of $\ln(RAE)$ gave a combined estimate for RAE of 2.05 [95% confidence interval (CI) 1.28–3.27], a very similar estimate with almost identical precision to that of Liddell, 2.04 (95% CI 1.28–3.25), so that this method may be used in an analysis of the modified measure.

The values of the modified measure are given in Table 1. For study [e] the SMR for non-smokers is so close to 1 that the denominator in the expression for RAE_m is almost 0 and the estimate of RAE_m is highly unstable. The standard error of $\ln(RAE_m)$ is over four times as high as that of study [r], the next least precise estimate. Consequently, in the meta-analysis of RAE_m , study [e] has a weight of only 0.1% of the total weight, i.e. it scarcely contributes to the combined estimate. In contrast, in the meta-analysis of RAE, study [e] provided the most accurate estimate and contributed 25% of the total weight.

Table 1. Results of the meta-analysis for RAE and the modified measure, RAE_m

Study reference	Relative risk due to asbestos exposure		Original measure			Modified measure		
	RR(NS)	RR(S)	RAE	SE[ln(RAE)]	95% CI	RAE_m	SE[ln(RAE_m)]	95% CI
[r]	2.70	1.65	1.64	1.40	0.11–25.4	2.63	2.28	0.03–227
[o]	5.00	7.37	0.68	1.41	0.04–10.7	0.63	1.75	0.02–19.4
[p]	7.27	2.42	3.01	0.58	0.96–9.44	4.42	0.69	1.14–17.2
[m+h]	4.88	5.07	0.96	0.57	0.31–2.97	0.95	0.72	0.23–3.93
[q]	25.00	4.69	5.33	0.53	1.90–15.0	6.51	0.56	2.17–19.5
[e]	1.65	1.01	1.63	0.45	0.67–3.96	53.5	10.1	^a
[d]	2.98	1.66	1.79	0.52	0.64–5.01	2.98	0.86	0.55–16.2
Combined value			2.05	0.24	1.28–3.27	3.19	0.33	1.67–6.13

^aThe confidence interval is extremely wide due to the denominator (0.01) being so low.

The combined estimate of RAE_m is 3.19 (1.67–6.13). The test of heterogeneity gave $Q = 5.59$ with 6 df, so that no correction for heterogeneity was necessary. The confidence intervals for $\ln(RAE_m)$ are wider than those of $\ln(RAE)$, since each RAE_m is less accurate than RAE because of the reduction in the size of the denominators. RAE_m is larger than RAE , so that a test that it exceeds unity ($z = 3.50$ on a log scale) exceeds the corresponding test for RAE ($z = 3.14$).

DISCUSSION

Liddell (2002) noted that the interaction takes several forms. If there is interaction then the reduction in relative risk due to asbestos exposure for smokers, compared with non-smokers, would be expected to increase with the amount smoked. The measures discussed above, where smoking was simply dichotomized into non-smokers and smokers, make no allowance for this. A more general definition of interaction may be developed as follows.

The θ measure of interaction

Working relative to non-smokers unexposed to asbestos, the (independent) smoking effect in those unexposed to asbestos is R_s , and assume $R_s = 1 + s$. The (independent) asbestos effect in non-smokers is R_a , and assume $R_a = 1 + a$. Call the combined smoking–asbestos effect R_{as} , and write $R_{as} = 1 + s + a + \theta as$. The multiplicative and additive models are given by θ equal to 1 and 0, respectively. Then

$$RR(NS) = 1 + a$$

$$RR(S) = (1 + a + s + \theta as)/(1 + s)$$

and θ may be estimated as:

$$\theta = 1 - (R_a R_s - R_{as}) / [(R_a - 1)(R_s - 1)].$$

The measures of interaction are:

$$RAE = RR(NS)/RR(S) = (1 + a)(1 + s)/(1 + a + s + \theta as)$$

$$RAE_m = [RR(NS) - 1]/[RR(S) - 1] = (1 + s)/(1 + \theta s)$$

so that RAE depends on a and s but RAE_m is independent of a .

More information is required to estimate θ than RAE and RAE_m , since the relative risk due to smoking in those unexposed to asbestos is needed, in addition to the relative risks due to asbestos in non-smokers and smokers. If the value of θ is known, then one can calculate RAE , RAE_m or anything else for a range of values of the a and s risks. RAE and RAE_m are less versatile as they are each a single value

applying to a particular s and a , calculated from a 2×2 table, with no way of interpolation possible.

As an example, suppose that for moderate smokers RAE_m is 3 and $1 + s$ is 15. Then if asbestos exposure doubles the risk in moderate smokers, the relative risk from asbestos in non-smokers is 4 ($1 + a = 4$), $\theta = 0.2857$, and the values of the relative risk due to asbestos with different degrees of smoking are: non-smoker, 4.00; very light smoker, ($1 + s = 2$) 2.93; light smoker ($1 + s = 5$), 2.29; moderate smoker ($1 + s = 15$), 2.00; heavy smoker ($1 + s = 25$), 1.94; very heavy smoker ($1 + s = 50$), 1.90.

Most of the decrease in the relative risk due to asbestos exposure with increasing smoking occurs between non-smokers and light smokers, with less further decrease from light to very heavy smokers.

Similarly, the relative risk due to smoking is lower in those exposed to asbestos than in the unexposed. In the above example the relative risk due to moderate smoking is 7.5, compared with 15 in the unexposed.

The relative risk due to asbestos exposure has usually been estimated from epidemiological studies in which the exposed population has consisted of a mix of non-smokers, light, moderate and heavy smokers. Since the majority of the lung cancers are in smokers the estimated relative risk corresponds to that in smokers. For example, if the population consisted of 40% non-smokers, 15% light smokers, 30% moderate smokers and 15% heavy smokers, then the relative risk due to asbestos is 2.09, i.e. close to the risk in moderate smokers. Thus the relative risk due to asbestos exposure as estimated from epidemiological studies can reasonably be taken (to within 10%) to apply to light, moderate, heavy and very heavy smokers; only for very light and non-smokers would a higher relative risk be appropriate.

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