PostScript

LETTERS

Mortality from cardiovascular diseases and exposure to inorganic mercury

Paolo Boffetta and his coworkers presented a comprehensive cohort study comprising 6784 male and 265 female workers from four mercury mines and mills in Spain, Slovenia, Italy, and the Ukraine.[1] The expected number of deaths were derived from the national rates specific for sex, age, and calender period. Slovenia was the only country with an increased mortality of ischaemic heart disease among men (SMR 1.66, 95% CI 1.35 to 2.02). In the Slovenian mine, dust measurements showed concentrations between 30 and 70 mg/m^3 with 10–35% free silica in the 1960s, and about 40 mg/m^3 in the 1970s. An increased mortality from pneumoconiosis was present in all countries. Mortality from ischaemic heart disease was positively correlated with duration of employment but not with cumulative exposure to mercury. Smoking habits was an unlikely confounder as mortality from diseases strongly asssociated with tobacco smoking—such as bronchitis, emphysema, and asthma—was not increased and mortality from lung cancer showed only a small increase (SMR 1.19). The purpose of this letter is to discuss further a possible relation between silica exposure and ischaemic heart disease (IHD).

A recently published study comprised 4626 industrial sand workers exposed to crystalline silica.[2] The study showed a higher standardised mortality ratio regarding IHD (SMR 1.22, 95% CI 1.09 to 1.36). Smoking might hypothetically be responsible for 2–4% of this increase.

A Swedish case–control study comprised 26 847 men with myocardial infarctions; for each case, two controls were selected from the study base through random sampling, stratified by age, county, and socioeconomic group. The second highest risk was found among stonecutters and carvers (RR 1.9, 95% CI 1.1 to 3.4). This high risk could not be explained by differences in smoking habits.[3]

A cohort consisted of 597 miners from North Karelia in Finland employed for at least three years in a copper mine or a zinc mine.[4] The excess mortality was mainly due to IHD; 44 were observed, the expected number was 22.1 based on the general male population, and the North Karelian expected number was 31.2 ($p < 0.05$).

A cohort of 3971 white South African gold miners was followed from the beginning of 1970. Most of the miners worked that year and the age of the workers was 39–54 years. The participants of the study were followed for nine years. A case–referent analysis was conducted comprising the miners who had had at least 85% of their service in gold mines. Ten years of underground mining was associated with a risk ratio of 1.5 ($p = 0.004$) regarding IHD after adjustment for smoking, blood pressure, and body mass index.[5]

A large cohort comprised 68 241 miners as well as pottery workers from south central China.[6] The participants were employed between 1972 and 1974 and followed until 1989. There was an increased mortality due to IHD (SMR 1.25, 95% CI 1.05 to 1.45). Smoking habit was unlikely to be responsible for this risk as the mortality from lung cancer was lower than expected (SMR 0.8, 95% CI 0.7 to 0.9). There was no significant trend regarding mortality due to IHD when medium and high dust exposed workers (RR 1.16) were compared with low dust exposed workers (RR 0.65). Silicotics did not have an increased mortality due to IHD (RR 1.1, 95% CI 0.7 to 1.8).

A general hypothesis about exposure to inhaled particles and the occurrence of IHD can be expressed in the following way. Long term inhalation of particles retained in the lungs will create a low grade inflammation associated with an increase in plasma fibrinogen. The high concentration of fibrinogen will increase the likelihood for blood clotting and thereby the risk for myocardial infarction and IHD.[7 8] A high concentration of fibrinogen in plasma is an established risk factor for IHD.[9] An increased concentration of fibrinogen has been observed among tunnel construction workers after a workshift with a dust exposure of less than 2 mg/m^3.[10] Thus dust exposure in general and silica exposure in particular could be interesting to discuss in relation to ischaemic heart disease in this study by Boffetta and coworkers.[1]

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Joint action of smoking and asbestos exposure on lung cancer

This subject has long been bedevilled by unwarrantable assumption and circular argument. Why should there be only two possible hypotheses of interaction (additive and multiplicative)? Theory expects multiplicativity; epidemiology can seldom reject this hypothesis; so theory is "accepted", and deviations from multiplicativity must be explained away. Resolution is made especially difficult because the nature of the data imposes very large error; also it has to be assumed that the exposed smoked as many cigarettes as the unexposed, and that smokers and non-smokers were exposed equally.

Thus the "comprehensive" review by Lee[1] was to be welcomed. However, discrepancies, particularly with another review,[2] demanded discussion: this letter is the result.

From almost 40 "results" in 25 reports, Lee makes two selections to confirm the well known facts that asbestos can increase lung cancer risk in non-smokers and that the additive theory (of independent action) does not explain many of the data. Then, for 16 results, Lee calculates a statistic V; for an observed multiplicative interaction, $V = 1$. The weighted average $V = 0.90$ (95% CI: 0.67 to 1.20) leads to Lee's conclusion.[1] Repair of (acknowledged) imperfections (one misquoted result; two incorrect omissions) reduced V only slightly, to 0.83 (95% CI: 0.63 to 1.08); for nine cohorts and nine case–referent studies, respectively, $V = 0.63$ and 1.08, a "significant" difference ($p = 0.049$).

There are, however, other imperfections: two cohorts[3 4] broke the rule of independence; in another,[5] asbestos had a minuscule (protective) effect on lung cancer in both non-smokers and smokers (that is, no action, so no interaction); and in a Chinese cohort,[6] risks from cigarette smoke were dramatically lower than in the West. After exclusion, the cohorts' $V = 0.54$ (95% CI: 0.35–0.82), and the difference between types is much wider ($p = 0.017$).

Problems with case–referent designs are well known; here they are compounded by impure definitions of non-smokers and by retrospective assessment of exposure. It is clear from personal experience over five decades that, unless obtained from employers' records, job histories can be quite unreliable, even in basic facts, especially when reported by proxies. The assumption that the interactions between smoking and exposure to asbestos plus other carcinogens and between smoking and asbestos alone take the same form is untested and so indefensible. Thus, Lee's grounds for his unprecedented incorporation of the Italian study in which all concerned were exposed to PAHs,[7] namely, that subjects in many studies would have been exposed to "other" carcinogens, far from justifying inclusion, provide strong additional reasons for excluding all such studies, the majority of the case–referent studies in particular. It becomes obvious that inferences from the latter cannot overthrow conclusions from the cohorts.

The potential risks from dusty coal reinforce the need to exclude the Chinese cohort.[6] Undoubtedly, the North American insulation workers were not exposed only to 4–12 fibres/ml of chrysotile,[8] so there is a good case for discarding this result, although it forms a cornerstone of the evidence for multiplicativity. On the other hand, the study of crocidolite miners[9] might be taken into account, despite faults.[2] The resultant is $V = 0.47$ (95% CI: 0.29 to 0.75).

Lee proceeds from $V = 0.83$ (for 18 studies), noting that the significance of the difference between study types is not great, and "is removed" by an (admittedly dubious) adjustment of the lowest V. He "sides with other reviewers" and includes all data, concluding that "they do not clearly allow rejection of the simple multiplicative relationship".

Despite some doubt about the "best" estimate of V from cohort studies, most reasonable people would accept that it is <1, as shown even by Lee's $V = 0.63$, with $p = 0.018$.

Therefore, the multiplicative hypothesis is not generally satisfactory. Nor, of course, is the additive hypothesis, although it does fit some data sets very well.[10]

Evidently, interaction takes several forms.

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Author's reply

Having read Liddell's paper[1] and the comments he expressed in his letter and at a recent meeting, it is useful to clarify where we agree and disagree. Originally I included estimates 1–16 shown in table 1, and estimated V, the ratio of the asbestos relative risk in smokers to that in non-smokers, as 0.90 (95% CI: 0.67 to 1.20). Omitting estimate 18 was an unfortunate error, and I also agree with Liddell that it is better to include estimate 17 and replace estimate 13 by estimate 19. Accounting for this reduces V to 0.83 (95% CI: 0.63 to 1.08).

Liddell also suggests excluding estimates 4, 11, 12, and 14, but for reasons I consider unconvincing. He would exclude estimate 4 as the population was exposed to PAHs. However, virtually all populations have exposure to carcinogens other than asbestos or tobacco smoke and anyway exposure to other carcinogens may simply multiply risk by about the same factor in each of the four groups being studied, little affecting the nature of the joint relation of asbestos and smoking to lung cancer. He would exclude estimate 11 because of low smoking risks, but these are typical of China[2] and do not invalidate the study. He would exclude estimate 12 as no asbestos effect was seen, but doing so based on

Table 1 Assessing the multiplicative relationship of smoking and asbestos in lung cancer risk

	Estimate*	Study type	V (95% CI)	Heterogeneity χ^2	Degrees of freedom
1.	DeKlerk	CC	1.25 (0.19 to 8.08)		
2.	Martischnig	CC	2.89 (0.87 to 9.62)		
3.	Pastorino, no PAH	CC	0.64 (0.10 to 4.06)		
4.	Pastorino, PAH	CC	1.01 (0.13 to 7.94)		
5.	Bovenzi	CC	0.86 (0.31 to 2.39)		
6.	Kjuus	CC	1.52 (0.39 to 5.93)		
7.	Blot, Georgia	CC	1.26 (0.54 to 2.93)		
8.	Blot, Virginia	CC	0.84 (0.39 to 1.81)		
9.	Blot, Florida	CC	0.72 (0.22 to 2.36)		
10.	McDonald	P	0.61 (0.25 to 1.49)		
11.	Zhu	P	1.60 (0.43 to 5.90)		
12.	Meurman	P	1.19 (0.07 to 20.4)		
13.	Berry, 1960–70 M+F	P	0.61 (0.10 to 25.7)		
14.	Selikoff and Hammond	P	1.22 (0.32 to 10.4)		
15.	Selikoff	P	0.19 (0.07 to 0.61)		
16.	Hammond	P	0.95 (0.47 to 2.21)		
17.	Berry, 1971–80 M+F	P	0.33 (0.13 to 1.25)		
18.	Liddell[3]	P	0.56 (0.20 to 1.56)		
19.	Berry, 1960–70 F	P	1.47 (0.22 to 50.0)		
Original analysis					
Estimates 1–16		All	0.90 (0.67 to 1.20)	14.88	15
Revised analysis					
Estimates 1–12, 14–19		All	0.83 (0.63 to 1.08)	18.39	17
Estimates 1–9		CC	1.08 (0.74 to 1.59)	4.33	8
Estimates 10–12, 14–19		P	0.63 (0.43 to 0.92)	10.17	8
Revised analysis with exclusions					
Estimates 1–3, 5–10, 15–19		All	0.79 (0.59 to 1.05)	17.00	13
Estimates 1–3, 5–9		CC	1.09 (0.74 to 1.60)	4.33	7
Estimates 10, 15–19		P	0.54 (0.35 to 0.82)	6.95	5

*References and fuller details given elsewhere[4] except where stated.
C, case–control; P, prospective.
V is the ratio of the asbestos relative risk in smokers to that in non-smokers.

observed results can cause bias. He would exclude estimate 14 as the study population is a subset of that for estimate 15. However, the follow up period was much longer for estimate 14 (1943–74) than for estimate 15 (1967–76), so omitting it would have lost data. Anyway, omitting estimates 4, 11, 12, and 14 only has a minor effect, V reducing to 0.79 (95% CI: 0.59 to 1.05) (table 1).

At face value, the combined data appear reasonably homogeneous and compatible with the multiplicative model. However, as Liddell notes, estimates for prospective and case–control studies differ. Using my revised analysis, prospective studies give $V = 0.63$ (95% CI: 0.43 to 0.92) and case–control studies $V = 1.08$ (95% CI: 0.74 to 1.59), a statistically significant difference ($p = 0.049$). With Liddell's four suggested exclusions, $V = 0.54$ (95% CI: 0.35 to 0.82) for prospective studies and $V = 1.09$ (95% CI: 0.74 to 1.60) for case–control studies, with $p = 0.017$.

He stresses this significant difference, rejects the case–control data due to data unreliability, use of proxies, and inclusion of ex or light smokers in the reference group and argues that inferences should be drawn only from the prospective studies. I regard these arguments as dubious. The significance of the difference is not great and is removed ($p = 0.089$ for the revised data) if the estimate of V for the one study (estimate 15) showing a very low value is revised based on "best available evidence" rather than on death certificate diagnosis (though this revision is itself questionable). Prospective studies may be limited by failure to record changes in smoking status after follow up starts. The Quebec prospective study[3] obtained data from proxies; many case–control studies did not. While data on accuracy of exposure is no doubt better in prospective studies, I side with other reviewers in considering the whole data.

The asbestos relative risk may be somewhat lower in smokers than non-smokers, but the available data do not clearly reject the simple multiplicative relation. More complex models of joint action might indeed fit the data better, but in view of the general problems with the data, it seems doubtful whether more detailed statistical analysis would shed any greater insight.

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Occupational exposure to magnetic fields

While Savitz's point of view expressed in the editorial[1] that epidemiological methodology faces its limits when the risk is small, exposure assessment is poor, and biological insight is lacking, must be reinforced, it is not so clear whether or not this view is applicable to the field of exposure to extremely low frequency electromagnetic fields (ELF EMF). Unfortunately some of the studies that could contribute to an evaluation of the relation between ELF EMF exposure and cancer have serious deficits. This is apparently also the case for the paper by Sorahan and colleagues.[2] First it has to be stressed that there is no such diagnostic entity as "brain tumour". Brain tumours comprise a heterogeneous group of both malign and benign neoplasms generating from different tissues, with different growth rates and other essentially different features (for an overview see Black[3]). The authors do not even mention the number of cases of different tumour types, let alone discuss why they feel that all these completely different entities could be affected by a single cause.

Another crucial point is latency. The only essential criterion of causation in the assessment of epidemiological evidence is "temporal relation". It is crucial that provisions are made to allow for biologically reasonable latencies. Instead the authors report on estimates based on the most recent (!) five years of exposure, thus choosing an exposure metric that has nothing to do with the vast majority of brain tumours that have latencies of at least five (but many 20 or more) years (for example, Strojan *et al*[4]). Most of the brain tumours will have been already initiated before the point in time the exposure was accumulated to give the indicator the authors have chosen. At least the last 10 years prior to diagnosis of the tumour have to be truncated in computation of the exposure metric and all cases occurring earlier than 10 years after onset of exposure have to be omitted.

To choose Tesla-years as the exposure variable is also questionable because we do not know whether or not risk is cumulative. A more sophisticated exploitation of information on exposure could be expected from the authors. For example, time spent under peak exposures (e.g. exceeding 10% of the exposure limit) would be a meaningful surrogate. Tesla-years introduces an equivalence that has never shown to be meaningful: that exposure duration and intensity are commutative (that is, 10 years exposure to 1 μT is equivalent to one year exposure to 10 μT).

Overall the study in its presented form cannot be considered to contribute to the assessment of a relation between ELF EMF exposure and brain tumours.

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Authors' reply

Professor Kundi implies that, in our analyses of brain tumour risks and magnetic field exposure, we only considered exposures occurring in the most recent five years. We did not. Analyses of total cumulative exposures to magnetic fields in relation to mortality risks from primary brain tumours were reported in table 3, and analyses of the potential role of recent exposures were reported in table 4.[1] Confirmation of diagnosis had also been sought from cancer registration particulars. These analyses were planned in advance as tests of the main hypotheses of interest. These hypotheses had been derived from a review of the current literature, and for neither analysis was there any suggestion of magnetic field exposure being implicated in mortality risks for brain tumours. The ICD codes we used to define the health outcome and the use of micro-Tesla years as the unit of magnetic field exposure enabled our study findings to be compared to other reports. Their use appears, at least to us, to be eminently sensible. We remain open to the possibility that other exposure metrics may come to be appreciated as more biologically relevant but we doubt whether the proposal of Prof. Kundi (time spent exceeding an arbitrary percentage of a contemporaneous exposure limit) will gain favour.

We hope our study makes a useful contribution to the practice of occupational health and that employees in the UK electricity supply and transmission industry treat the findings as good news.

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Reference

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BOOK REVIEW

Innovation in Chinese Medicine

Elisabeth Hsu (pp 426; £55) 2001. Cambridge: Cambridge University Press. ISBN 0 521 80068 4

With increasing popularity of Chinese medicine in the West, there has been an increasing number of books published in this field. Some of them have dealt with the philosophical aspect of Chinese medicine, and others concentrated on the diagnosis and treatments. All of them referred to ancient texts such as the *Yellow Emperor's Inner Cannon* and used terminology from them. The uses of