PLEURAL MESOTHELIOMA WITH NON-HODGKIN’S LYMPHOMA

Tondini and colleagues (December 1994;49:1269–70) have presented an interesting case of non-Hodgkin’s lymphoma in an asbestos worker with mesothelioma. Lymphoproliferative disorders are not recognised as prescribed asbestos-related diseases, although their case and others attempt to make this relationship.

We would like to add to the literature the case of a 60-year-old man who developed histologically proven mesothelioma after heavy exposure to asbestos in the Devonport dockyard. Death occurred 15 months after presentation with a pleural effusion and at necropsy an ulcerating mass was found in the stomach. Biopsies of the lesion showed a lymphocytic lymphoma.

Contrary to the view of Tondini and colleagues, the association between gastrointestinal cancer and asbestos has not been conclusively proven, although an increased incidence of exposure to asbestos has been noted in a study of gastric lymphoma.

We wish to add our case to those referred to by Tondini et al and agree that further study into the relationship between lymphoma and asbestos should be conducted.

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Vegetarian diet and tuberculosis in immigrant Asians

The paper by Dr D P Strachan and colleagues (February 1995;50:175–80) is a valuable contribution to the debate on vegetarian diet and tuberculosis; however, we do not believe a causal relationship between vegetarianism and the development of tuberculosis in immigrant Asians can be inferred from this study.

The response rate amongst cases (33%) and community controls (12%) was very low and was not stated in clinic controls. It was unclear whether community controls were all first generation immigrants (a selection criterion for cases and clinic controls). Not enough was known about the characteristics of non-responders to make a confident assessment of the direction in which selection biases might act. Non-responders may differ from responders in several important respects other than religion, age, and sex, such as time since immigration and socioeconomic class.

The effects of many confounders on the relationship between vegetarianism and tuberculosis were investigated but diabetes (a risk factor for tuberculosis which is also related to diet) was not controlled for.

There were no vegetarians in the Muslim group, so presenting an odds ratio for vegetarianism controlled for religion is inappropriate due to the heterogeneity between the hypothesised exposure (vegetarianism) and the potential confounder (religion). It would have been more appropriate to examine the interaction between religion and vegetarianism and to present the odds ratio for the Hindu population separately.

We were interested in the selection of dietary groups used to calculate the dose–response relationship. They were based on the number of meat/fish eating days per month and seem unlikely to reflect substantial differences in micronutrient deficiency. The only group which significantly differed from the vegetarians was the group eating meat daily.

We feel that this study highlights an important area for further research but does not provide strong evidence for vegetarian diet as a risk factor for tuberculosis.

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AUTHORS’ REPLY

The purpose of our paper was to demonstrate that diet, rather than religion, was the statistically independent risk factor influencing the distribution of tuberculosis among Asian immigrants in our area. Although we speculated on possible mechanisms, we did not set out to prove a causal relationship.

All religious groups were included in our analysis because we wished to explore the relative influences of diet and religion on the risk of tuberculosis. If the analysis is restricted to Hindus only, the association of vegetarianism with tuberculosis is stronger, although less precisely estimated due to smaller numbers of subjects. The unadjusted odds ratio for vegetarianism comparing Hindu cases with Hindu community controls is 3.4 (95% CI 0.9 to 12.8, p > 0.05), and comparing Hindu cases with Hindu clinical controls is 4.9 (95% CI 1.4 to 17.6, p < 0.01). Our published analyses, based on all subjects, are therefore conservative. It is not possible to address statistical interactions between religion and vegetarianism as there were no vegetarian Muslims.

We acknowledged in our paper that the low response rate poses problems of interpretation. However, as this is an analytical rather than a descriptive study, the characteristics of the respondents are less relevant than the strength of association between exposure and disease among respondents and non-respondents. We were able to assess this for religion, but not (as would ideally have been the case) for vegetarianism. The findings for religion suggest a confounding selection bias, as discussed in the paper and illustrated in table 2. Analyses based on the clinic controls, among whom the response was 100%, yield higher odds ratios than similar analyses based on the community controls, supporting our conclusion that the relative risk of tuberculosis among vegetarians is more likely to have been underestimated than inflated by non-response bias.

All community controls were first generation Asians and there were only two diagnosed diabetics in our series, one Hindu case (vegetarian) and one Muslim community control (non-vegetarian).

The precision of the relative risk estimates presented in the figure depends on how finely the data are divided, and particularly on the size of the reference group. The important statistic is the test for linear trend. We chose to subdivide the non-vegetarians into five groups to illustrate that frequency of meat and fish consumption influences the risk of tuberculosis even after excluding the vegetarian group, and with no evidence of a threshold. Further work is required to determine whether micronutrient levels are affected by frequency of meat and fish consumption within this range, but this trend suggests that the association between diet and disease is not wholly confined to vegetarians.

If the data in the figure are reanalysed with the non-vegetarians being divided into two groups (eating meat or fish > 20 days/month or 1–20 days/month) then a significant relative risk emerges in the group with less frequent consumption (odds ratio, adjusted for age, sex, and religion: 3.5, 95% CI 1.4 to 8.7), with the risk among vegetarians relative to frequent meat/fish eaters being even higher (adjusted odds ratio: 8.9, 95% CI 2.7 to 29).

Risk factors may or may not be causal, and we pointed out in our paper that further work is required to elucidate the mechanisms underlying the association between diet and tuberculosis. Faced with adjusted relative risks of the magnitude presented here and in our paper, we find it hard to concur with the assessment by Dr Hayward et al that our findings provide no strong evidence for vegetarian diet as a risk factor for tuberculosis, but agree that it would be premature to assume a causal relationship.

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The retrospective case-control study of Drs Strachan et al on diet and tuberculosis (February 1995;50:175–80) is methodologically highly sound. To attempt to assess the potential dietary causes of tuberculosis by administering a dietary questionnaire up to 10 years after the illness is, in itself, highly unreliable since diet may have changed in the intervening period. In addition, to examine only the diets of 15% of the total number of tuberculosis cases who could have become part of the study leaves altogether too much room for selection bias and error. It seems that the BMJ Publishing Group’s normally fastidious standards for papers on the health effects of vegetarian diet appear not to have been applied to this paper.
Ironically, the recognised healthiness of vegetarians in terms of reduced mortality and morbidity\(^1\) may have biased the results in the direction of a spurious health risk. If, for instance, out of the 400 original vegetarian and non-vegetarian tuberculosis cases between 1982 and 1993 the vegetarians amongst them survived in greater numbers and were more represented in the 56 cases in the study, then we are left with a false impression that vegetarian diet is more common amongst cases of tuberculosis.

In the clinic control group there could have been an abnormally low proportion of vegetarians deriving from their better health and lower clinic attendance.\(^2\) Then, even with a normal proportion of vegetarians in the cases of tuberculosis, this figure would have appeared higher than the proportion in the control, leading to the spuriously elevated risk. The same selection mechanisms may have produced a spurious correlation between the level of vegetarianism and risk of tuberculosis.

The postmortem study of Chanarin\(^3\) quoted by the authors, purporting to show a 2.8-fold increased incidence of tuberculosis in Hindu Asian strict vegetarians, should be discounted since it does not account for the fact that there were many more vegetarians in the older age groups where the risk of having had tuberculosis is higher. Finally, stricter Hindu vegetarians may also be more inclined to follow the traditional habit of avoidance of sunlight exposure which might give rise to a surrogate mistaken association of vegetarian diet with tuberculosis since, as the authors point out, vitamin D deficiency from lack of sunlight may weaken the immune system. While the data have been presented quite strongly as indicating a potential weakening effect of vegetarian diet on the immune system, they may also be taking account the selection effects of a health-promoting influence of vegetarian diet consistent with the strengthening of the immune system.

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AUTHORS' REPLY

We recognise that British vegetarians have somewhat lower mortality rates than non-vegetarians, but this difference is not large enough to introduce substantial bias as suggested by Dr Davis. In the study by Thorogood \textit{et al.} adjusted mortality rates from ischaemic heart disease and cancer amongst vegetarians were, respectively, 72% and 61% of the corresponding mortality rates for non-vegetarians. If all-cause mortality is reduced by about one third among vegetarians, who accounted for about half of our case group, then, on the most extreme assumption that 15% of non-vegetarian cases died after the follow up period, we would expect 10% of vegetarian cases to die also. This difference in survival would increase the proportion of vegetarians among survivors by no more than 1–2%, generating a spurious elevation in odds ratio of about 6%. This is far too small to account for the observed odds ratios of 2.5 or greater.

Our suggestion of an increased risk of tuberculosis among vegetarian Asians is not a recommendation against adherence to a vegetarian diet. Dietary advice needs to take account of the balance of risks and benefits across a wide range of major disease outcomes. The importance of our findings is that they may be pointing to a hitherto unrecognised risk associated with vegetarianism which, if our provisional hypothesis is correct, may be remediable by vitamin supplementation without the need for major dietary change. Indeed, prevention of vitamin D deficiency may be particularly important for the stricter Hindu vegetarians with reduced sunlight exposure who are already recognised as a group at risk of osteomalacia.\(^2\)

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Data in the third column show the likely benefit per 1000 people treated; it may be substantially less than expected. US children in the first trial are comparable to non-immunised UK children undergoing testing before BCG vaccination. The end point of this trial was symptomatic disease: two of the five children in the placebo arm developed tuberculosis meningitis compared with none of those given chemoprophylaxis, although the difference is not statistically significant. The benefit (five symptomatic cases prevented per 1000 children treated) is small and raises questions about a policy of routine chemoprophylaxis for low risk/low benefit groups.

The end point of the second trial was new cases of tuberculosis in a population of mixed exposure risk (37 US centres, 19 Puerto Rican, and one Mexican). Extrapolation from these data to the UK suggests that nationwide compliance with the guidelines might result in about 980 people per 1000 receiving treatment without expectation of benefit. In view of this evidence, the benefit of chemoprophylaxis is measured in the UK subgroups according to high risk to justify future policy recommendations.

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AUTHOR'S REPLY

A UK study to establish the benefits of chemoprophylaxis would be very difficult in view of the number of subjects needed, coordination required, and ethical difficulties. However, such a study is unnecessary because the effectiveness of chemoprophylaxis is known. It depends on two factors: firstly, the efficacy of chemoprophylaxis and, secondly, the risk of tuberculosis in the population treated. Efficacy is known to be around 60% from the studies Dr Harding quotes, and others. If we assume 60% efficacy and include a "knock on" factor (1.33) for secondary cases prevented as a result of cases prevented by chemoprophylaxis, we arrive at estimates of effectiveness for a range of at-risk populations as shown in table 2.

The 10 year risk of disease in infected children (most of which is in the first two years) is 9–11%, giving an NNT of 15. The two year risk of disease in contacts of smear

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**Table 1**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tuberculosis morbidity</th>
<th>Difference in number of 1000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Trial 1: US children (1955–77) with &quot;asymptomatic primary TB&quot; and normal chest radiograph</td>
<td>5/495</td>
<td>3/566</td>
</tr>
<tr>
<td></td>
<td>Trial 2: Household contacts of new &quot;active&quot; cases (1957–9) in the USA, Puerto Rico, and Mexico</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>Tuberculosis reaction &gt;10 mm</td>
<td>147/4992</td>
</tr>
<tr>
<td>All ages</td>
<td>Tuberculosis reaction 5–9 mm</td>
<td>31/1616</td>
</tr>
<tr>
<td>All ages</td>
<td>Initial negative tuberculin reaction bars 5 mm+ at 12 months (recent converters)</td>
<td>32/867</td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>Tuberculosis reaction &gt;4 mm</td>
<td>52/3132</td>
</tr>
</tbody>
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