Commentary

Multiple sclerosis and lung cancer: an unexpected inverse association

A.E. HANDEL\textsuperscript{1,2}, A. JOSEPH\textsuperscript{1,2} and S.V. RAMAGOPALAN\textsuperscript{1,2}

From the \textsuperscript{1}Wellcome Trust Centre for Human Genetics and \textsuperscript{2}Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, UK

Address correspondence to Dr S.V. Ramagopalan, The Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK. email: sreeramr@well.ox.ac.uk

Summary

Multiple sclerosis is associated with a decreased risk of cancer. Smoking is a risk factor both for multiple sclerosis and lung cancer. We performed a meta-analysis on studies of cancer frequency in multiple sclerosis.

Surprisingly, we found that the risk of lung cancer is reduced in multiple sclerosis [odds ratio 0.67 (95% confidence interval 0.59–0.76) \(P<0.00001\)]. Since this does not appear to be secondary to altered smoking behaviour, we hypothesise that this may be secondary to altered immune surveillance.

We recently reported a meta-analysis of cancer from all causes in multiple sclerosis (MS) and showed a significant decrease in risk [odds ratio (OR) 0.92 (95% confidence interval (CI) 0.87–0.97) \(P=0.004\)].\textsuperscript{1} Some cancers would be expected to be found in higher frequencies within MS cohorts. One type that is important to consider is lung cancer. Since cigarette smoking and vitamin D deficiency are likely to be important factors in increased susceptibility to MS and are also risk factors for lung cancer,\textsuperscript{2,3} one would expect a much elevated prevalence of lung cancer amongst MS patients.

We investigated all studies published in the last 15 years reporting measures of the risk of lung cancer for an MS cohort relative to population controls, using the methods for ascertainment described previously.\textsuperscript{1} This yielded a total of five studies: Fois and colleagues from the UK;\textsuperscript{4} Bahmanyar and colleagues from Sweden;\textsuperscript{5} Lebrun and colleagues from France;\textsuperscript{6} Midgard and colleagues from Norway;\textsuperscript{7} and Nielsen and colleagues from Denmark.\textsuperscript{8} We used the figures presented by Fois et al.\textsuperscript{4} for lung cancer diagnosed after presentation with MS and lung cancer in males from Lebrun and colleagues. Using the generic inverse variance with random effects model in Review Manager 5.0, we calculated the combined OR for lung cancer.

By pooling these studies, data were available on 43,761 MS patients. There was no significant heterogeneity between studies \(P=0.87\). We found that there was a significantly decreased risk of lung cancer in the MS cohort relative to controls [OR 0.67 (95% CI 0.59–0.76) \(P<0.00001\)] (Figure 1).

This is unlikely to be due to decreased survival in MS patients since an age-adjusted Cox survival analysis still showed a decreased risk and similarly under-diagnosis is unlikely as MS patients are more in contact with health professionals than the normal population.\textsuperscript{5} Furthermore, MS patients do not seem to stop smoking post-diagnosis.\textsuperscript{9,10} This
means that altered smoking behaviour, more frequent in MS patients than the normal population, is unlikely to be the cause of this reduction in lung cancer risk. This is in contrast to another neurological condition, Parkinson’s disease, where reduced risk of lung cancer was shown to be related to changed smoking habits.11 The other major risk factor in MS aetiology, Epstein–Barr virus, has not been shown to have a role in the pathogenesis of common lung cancers;12 it may be that the conundrum of decreased lung cancer prevalence represents increased immune surveillance in MS. Interestingly, one key cell type involved in MS pathogenesis, natural killer cells, has been shown to reduce the spread of lung cancer in a preclinical model.13,14 The highly significant reduction in lung cancer in MS patients despite a predicted increase in risk warrants intensive in vitro and in vivo study of mechanisms that might underlie this and may help to explain the previously described overall decrease in risk of all cancers, as well as aid in the study of MS pathogenesis.

Acknowledgements
We would like to thank all members of the Ebers group for helpful discussion and frequent support.

Funding
Wellcome Trust (grant number 075491/Z/04).

Conflict of interest: None declared.

References