Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case-control study based on death certificates

D Michal Freedman, Mustafa Dosemeci, Michael C R Alavanja

Abstract

Objectives—To explore whether mortality from multiple sclerosis is negatively associated with exposure to sunlight.

Methods—Two case-control studies based on death certificates were conducted for mortality from multiple sclerosis and non-melanoma skin cancer (as a positive control) to examine associations with residential and occupational exposure to sunlight. Cases were all deaths from multiple sclerosis between 1984 and 1995 in 24 states of the United States. Controls, which were age frequency matched to a series of cases, excluded cancer and certain neurological deaths. The effects of occupational exposure to sunlight were assessed among subjects with usual occupations requiring substantial activity, so as to exclude those whose indoor jobs resulted from disabilities subsequent to the onset of the disease. Multiple logistic regression analyses were applied, with adjustment for age, sex, race, and socioeconomic status.

Results—Unlike mortality from skin cancer, mortality from multiple sclerosis was negatively associated with residential exposure to sunlight (odds ratio (OR)=0.53 (multiple sclerosis) and OR=1.24 (skin cancer)). Odds ratios for the highest occupational exposure to sunlight were 0.74 (95% confidence interval (95% CI) 0.61 to 0.89) for mortality from multiple sclerosis, compared with 1.21 (1.09 to 1.34) for mortality from non-melanoma skin cancer. The OR was 0.24 for the combined effect of the highest levels of residential and occupational exposure to sunlight on multiple sclerosis, compared with an OR of 1.38 for skin cancer.

Conclusions—In this exploratory study, mortality from multiple sclerosis, unlike mortality from skin cancer, was negatively associated with both residential and occupational exposure to sunlight.

Keywords: multiple sclerosis; etiology; latitude; ultraviolet radiation; sunlight; occupation; residence; skin cancer

Little is known about the etiology of multiple sclerosis. Epidemiological evidence suggests that increased risk may be related to higher socioeconomic factors, viral infections, environmental influences before the age of 15, and genetics, among other factors. Many epidemiological studies have also found a positive association between multiple sclerosis and residential latitude in the United States and other parts of the world. Whether the geographical association reflects a strong role for environmental risk factors, and what those factors might be, remains unclear. Some investigators have suggested that the geographical gradient of multiple sclerosis may reflect the role of sunlight in the etiology of disease. In a report which hypothesized that ultraviolet radiation explains the latitude gradient in multiple sclerosis, McMichael and Hall predicted that if ultraviolet radiation is an etiological agent, outdoor occupations would be expected to protect against multiple sclerosis. To our knowledge, conditions related to residence or latitude have been the sole indicators of solar radiation explored in epidemiological studies of multiple sclerosis. We conducted a case-control study based on death certificates about mortality from multiple sclerosis in the United States, to explore the effects of potential residential as well as occupational exposure to sunlight. The findings for multiple sclerosis were compared with findings for non-melanoma skin cancer, which has been causally linked to sunlight, and served as a positive control.

Materials and methods

The National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics maintain a database of all deaths in 24 states, which coded occupation, state of residence at birth and at death, and other information from death certificates, as described by Figgs et al. Cases included all underlying causes of deaths between 1984 and 1995 from multiple sclerosis (international classification of diseases, ninth revision (ICD-9), code 340) and non-melanoma skin cancer (code 173). A common set of controls was used across a series of case-control studies on neurological and cancer mortality (including breast, prostate, ovarian, and colon cancer) and solar radiation. Deaths from cancer (ICD 140–239), multiple sclerosis (ICD 340), and some diseases of the central nervous system (ICD 330–337), were excluded. Controls were frequency matched by five year age group to the combined group of multiple sclerosis, non-melanoma skin cancer, and other causes of death of the cases in the series. The controls represent a one to one ratio with the most common cause of death in the

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series (colon cancer), but a ratio of about 25 to 1 with multiple sclerosis and with skin cancer. The data were also analysed with an alternative subset of controls, excluding those with deaths due to heart disease or accidents, causes which may be related to regional weather. 17 18

Residential exposure to sunlight was assessed by state residence recorded on the death certificate. We assigned each state one of three levels of solar radiation based on United States Weather Bureau data. 19 Subjects were limited to those who resided in the same solar radiation region at birth and at death to reduce misclassification in analyses based on lifetime residential solar exposure. This included 4282 cases of multiple sclerosis, 4929 skin cancer cases, and 115 195 controls (about 75% of each).

Occupational exposure to sunlight was based on usual occupation classified by an industrial hygienist (MD) into three categories: indoor work, work that combined indoor and outdoor exposure, and outdoor work. Occupation was also used to assess socioeconomic status based on a method of scoring occupation developed by Green 20 and to create an index of occupational physical activity with four levels of physical activity. The effects of occupational exposure to solar radiation were assessed among all subjects and among the subjects in occupations categorised as requiring high or moderate levels of activity, so as to exclude those whose indoor jobs resulted from disabilities subsequent to onset of the disease. This resulted in 1562 (27%) cases of multiple sclerosis, 2849 (43%) cases of skin cancer, and 59 690 (39%) controls.

The effects of ethnic origin and race were assessed by classifying subjects based on national origin and race as recorded on the death certificate. Northern European ancestry in particular was assessed because of its possible role in the higher risk previously found with higher latitudes in the US.22

Table 1 provides the characteristics of cases and controls for deaths from multiple sclerosis and non-melanoma skin cancer, as well as for those with the same residential region at birth and at death, and the group with active occupations. Of those with active occupations, about 10% of cases of multiple sclerosis had outdoor jobs.

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Residence in states with the highest potential exposure to solar radiation, adjusting for age, sex, race, and socioeconomic status. The models were applied to the entire population; sex and race subpopulations (adjusting only for age and socioeconomic status); as well as subpopulations of residents of eastern and western states (to examine whether possible ethnic differences between eastern and western regions accounted for any observed patterns). The measures of association were the mortality odds ratio (OR) and 95% confidence interval (95% CI) derived by standard logistic regression methods in SAS. 3

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origin from a northern European country was not associated with risk of mortality from multiple sclerosis, after controlling for residence, age, sex, and socioeconomic status (OR=1.0).

Occupational solar radiation (among active jobs) was associated with reduced risk of mortality from multiple sclerosis (table 2). This association was generally found in racial and sex subpopulations, although the numbers of cases were especially small for minorities (data not shown). By contrast, occupational solar radiation was positively associated with risk of skin cancer in the total population, and generally among sex and race subpopulations (data not shown). We also found that the residential and occupational solar radiation gradient in risk remained in analyses with the alternative subset of controls.

Table 3 shows the combined effect of residential and occupational solar exposure among those in active jobs. With the referent category comprised of indoor workers in residential areas receiving least solar radiation, increased potential exposure to sunlight was generally associated with reduced risk of multiple sclerosis in each residential and occupational category. In the highest combined (occupational and residential) sunlight category, the OR was 0.24 (95 % CI 0.15 to 0.38).

By contrast, the risks for skin cancer increased with potential occupational exposure to sunlight in each residential category, and with residential exposure among indoor workers, although not consistently among outdoor workers.

**Discussion**

By contrast with the mortality from skin cancer, our study found that both residential and occupational solar radiation were inversely associated with mortality from multiple sclerosis, and that the associations generally characterised sex and race subpopulations. Ethnicity does not seem to explain the geographical gradient because northern European ancestry was not a risk factor and a negative gradient was found in both eastern and western regions of the country, although it was weaker in the west. By assessing the effects of potential occupational exposure to solar radiation only among those with the most active jobs, we also increased the likelihood that the inverse association reflects causal factors, rather than occupational changes after the onset of disease.

Death certificate studies, such as this, have recognised limitations, including potential misclassification of occupation and residential exposure, and lack of information on potential confounders—such as viral infections, environmental childhood exposures, genetics, and other sources of exposure to sunlight. As noted, residence was based simply on place of birth and residence at death, whereas occupational exposure was limited to usual occupational exposure. If the misclassification of cases does not differ from those of controls, any error in the association will at most reduce the association found between exposure and mortality.

One of the most problematic limitations is the potential bias in use of deaths rather than population as the study base, which may result in biased associations, unless the distribution of exposure of the dead controls reflects that of the living source or base population from which the cases came. Although the similarity of our findings with an alternative subset of controls

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### Table 2

Crude and adjusted ORs (95% CIs) for mortality from multiple sclerosis associated with indicators of exposure to sunlight and socioeconomic status, USA, 1984–95

<table>
<thead>
<tr>
<th>Sociodemographic characteristics</th>
<th>Multiple sclerosis</th>
<th></th>
<th>Skin cancer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted*</td>
<td>Crude</td>
<td>Adjusted*</td>
</tr>
<tr>
<td><strong>Residence sunlight†:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.58 (0.54 to 0.62)</td>
<td>0.59 (0.55 to 0.63)</td>
<td>1.12 (1.04 to 1.20)</td>
<td>1.15 (1.07 to 1.23)</td>
</tr>
<tr>
<td>High</td>
<td>0.55 (0.51 to 0.59)</td>
<td>0.53 (0.48 to 0.57)</td>
<td>1.15 (1.07 to 1.24)</td>
<td>1.24 (1.15 to 1.35)</td>
</tr>
<tr>
<td><strong>Occupational‡:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mixed</td>
<td>0.87 (0.77 to 0.97)</td>
<td>0.89 (0.78 to 1.02)</td>
<td>1.30 (1.19 to 1.42)</td>
<td>1.03 (0.93 to 1.14)</td>
</tr>
<tr>
<td>Outdoor</td>
<td>0.40 (0.33 to 0.47)</td>
<td>0.74 (0.61 to 0.89)</td>
<td>1.53 (1.40 to 1.68)</td>
<td>1.21 (1.09 to 1.34)</td>
</tr>
<tr>
<td><strong>Socioeconomic status:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.36 (1.19 to 1.55)</td>
<td>1.00 (0.88 to 1.15)</td>
<td>0.92 (0.84 to 1.00)</td>
<td>0.93 (0.85 to 1.01)</td>
</tr>
<tr>
<td>3</td>
<td>2.45 (2.19 to 2.75)</td>
<td>1.90 (1.68 to 2.13)</td>
<td>0.90 (0.83 to 0.97)</td>
<td>0.89 (0.82 to 0.96)</td>
</tr>
<tr>
<td>4</td>
<td>3.08 (2.73 to 3.49)</td>
<td>2.26 (1.99 to 2.57)</td>
<td>0.87 (0.79 to 0.95)</td>
<td>0.90 (0.82 to 1.00)</td>
</tr>
<tr>
<td>5 High</td>
<td>3.39 (2.89 to 3.99)</td>
<td>3.07 (2.59 to 3.62)</td>
<td>1.19 (1.04 to 1.36)</td>
<td>1.07 (0.94 to 1.23)</td>
</tr>
</tbody>
</table>

*Adjusted ORs were calculated with logistic regression, adjusting for age, sex, race, socioeconomic status, metropolitan residence, and occupational physical activity among subjects with high or moderate activity jobs. Homemakers were also excluded.

†Residence sunlight was defined as residing in a region both at birth and at the time of death. Regions are defined in table 1. Subjects who resided in different regions at birth and at the time of death were excluded.

‡Residential sunlight was defined as residing in a region both at birth and at the time of death. Regions are defined in table 1. Subjects who resided in different regions at birth and at the time of death were excluded.

### Table 3

ORs (95% CIs) for mortality from multiple sclerosis and skin cancer by exposure to occupational and residential sunlight, USA, 1984–95

<table>
<thead>
<tr>
<th>Occupational exposure</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted*</td>
<td>Crude</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Crude</td>
<td>Adjusted*</td>
<td>Crude</td>
</tr>
<tr>
<td>Indoor</td>
<td>1.0</td>
<td>0.57 (0.48 to 0.68)</td>
<td>0.54 (0.44 to 0.66)</td>
</tr>
<tr>
<td>(350; 7418)</td>
<td>(295; 10140)</td>
<td>(148; 5830)</td>
<td></td>
</tr>
<tr>
<td>Outdoor</td>
<td>0.89 (0.84 to 1.22)</td>
<td>0.52 (0.38 to 0.71)</td>
<td>0.24 (0.15 to 0.38)</td>
</tr>
<tr>
<td>(50; 2249)</td>
<td>(58; 4875)</td>
<td>(20; 3428)</td>
<td></td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Crude</td>
<td>Adjusted*</td>
<td>Crude</td>
</tr>
<tr>
<td>Indoor</td>
<td>1.0</td>
<td>1.08 (0.92 to 1.26)</td>
<td>1.17 (0.98 to 1.41)</td>
</tr>
<tr>
<td>(301; 7418)</td>
<td>(409; 10140)</td>
<td>(227; 5830)</td>
<td></td>
</tr>
<tr>
<td>Outdoor</td>
<td>1.07 (0.85 to 1.35)</td>
<td>1.42 (1.18 to 1.71)</td>
<td>1.38 (1.12 to 1.69)</td>
</tr>
<tr>
<td>(117; 2249)</td>
<td>(322; 4875)</td>
<td>(202; 3428)</td>
<td></td>
</tr>
</tbody>
</table>

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supports the findings, uncertainties remain about whether the dead controls reflect the underlying exposure profile of the base population.

Despite these limitations, our study confirmed many of the findings previously reported. The validity of the solar radiation indices was supported by the positive association we found between the exposure to solar radiation and mortality from non-melanoma skin cancer, which is consistent with previous studies linking incidence of skin cancer to cumulative exposure to sun.15 24 Also, although socioeconomic status was based on usual occupation, and not on other possible indicators, the positive relation we found between socioeconomic status and risk of multiple sclerosis is consistent with other studies.25 26 Our finding that northern European ancestry is not related to risk, after controlling for residence, is consistent with the results of Page et al27 in another of the veteran series studies.

Several mechanisms have been presented about how sunlight may affect multiple sclerosis.10 11 13 Hayes et al11 proposed that the role of sunlight on immune function may be mediated by hormonal vitamin D. Hutter and Laing13 suggested that the effect of sunlight may be mediated by the secretion of melatonin, which is both sensitive to light and may affect the cellular structure of the thymus. McMichael and Hall13 also suggested that sunlight may suppress immune functions, either by reducing early T cell sensitisation to antigens that mimic myelin or subsequent cell mediated responses to these antigens.

As our study was based on death certificates, our findings are necessarily exploratory. The negative associations between mortality from multiple sclerosis and both residential and occupational exposure to sunlight found here warrant future study based on incident cases and more refined assessments of exposure to sunlight.

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