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Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study

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Abstract

Objective To examine whether past high sun exposure is associated with a reduced risk of multiple sclerosis.

Design Population based case-control study.

Setting Tasmania, latitudes 41-3°S.

Participants 136 cases with multiple sclerosis and 272 controls randomly drawn from the community and matched on sex and year of birth.

Main outcome measure Multiple sclerosis defined by both clinical and magnetic resonance imaging criteria.

Results Higher sun exposure when aged 6-15 years (average 2-3 hours or more a day in summer during weekends and holidays) was associated with a decreased risk of multiple sclerosis (adjusted odds ratio 0.31, 95% confidence interval 0.16 to 0.59).

Higher exposure in winter seemed more important than higher exposure in summer. Greater actinic damage was also independently associated with a decreased risk of multiple sclerosis (0.32, 0.11 to 0.88 for grades 4-6 disease). A dose-response relation was observed between multiple sclerosis and decreasing sun exposure when aged 6-15 years and with actinic damage.

Conclusion Higher sun exposure during childhood and early adolescence is associated with a reduced risk of multiple sclerosis. Insufficient ultraviolet radiation may therefore influence the development of multiple sclerosis.

Introduction

Contributing factors in the cause of multiple sclerosis include a defect in immunological self tolerance result-

ing in a T helper cell type 1 mediated attack on myelin proteins.¹ One of the most striking features of multiple sclerosis is a gradient of increasing prevalence with latitude.² Recent photoimmunological work has rekindled interest in this observation because ultraviolet radiation can attenuate T helper cell type 1 mediated immune responses through several mechanisms.³ Also, administration of ultraviolet radiation or 1,25-dihydroxycholecalciferol, the active form of vitamin D₃, which is produced under the influence of ultraviolet radiation, has shown protective effects against the induction or progression of experimental allergic encephalomyelitis.^{4,5} In humans, ultraviolet radiation or vitamin D may also protect against multiple sclerosis.^{6,7} Exposure to ultraviolet radiation during a critical period in early life may be important as may cumulative or later life exposure.⁸

Tasmania is located at latitudes 41-3°S and has a high prevalence of multiple sclerosis at 75.6 per 100 000 population.⁹ We conducted a case-control study in Tasmania to examine whether high past sun exposure was associated with a reduced risk of multiple sclerosis.

Participants and methods

Our source population consisted of people aged under 60 years who were residents of Tasmania and who had at least one grandparent who was born in Tasmania. Cases were members of a source population who had a diagnosis of multiple sclerosis. To recruit participants, information evenings were held for members of the local multiple sclerosis societies, and information packs were sent to doctors and pharmacists, who were to inform people with multiple sclerosis about the

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programme. Letters were sent to eligible patients in the south of the state encouraging them to participate. In total, 169 people responded. We included 136 cases in the final sample: 30 people (18%) did not meet the study criteria for diagnosis of multiple sclerosis, one person refused a neurological assessment, one person died before interview, and one person deteriorated and was unable to take part. Respondents were interviewed and examined by one of the participating neurologists. Magnetic resonance images subsequently confirmed the diagnosis for 134 cases (99%), and for the other two cases we obtained the reports of previous scans.

Controls were selected from the source population using the roll of registered electors, a comprehensive listing of the population of Tasmania. We randomly selected two controls for each case and matched them to the index case on sex and year of birth. Overall, 272 of 359 eligible controls participated (response rate 76%). In an unmatched design, we required at least 100 cases and 200 controls to detect an odds ratio of 2.0 or 0.5 for the effect of a dichotomous exposure where 40% of the controls were exposed.

Time in sun

Two research assistants conducted all interviews and measurements between March 1999 and June 2001. Participants were asked validated questions about the amount of time they would normally have spent in the sun during weekends and holidays in winter and summer ("time in the sun" question). Answers to the time in the sun question for winter predict levels of serum 25-hydroxycholecalciferol in 8 year old Tasmanian children.¹⁰ The standardised questionnaire included questions on measures to protect against the sun, use

of vitamin D supplements at ages 10-15 years, medical history, and other factors thought to be associated with multiple sclerosis. For the timing of exposures we obtained either the exact age or the five year age range in which the exposure occurred. Before interview, participants were asked to fill in a lifetime calendar for each year of their life. During the interview, participants answered the time in the sun question for summer only for each year of their life, and from the information in the calendar we identified blocks of years where time in the sun was constant or not. There was moderate agreement between the questionnaire based measure and the calendar measure for both cases and controls.

Actinic damage and skin phenotype

Silicon casts of the skin surface of the hand, measuring actinic damage, were used as an objective marker of cumulative lifetime sun exposure (see bmj.com). Skin phenotype and cutaneous melanin density were assessed with a spectrophotometer at the upper inner arm and buttock-body sites usually not exposed to sunlight. Skin colour was also assessed visually by the research assistants who also recorded the number of naevi greater than 5 mm on the left arm, hair and eye colour, height, and weight. The standardised questionnaire included a question on lifetime sunburns where the pain lasted more than two days, a measure that reflects both skin phenotype and exposure behaviour.

Data analysis

Correlations were calculated as measures of linear association, and odds ratios and 95% confidence intervals were estimated by conditional logistic regression.

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Odds ratios for multiple sclerosis and reported measures of sun exposure in childhood and adolescence

Sun exposure	Age 6-10			Age 11-15			Age 16-20		
	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)
In winter, by questionnaire									
Time in sun (h/day):									
<1	26 (19.1)	27 (10.0)	1	22 (16.3)	28 (10.3)	1	29 (21.3)	37 (13.6)	1
1-2	29 (21.3)	61 (22.7)	0.50 (0.24 to 1.00)	29 (21.5)	69 (25.4)	0.55 (0.27 to 1.10)	37 (27.2)	84 (30.9)	0.59 (0.32 to 1.07)
2-3	26 (19.1)	64 (23.8)	0.43 (0.21 to 0.87)	30 (22.2)	65 (23.9)	0.61 (0.30 to 1.22)	26 (19.1)	53 (19.5)	0.63 (0.32 to 1.24)
3-4	14 (10.3)	34 (12.6)	0.44 (0.19 to 1.01)	22 (16.3)	37 (13.6)	0.76 (0.36 to 1.61)	17 (12.5)	39 (14.3)	0.56 (0.26 to 1.22)
>4	41 (30.2)	83 (30.9)	0.50 (0.26 to 0.98)	32 (23.7)	73 (26.8)	0.57 (0.28 to 1.14)	27 (19.9)	59 (21.7)	0.60 (0.30 to 1.17)
Linear trend	P=0.18			P=0.45			P=0.22		
Dichotomised ($\geq 1-2$ v < 1)	0.47 (0.26 to 0.84)			0.60 (0.33 to 1.09)			0.59 (0.35 to 1.01)		
In summer, by questionnaire									
Time in sun (h/day):									
<1	6 (4.4)	8 (3.0)	1	3 (2.2)	2 (0.7)	1	11 (8.1)	13 (4.8)	1
1-2	15 (11.0)	15 (5.6)		13 (9.6)	26 (9.6)		19 (14.0)	37 (13.6)	
2-3	20 (14.7)	39 (14.4)	0.59 (0.27 to 1.28)	20 (14.7)	37 (13.6)	0.94 (0.40 to 2.17)	22 (16.0)	64 (23.6)	0.55 (0.28 to 1.10)
3-4	17 (12.5)	48 (17.8)	0.39 (0.17 to 0.88)	27 (19.9)	61 (22.4)	0.77 (0.35 to 1.68)	26 (19.1)	61 (22.5)	0.71 (0.38 to 1.35)
>4	78 (57.4)	160 (59.3)	0.55 (0.30 to 1.03)	73 (53.7)	146 (53.7)	0.88 (0.44 to 1.74)	58 (42.7)	96 (35.4)	1.00 (0.57 to 1.78)
Linear trend	P=0.15			P=0.72			P=0.56		
Dichotomised ($\geq 2-3$ v $\leq 1-2$)	0.50 (0.24 to 1.02)			0.86 (0.44 to 1.66)			0.79 (0.47 to 1.33)		
In summer, by calendar									
Time in sun (h/day):									
<1	2 (1.5)	2 (0.7)	1	4 (2.9)	2 (0.7)	1	6 (4.4)	8 (2.9)	1
1-2	17 (12.5)	14 (5.2)		11 (8.1)	12 (4.4)		20 (14.7)	47 (17.3)	
2-3	18 (13.2)	23 (8.5)	0.63 (0.23 to 1.73)	27 (19.9)	40 (14.7)	0.65 (0.26 to 1.61)	27 (19.9)	58 (21.3)	0.99 (0.50 to 1.95)
3-4	19 (14.0)	44 (16.3)	0.35 (0.14 to 0.88)	22 (16.2)	53 (19.5)	0.39 (0.16 to 0.95)	30 (22.1)	55 (20.2)	1.16 (0.59 to 2.26)
>4	80 (58.8)	187 (69.3)	0.34 (0.16 to 0.74)	72 (52.9)	165 (60.7)	0.40 (0.18 to 0.89)	53 (39.0)	104 (38.2)	1.09 (0.60 to 1.97)
Linear trend	P<0.01			P=0.01			P=0.70		
Dichotomised ($\geq 2-3$ v $\leq 1-2$)	0.36 (0.17 to 0.76)			0.44 (0.20 to 0.94)			1.07 (0.63 to 1.85)		

Tests for trend were performed. Analysis of actinic damage was restricted to 323 high quality casts. The recording of year by year exposure by the lifetime calendar allowed an estimation of average exposure for any age span. To take account of duration of disease, we stratified by time elapsed since the first symptom of multiple sclerosis. Controls were given the years of duration of the age at onset of their case pair. See bmj.com for details.

Results

Overall, 68% (n=92) of the cases were female, and most of the cases (96%; n=131) and controls (95%; n=258) were born in Tasmania and living there at age 10. Sixty six per cent of the cases had relapsing remitting multiple sclerosis. Although only of borderline significance, the odds of having light skin colour (<2% melanin) was 1.59 times higher for cases than for controls. Skin colour assessed by the research assistant showed a significant relation with multiple sclerosis (odds ratio 1.62, 95% confidence interval 1.05 to 2.51), but reported tendency to burn or tanning ability did not.

Childhood sun exposure

People with multiple sclerosis were less likely to report severe sunburn episodes during their lifetime, despite their fairer skin (0.55, 0.32 to 1.63). We observed a strong inverse association between sun exposure in childhood and adolescence and multiple sclerosis (table). This inverse association was observed for exposure both in winter and in summer. Compared to bivariate analysis, including both summer and winter questionnaire based measures for exposure as dichotomised terms in the model left the estimated effect of exposure in winter almost unchanged (adjusted odds ratio 0.52, 0.28 to 0.95 at ages 6-10 years), but greatly reduced the effect of exposure in summer (0.63, 0.30 to 1.35 at ages 6-10 years). This was found irrespective of the age at exposure.

We then estimated the effect of average exposure at ages 6-15 years on multiple sclerosis from the year by year calendar taking into account other factors that related to multiple sclerosis. After controlling for smoking and melanin density at the upper inner arm, the magnitude of the odds ratio increased from 0.39 (0.22 to 0.70) to 0.31 (0.16 to 0.59) for higher sun exposure (average 2-3 hours or more a day in summer). Additional adjustment for the other factors made no important difference to the results.

Lifetime sun exposure

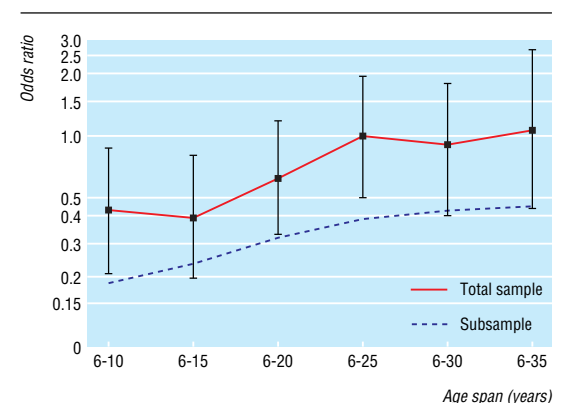
The figure shows the odds ratios for higher sun exposure by age using the calendar data. The odds ratio estimates of the apparent protective effect of higher exposure were greatest for age spans before 15 years (6-10 years: 0.43, 0.21 to 0.88; 6-15 years: 0.40, 0.20 to 0.80). Inclusion of later years into the cumulative lifespan measure diluted the effect. We repeated the analysis on a subgroup of participants who had indicated on a checklist before interview that they did not believe that climatic factors such as sun exposure were an important cause of multiple sclerosis. For this group, the protective effect of past exposure was even stronger than for the total group (figure).

Greater levels of actinic damage were also associated with a reduced risk of multiple sclerosis (adjusted odds ratios 0.32, 0.10 to 0.98 for grade 4; 0.33, 0.12 to 0.96 for grade 5; 0.17, 0.05-0.60 for grade 6, compared with grade 3) with evidence of a dose-response relation ($P < 0.01$ for test for trend). After controlling for smoking before the age of onset, melanin density at the upper inner arm, and amount of sun exposure after disease onset, the magnitude of the odds ratio increased from 0.39 (0.17 to 0.90) to 0.32 (0.11 to 0.88) for greater actinic damage (grades 4-6). Duration of disease was not strongly associated with past sun exposure or actinic damage after adjustment for age. Moreover, the relative risk estimates for neither exposure to age 15 nor actinic damage differed by duration of disease, and the protective effects were also observed among cases of recent (≤ 5 years) onset. We then assessed whether higher exposure before age 15 and greater actinic damage were each important in predicting the risk of multiple sclerosis. Compared to bivariate analysis, including both in the same model as linear terms left the effect of each factor almost unchanged.

Age at onset

The odds ratios for 2-3 hours or more sun exposure in summer during weekends and holidays were 0.95 (0.55 to 1.64), 0.92 (0.55 to 1.54), and 1.06 (0.65 to 1.74) for 10 years, five years, and one year before the onset of multiple sclerosis, respectively. Thus, in contrast to the inverse association between sun exposure in early life or actinic damage and multiple sclerosis, there was no evidence that exposure at these particular years in the decade before the onset of disease was important.

Finally, we examined age at onset of multiple sclerosis among cases. No evidence was found that increasing exposure from ages 6-15 years or lifetime actinic damage were associated with earlier onset of disease. However, skin phenotype did relate to age at onset. Low melanin density at the buttock and fair skin assessed by the research assistant were associated with earlier onset of disease.



Association between sun exposure and multiple sclerosis for different age spans. Odds ratios and 95% confidence intervals for higher (average 2-3 hours or more a day) sun exposure in summer during weekends and holidays. Subgroup is participants who did not believe that sun exposure was an important cause of multiple sclerosis

Discussion

Higher sun exposure during childhood and early adolescence and greater actinic damage are associated with a decreased risk of multiple sclerosis. Both exhibited a dose-response relation with multiple sclerosis. The inverse association between past exposure to ultraviolet radiation and multiple sclerosis was consistently found regardless of whether exposure was measured by questionnaire, calendar, or actinic damage. Both ultraviolet radiation and vitamin D₃ have been found to suppress T helper cell type 1 immune responses.^{4–11} Clinical symptoms of experimental allergic encephalomyelitis—an animal model of multiple sclerosis—can be prevented or delayed by providing ultraviolet radiation or 1,25-dihydroxycholecalciferol (the active form of vitamin D₃) at the time of immunisation.^{4–5, 12} High residential or occupational sunlight exposure was found to be negatively associated with mortality due to multiple sclerosis in a death certificate based case-control study.¹³ Regular vitamin D supplementation in the first year of life in a Finnish cohort was associated with a reduced risk of subsequent type 1 diabetes, another T helper cell type 1 autoimmune disease.¹⁴

The case sample was similar to other populations with multiple sclerosis of north European ancestry for disease related features such as type of disease, age at diagnosis, and sex ratio. Tasmania provides a good setting for this type of study. Unlike northern Australia, the region has relatively low levels of ambient ultraviolet radiation in winter, and exposure to sun in winter is a major determinant of serum 25-hydroxycholecalciferol concentration.¹⁰ Participation rates were high, reducing non-response bias, but it is possible that some selection bias may have occurred. The use of measures of past time in the sun could have led to substantial misclassification of the measurement of past exposure if participants had resided in locations with varying levels of ambient ultraviolet radiation, but a high proportion of participants had lived in Tasmania for most of their life. A possible weakness of our study was that prevalent, not incident, cases were studied. It is unlikely that recall bias fully explains the observed strong reported associations. The inverse association did not seem to be caused by the participants' knowledge of the hypothesis, because the odds ratios for exposure were more protective for the participants who did not believe sun exposure was an important cause of multiple sclerosis. Also, if the results were caused by recall bias, we would expect this to affect the results of exposure after age 20 or exposure immediately before the age at onset in a similar manner, but this was not the case. In addition, actinic damage, an objective marker of past exposure, also showed an inverse association with multiple sclerosis, and this objective marker is free of recall bias. Also disease related changes in behaviour did not explain the findings.

We found that higher sun exposure in winter was particularly important. In Tasmania, the daily levels of ambient ultraviolet radiation are more than 10-fold lower in mid-winter than they are in mid-summer, compounded by less time spent outdoors. This suggests that, in winter in particular, minimum threshold requirements for ultraviolet radiation and vitamin D may not have been met.

The apparent protective effect seemed to be greatest for sun exposure during childhood and early

What is already known on this topic

Multiple sclerosis shows a gradient of increasing prevalence with latitude

This has been attributed to differences in regional levels of ultraviolet radiation

Ultraviolet radiation may have a protective role in T helper cell type 1 mediated autoimmune disease

What this study adds

Higher sun exposure during childhood and early adolescence and greater actinic damage are associated with a reduced risk of multiple sclerosis

These associations persisted after adjustment for fair skin and exposure after onset of disease

Insufficient ultraviolet radiation or vitamin D, or both, may influence the development of multiple sclerosis

adolescence. However, we can only address the timing issue through self reported data, because actinic damage measures cumulative damage but cannot provide data on timing of sun exposure. The finding of no association between sun exposure in the decade before onset of multiple sclerosis may indicate that the timing of low exposure may relate more to age related immunological development than to onset of disease.

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Ethical approval: The project was approved by the human research ethics committee of the Royal Hobart Hospital.

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Rate limiting factors in recruitment of patients to clinical trials in cancer research: descriptive study

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In 2004 the national cancer research network, established in 2001, will be evaluated on a performance target of increasing recruitment of patients into cancer clinical trials. The national average in 2000-1 was 3.5% of incident cancer cases and the target was set at 7.5%. Much may depend on this target being met as £11.5m of government funding is being invested annually to provide infrastructure to conduct clinical trials within 34 networks across England. The future of this funding is not secure. We audited patients' involvement in clinical trials from a cohort of new cancer cases managed within a single research network to identify obstacles to recruitment.

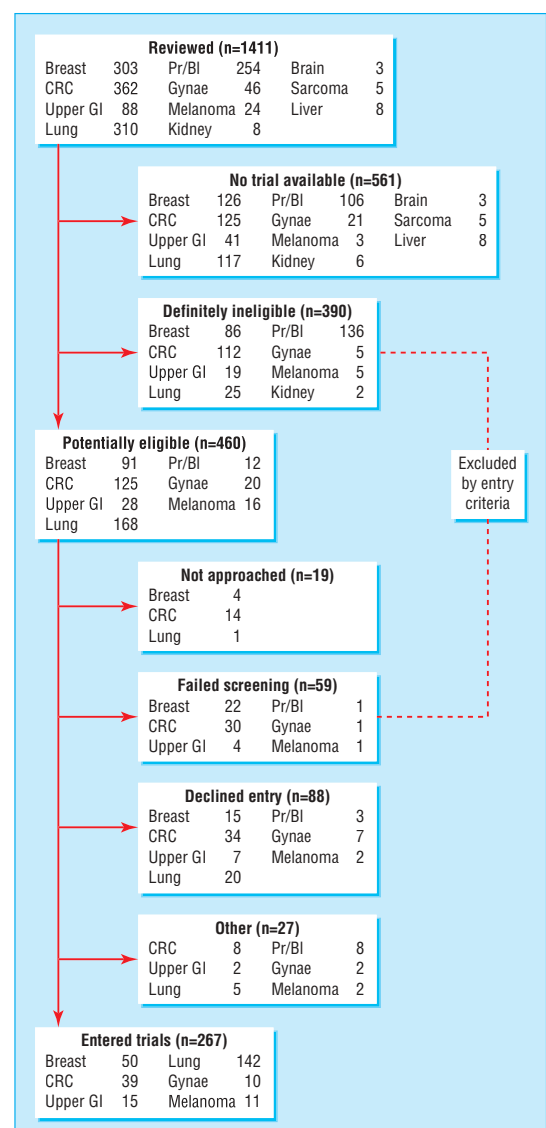
Participants, methods, and results

The West Anglia cancer research network, a first wave regional research network, was established in 2001. It functions in close collaboration with the service based network. It covers a population of 1.65 million, and about 8000 new cases are seen each year. Patients discussed at weekly multidisciplinary team meetings are reviewed for their potential entry into trials. A database is kept of all patients considered for any clinical trial.

The figure summarises patients' data collected from team meetings in the cancer centre and four of the seven network cancer units during 2002. Of 1411 patients reviewed, 267 (19%) eventually entered a trial (the overall recruitment rate for our network in 2002 was actually 10%). No trial was available for 561 (40%) patients, and 390 (28%) were immediately excluded as they failed entry criteria. Of the 460 patients considered potentially eligible for trial entry, only 19 (4%) were not approached at all, 88 (19%) declined to take part, and 59 (13%) of those prepared to consider doing so ultimately failed screening procedures for specific trials. Overall, entry criteria disqualified 449 (53%) of the 850 patients for whom a trial was available.

Comment

The main reasons for cancer patients not entering a trial were lack of an available study and failure to meet entry criteria. The task of doubling numbers of patients in cancer clinical trials by 2004 would therefore be made easier if a wider range of pragmatic trials was available. There is growing pressure on cancer specialists to



Outcome for patients reviewed for entry into clinical trials according to type of cancer (CRC=colorectal; Pr/Bl=prostate/bladder; GI=gastrointestinal). Where cancer type is not mentioned there were no relevant patients

ensure an active rolling national trial programme for each tumour type. Even so, funding for clinical research is limited. Research expenditure in the United Kingdom