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Exposure to ultraviolet radiation and risk of malignant lymphoma and multiple myeloma—a multicentre European case–control study

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Background Three recent studies have reported a decreased risk of non-Hodgkin lymphoma (NHL) for high ultraviolet (UV) radiation exposure.

Methods We conducted a multicentre case–control study during 1998–2004 in France, Germany, Ireland, Italy and Spain, comprising 1518 cases of NHL, 268 cases of Hodgkin lymphoma, 242 cases of multiple myeloma and 2124 population or hospital controls. We collected information on sensitivity to sun and personal exposure to UV radiation in childhood and adulthood via interview, and assessed occupational exposure to UV radiation from the occupational history.

Results The risk of Hodgkin and NHL was increased for increasing skin sensitivity to the sun [odds ratio (OR) for no suntan vs very brown 2.35, 95% CI 0.94–5.87 and 1.39, 95% CI 1.03–1.87, respectively]. The risk of diffuse large B-cell lymphoma was reduced for increasing adult personal (OR for highest vs lowest quartile of exposure in free days 0.62, 95% CI 0.44–0.87) and for occupational exposure to UV radiation (OR for highest vs lowest exposure tertile 0.63, 95% CI 0.37–1.04). The risk of multiple myeloma was increased for personal exposure to UV radiation during adulthood (OR for highest vs lowest quartile of exposure in free days 1.49, 95% CI 0.88–2.50). A protective effect was observed for use of sun lamps for diffuse large B-cell lymphoma (OR for 25+ times vs never 0.63, 95% CI 0.38–1.03).

Conclusions The hypothesis of a protective effect of UV radiation on lymphoma is supported by our results. The underlying mechanisms might differ from those operating in skin carcinogenesis. The increased risk of multiple myeloma is worth replication.

Keywords Non-Hodgkin lymphoma, UV radiation, multiple myeloma, Hodgkin lymphoma, lymphoma, epidemiology

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Introduction

In 1992, Zheng *et al.*[1] hypothesized that exposure to the sun increased the risk of non-Hodgkin lymphoma (NHL). This hypothesis was largely based on a consistently observed association between melanoma and lymphoproliferative malignancies in individual patients,[2] and was justified by an effect of ultraviolet (UV) radiation on the immune system.[3] The hypothesis was reinforced by results of ecological studies showing similar temporal trends in the incidence of melanoma and NHL.[4,5] Several studies of differing designs have since evaluated this hypothesis,[6–17] but their results have not been conclusive. The inconsistency can be explained by exposure misclassification, presence of effect modifiers (e.g. circumstances of UV exposure), as well as chance. Recently, three case–control studies, from Australia,[18] Sweden and Denmark[19] and United States[20] and an international pooled analysis[21] that were based on detailed individual exposure assessment, reported a decreased risk of NHL for high UV exposure. These unexpected findings require replication in independent populations. Furthermore, only a few studies addressed the possible effect of UV exposure on lymphopoietic neoplasms other than NHL.[15,16,19] We report here the results of a multicentre case–control study of Hodgkin and NHL and multiple myeloma in Europe. The data on NHL were included in the pooled analysis.[21]

Methods

The epilymph case–control study has been described in detail elsewhere.[22,23] Cases were patients with newly diagnosed, histologically or cytologically confirmed lymphoma or multiple myeloma, aged 17 or older and admitted to participating hospitals in several areas in seven European countries during 1998–2003. They were classified according to the World Health Organization classification;[24] slides of 20% of cases were reviewed centrally by a team of lymphoma pathologists. This analysis includes data from 2028 cases enrolled in five of the participating countries: France, Germany, Ireland, Italy and Spain. Although the current World Health Organization classification includes multiple myeloma among B-cell lymphomas, for the sake of comparability with previous studies, we have followed the traditional approach of treating multiple myeloma as a distinct entity from other non-Hodgkin B-cell lymphomas. A total of 2124 controls in this study were also recruited in the same countries during the same period: they were frequency-matched to cases on age (5-year groups), sex and study area, except in Germany where they were individually matched to cases on the same variables. Controls in Germany and Italy were randomly sampled from population registers, while in France, Ireland and Spain they were recruited from patients admitted to the same hospitals of the cases or to general hospitals serving the same population, for various diseases, excluding neoplasms and immunological diseases. The diseases of the hospital controls included infectious and parasitic diseases (16.7%), mental and nervous disorders (14.0%), circulatory diseases (8.3%), digestive diseases (8.2%), endocrine and metabolic diseases (6.5%), respiratory diseases (3.7%) and other, miscellaneous and unspecified non-neoplastic conditions (42.5%). Participation rate was 88% in cases, 81% in hospital controls and 52% in population controls. The study was approved by the relevant institutional ethics committees and informed consent was obtained from study subjects.

A standard questionnaire was developed and translated in the language of each country for trained interviewers to collect comparable information from study participants. It comprised questions about sociodemographic characteristics and lifestyle factors such as tobacco smoking and alcohol drinking, detailed occupational (see subsequently), residential and medical histories. It also contained questions on eye, skin and hair colour, skin sensitivity to the sun and sunlamp use for either sun tan or treatment and, if used, the total number of sessions. Regarding personal solar radiation exposure, participants from countries other than Germany were asked how many hours they would normally spend outdoors, not under any shade, between 9.00 am and 5.00 pm on working or school days, non-working days, weekends and vacations at age 10, 20, 30, 40, 50 and 60. This is an adaptation of the questionnaire used in the recent case–control study from Australia.[17] In Germany, the questionnaire was restricted to sun exposure during leisure time activities. A simplified questionnaire was used for 1320 participants who were asked for the hours they spent outdoors on working or school days and free days before age 20 and after that age; an additional 22 study participants had no data on personal solar radiation exposure. Sixty-seven individuals of non-European origin were excluded from the analyses of sun exposure because of their comparatively small numbers and generally much lower sun sensitivity.

Four measures of personal sun exposure were constructed for the statistical analysis: hours of exposure per day during free days and schooldays in childhood (<age 20) and during free days and working days in adulthood (age 20+), as the averages of reported hours of sun exposure at ages 10 and 20 (childhood) and at ages 30 and 40 (adulthood). Daily hours of sun exposure were then grouped into four categories: up to 1 h, 2–3 h, 4–6 h and >6 h. Sunlamp use was analysed in four categories as never, <10, 10–49 and 50 or more sessions.

Information on occupation was collected at interview for each job held for at least 1 year in a general questionnaire and in 14 questionnaires specific to jobs and industries likely to entail exposure to suspected lymphoma carcinogens (dry cleaners, farmers

or gardeners, textile workers, meat workers or slaughterers, chemical industry workers, painters, hairdressers, wood workers, printers, leather or tannery workers, teachers or others working with children, metal degreasers, health professionals and grain millers or bakers). Occupational exposures were assessed by local groups of industrial hygienists who participated in training workshops and regular validation exercises. The experts assessed the frequency and intensity of exposure to 66 agents and groups of agents, including natural and artificial UV radiation, and rated their level of confidence in their own assessment. Frequency of artificial UV exposure was categorized as 1–5, 5–30 and >30% of total working time and natural UV exposure as 10–40, 40–75 and >75% of outdoor working time. No assessment of intensity of exposure was made for natural UV exposure, and a semi-quantitative 3-point scale was constructed for artificial UV exposure (low, medium, high), but too few individuals were classified at high exposure to allow a meaningful analysis.

Two indices were constructed to model exposure duration. One calculated duration simply as the total number of years worked in an exposed occupation and the other totalled duration in years weighted by exposure frequency, based on the formula $\{\Sigma d_j f_j\}$ where d_j was the duration of exposure in a job and f_j was the frequency of the exposure in that job. Frequency was the midpoint of the appropriate frequency category, that is, 0.03, 0.175, 0.65 for artificial UV exposure and 0.25, 0.575 and 0.875 for natural UV exposure. Duration and weighted duration were examined in models that assigned no exposure as the reference category and divided exposure into tertiles of the distribution in controls.

We used a two-stage approach to calculate first the study-specific odds ratio (OR) and then to estimate pooled OR and their 95% CI for all NHL in dichotomous regression models and for NHL subtypes in polychotomous regression models.[25] In the first stage, each country was considered separately and analysed using country-specific exposure quartiles based on the distribution in controls. OR and 95% CI were calculated based on unconditional logistic regression modelling including adjustment for age (10-year intervals), sex, regional centres in each country, questionnaire type (full-length or simplified version) and education in three levels. In the analysis of sun and UV exposure, skin reaction to the sun was also adjusted for. We found only slight differences in estimates between matched and unmatched analyses for Germany and decided to use the larger numbers available in the unmatched approach. In the second stage, the adjusted study-specific OR and SE were combined in random effects models. Pooled random effects estimates were weighted by the inverse marginal variances: the sum of the individual study-specific variances and the variance of the random study effect (the extent of heterogeneity between studies). CI for the random effects estimates were based on the marginal variances, as a result of which CIs are wider when there is greater random study effects. We tested for statistical heterogeneity across the studies using a chi-square test and report the *P*-value for heterogeneity. All statistical tests were two-sided with a significance level of 0.05. We tested for interaction between sex and the sun sensitivity and sun exposure variables by including an interaction term for sex and exposure in the regression models in the first stage and testing the significance of the pooled interaction estimate. Stratified analyses were conducted according to the source of controls. Tests for trend across categories of quantitative variables were done by treating them as continuous variables and testing for significance according to Wald. All significance tests were two-sided. We applied Greenland's analysis of variance method[26] to the country-specific estimates calculated in the first stage of the two-stage method to detect the presence of systematic effects of sun exposure due to selection of hospital- or population-based controls. Our application of the method grouped countries by their control source and partitioned the total variance into between-group and within-group variance. We tested the impact of the different control sources on the heterogeneity of the country-specific estimates by a chi-square test of the between-countries variance.[26]

For sake of comparison with previous studies, the results are presented according to the traditional pathologic entities. However, an additional analysis was conducted according to the recent World Health Organization classification.[24]

Results

Selected characteristics of cases and controls are reported in Table 1. Fifty-five per cent of study subjects were men; Germany and Spain provided about 30% each of the total study population, while the other countries provided between 10% and 15% each. The control-to-case ratio ranged from 0.93 in France to 1.28 in Italy. As a result of the matching, the median age was very similar for all cases combined and for controls; as expected, it was lower for Hodgkin lymphoma cases than for NHL and multiple myeloma cases. The distribution of the cases by type of malignancy was as follows: NHL ($n=1518$), further classified as T-cell lymphoma ($n=125$), diffuse large B-cell ($n=448$), follicular lymphoma ($n=226$), chronic lymphocytic leukaemia/small lymphocytic lymphoma ($n=369$) and other and unspecified NHL types ($n=350$); Hodgkin lymphoma ($n=268$), and multiple myeloma ($n=242$).

Table 2 reports results for sun sensitivity characteristics. We found no association with eye colour and risk of NHL but a reduced risk of Hodgkin lymphoma (OR = 0.48, 95% CI 0.30–0.79) for black or dark brown eye colour, and an increased risk of multiple myeloma

Table 1 Selected characteristics of study subjects

Characteristics	All lymphoma	NHL	Hodgkin lymphoma	Multiple myeloma	Controls
Totals	2028	1518	268	242	2124
Country					
France	282 (14)	209 (14)	33 (12)	40 (17)	261 (12)
Germany	702 (35)	512 (34)	114 (43)	76 (31)	705 (33)
Ireland	200 (10)	140 (9)	33 (12)	27 (11)	206 (10)
Italy	262 (13)	222 (15)	24 (9)	16 (7)	336 (16)
Spain	582 (29)	435 (29)	64 (24)	83 (34)	616 (29)
Median age at diagnosis (range)	61 (17–89)	62 (18–89)	35 (17–80)	65 (31–89)	60 (17–96)
Sex					
Male	1135 (56)	857 (56)	138 (51)	140 (58)	1136 (53)
Female	893 (44)	661 (44)	130 (49)	102 (42)	988 (47)
Education					
Low	1034 (51)	809 (53)	88 (33)	137 (57)	1070 (50)
Medium	708 (35)	497 (33)	126 (47)	85 (35)	762 (36)
High	286 (14)	212 (14)	54 (20)	20 (8)	292 (14)

(OR 1.77, 95% CI 1.24–2.52) for hazel or green colour compared with blue, grey or mixed eye colour. There was no apparent association of any lymphatic neoplasm with skin colour. When compared with subjects with dark brown hair, subjects with red hair had an increased risk of NHL (OR 1.91, 95% CI 1.14–3.2) and specifically follicular lymphoma (OR 2.83, 95% CI 1.09–7.34), as well as multiple myeloma (OR 4.14, 95% CI 1.71–10.0). The risk of all NHL (OR for no suntan vs very brown 1.39, 95% CI 1.03–1.87, *P*-value of test for trend 0.01), and Hodgkin lymphoma (OR 2.35, 95% CI 0.94–5.87, *P*-value 0.02) increased for increasing skin sensitivity to the sun. A similar pattern was present for sensitivity at first exposure. There was evidence of an interaction between sex and sun sensitivity (several exposures) on the risk of Hodgkin lymphoma ($P = 0.02$): women experienced increasing OR for increasing sensitivity (*P*-value of test for trend <0.001), while such association was not present for men ($P = 0.87$)

Increased sun exposure in childhood (both during free days and school days) was not associated with the risk of other neoplasms included in the study (Table 3). Adult sun exposure during free days was associated with a reduced risk of diffuse large B-cell lymphoma (OR for highest vs lowest exposure quartile 0.62, 95% CI 0.44–0.87, *P*-value of test for trend 0.02): this pattern, however, was not evident for exposure during working days. The risk of multiple myeloma, on the other hand, was increased for adult sun exposure during free days (OR for highest vs lowest quartile 1.49, 95% CI 0.88–2.50, *P*-value of test for trend 0.10. No association was present with risk of other NHL types and of Hodgkin lymphoma. No heterogeneity by country was detected. Since questionnaires were used to assess sun exposure in childhood and adulthood, we conducted an additional analysis on the interaction between each of the variables listed in Table 3 and questionnaire type: for none was the interaction present.

Table 3 also reports results according to sun lamp use: the risk of all NHL decreased with increasing use of sun lamps (OR for 25+ times vs never 0.69, 95% CI 0.51–0.93, *P*-value of test for trend 0.004): this result is due to a reduced risk of diffuse large B-cell lymphoma (OR 0.63, 95% CI 0.38–1.03, *P*-value for test of trend 0.01) and, to a lesser extent, follicular lymphoma (OR 0.71, 95% CI 0.41–1.24, *P*-value for test of trend 0.36). No association was observed between sun lamp use and risk of Hodgkin lymphoma and multiple myeloma. No heterogeneity by country was detected (*P*-value 0.59).

Results for occupational UV exposure are reported in Table 4. Exposure to natural UV radiation was associated with a reduced risk of diffuse large B-cell lymphoma and follicular lymphoma, while no association was observed for other NHL types, Hodgkin lymphoma and multiple myeloma. There was no apparent association between occupational artificial UV radiation exposure and risk of any of the neoplasms under study, with the exception of a modest increase in risk of follicular lymphoma: the prevalence of long duration of exposure, however, was low. Restriction of the analysis to the assessments of occupational UV

Table 2 OR of lymphoma for indicators of sun sensitivity

		NHL													
	Controls		All NHL		T-cell lymphoma		Diffuse large B-cell lymphoma		Follicular lymphoma		Chronic lymphocytic leukaemia/small lymphocytic lymphoma		**Multiple myeloma**		**Hodgkin lymphoma**
	n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Eye colour															
Black, dark brown	585	430	1.04 (0.78–1.40)	39	1.06 (0.60–1.86)	121	0.90 (0.63–1.28)	59	1.29 (0.81–2.05)	108	1.15 (0.78–1.67)	57	1.07 (0.69–1.66)	48	0.48 (0.30–0.79)
Hazel green	777	526	0.98 (0.75–1.30)	37	0.66 (0.36–1.21)	159	0.92 (0.66–1.27)	81	1.19 (0.80–1.77)	134	1.14 (0.82–1.58)	106	1.77 (1.24–2.52)	109	0.94 (0.66–1.35)
Blue, grey, mix	758	555	Ref	46	Ref	167	Ref	85	Ref	126	Ref	77	Ref	111	Ref
P-value for linear trend			0.78		0.65		0.88		0.24		0.69		0.38		0.004
P-value for heterogeneity			0.08		0.66		0.33		0.97		0.15		0.26		0.72
Skin colour															
Dark olive	359	241	0.95 (0.71–1.27)	22	1.17 (0.68–2.01)	65	0.92 (0.55–1.54)	32	0.80 (0.51–1.25)	67	1.03 (0.73–1.47)	34	0.71 (0.46–1.10)	35	0.86 (0.55–1.35)
Light olive	715	534	1.14 (0.86–1.51)	43	1.40 (0.87–2.24)	177	1.36 (0.87–2.11)	85	0.99 (0.60–1.62)	119	0.98 (0.65–1.47)	72	0.82 (0.54–1.24)	81	0.79 (0.56–1.13)
White	1034	727	Ref	58	Ref	201	Ref	108	Ref	178	Ref	135	Ref	152	Ref
P-value for linear trend			0.83		0.37		0.75		0.30		0.79		0.32		0.24
P-value for heterogeneity			0.21		0.37		0.03		0.51		0.47		0.26		0.74
Hair colour															
Black	388	265	0.98 (0.71–1.34)	33	1.71 (0.64–4.57)	72	0.97 (0.69–1.36)	40	1.54 (0.96–2.49)	64	0.77 (0.55–1.10)	39	0.89 (0.57–1.38)	36	1.38 (0.83–2.28)
Dark brown	745	524	Ref	42	Ref	155	Ref	62	Ref	131	Ref	81	Ref	84	Ref
Light brown	635	452	1.01 (0.81–1.27)	31	0.93 (0.48–1.81)	139	1.22 (0.84–1.77)	70	1.50 (0.97–2.34)	109	0.93 (0.53–1.62)	80	0.90 (0.56–1.44)	105	1.91 (0.80–4.53)
Blond	310	222	1.01 (0.85–1.20)	14	0.96 (0.41–2.22)	71	1.03 (0.79–1.34)	45	1.21 (0.83–1.75)	54	1.02 (0.76–1.36)	30	1.22 (0.87–1.72)	36	1.67 (1.02–2.75)
Red	34	40	1.91 (1.14–3.22)	3	9.87 (1.72–56.63)	4	0.69 (0.23–2.10)	7	2.83 (1.09–7.34)	8	2.00 (0.80–4.97)	10	4.14 (1.71–10.0)	7	1.55 (0.53–4.51)
P-value for linear trend			0.26		0.78		0.46		0.31		0.17		0.48		0.16
P-value for heterogeneity			0.16		0.008		0.58		0.57		0.37		0.10		0.09

Skin reaction to sun (first exposure)																
Go brown	422	270	Ref	20	Ref	78	Ref	43	Ref	66	Ref	41	Ref	37	Ref	
Get mildly burnt	627	460	1.13 (0.92–1.40)	43	1.37 (0.66–2.83)	130	1.11 (0.79–1.56)	64	0.88 (0.57–1.37)	116	1.37 (0.96–1.97)	85	1.33 (0.81–2.18)	92	1.13 (0.62–2.04)	
Painful sunburn	755	547	1.21 (0.99–1.48)	44	1.12 (0.48–2.64)	169	1.31 (0.96–1.80)	85	1.05 (0.69–1.61)	127	1.38 (0.98–1.95)	74	1.22 (0.74–2.01)	106	1.13 (0.68–1.89)	
Severe sunburn	286	224	1.24 (0.96–1.59)	16	1.42 (0.66–3.07)	68	1.47 (0.96–2.26)	31	1.24 (0.72–2.12)	55	1.13 (0.73–1.74)	36	1.25 (0.75–2.09)	32	1.43 (0.77–2.67)	
P-value for linear trend			0.08		0.89		0.05		0.34		0.43		0.85		0.53	
P-value for heterogeneity			0.40		0.94		0.35		0.42		0.44		0.22		0.31	
Skin reaction to sun (several exposures)																
Very brown	616	391	Ref	35	Ref	108	Ref	64	Ref	107	Ref	58	Ref	65	Ref	
Moderately tanned	816	615	1.23 (1.04–1.46)	46	0.84 (0.33–2.19)	194	1.43 (1.09–1.87)	92	1.09 (0.76–1.55)	147	1.11 (0.83–1.48)	93	1.13 (0.78–1.62)	96	1.09 (0.58–2.06)	
Mildly tanned	495	365	1.21 (0.99–1.48)	29	1.05 (0.56–1.98)	105	1.33 (0.95–1.87)	51	1.09 (0.71–1.68)	83	1.04 (0.74–1.46)	62	1.25 (0.83–1.88)	84	1.81 (1.08–3.01)	
No suntan at all	149	126	1.39 (1.03–1.87)	12	1.69 (0.73–3.93)	38	1.71 (0.93–3.14)	14	1.89 (0.91–3.93)	28	1.18 (0.68–2.03)	24	1.53 (0.85–2.73)	22	2.35 (0.94–5.87)	
P-value for linear trend			0.01		0.58		0.13		0.70		0.78		0.18		0.02	
P-value for heterogeneity			0.60		0.16		0.07		0.15		0.65		0.96		0.18	

n, number of subjects; OR, odds ratio adjusted for age, sex, centre and education; CI, confidence interval.

Table 3 OR of lymphoma for indicators of personal UV radiation exposure

		NHL													
	Controls		All NHL		T-cell lymphoma		Diffuse large B-cell lymphoma		Follicular lymphoma		Chronic lymphocytic leukaemia/small lymphocytic lymphoma		**Multiple myeloma**		**Hodgkin lymphoma**	
	n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Free days during childhood															
1st Quartile	408	257	Ref	25	Ref	89	Ref	33	Ref	51	Ref	39	Ref	60	
2nd Quartile	414	280	1.06 (0.84–1.35)	20	0.75 (0.38–1.47)	82	0.87 (0.61–1.25)	46	1.72 (1.01–2.92)	68	1.36 (0.88–2.12)	50	1.07 (0.65–1.78)	57	0.71 (0.40–1.27)
3rd Quartile	529	356	1.12 (0.89–1.41)	26	0.66 (0.35–1.27)	89	0.76 (0.53–1.10)	54	1.29 (0.66–2.51)	99	1.65 (0.96–2.83)	49	0.83 (0.51–1.37)	62	0.66 (0.39–1.13)
4th Quartile	610	482	1.07 (0.81–1.43)	38	0.75 (0.40–1.40)	149	0.88 (0.60–1.28)	64	1.35 (0.80–2.26)	120	1.17 (0.70–1.97)	84	1.10 (0.68–1.78)	76	0.69 (0.32–1.48)
P-value for linear trend			0.51		0.40		0.93		0.49		0.31		0.91		0.71
P-value for heterogeneity			0.05		0.60		0.02		0.33		0.12		0.96		0.07
Schooldays during childhood															
1st Quartile	377	239	Ref	27	Ref	83	Ref	37	Ref	46	Ref	40	Ref	52	Ref
2nd Quartile	334	240	0.98 (0.74–1.31)	15	0.37 (0.16–0.84)	89	0.95 (0.64–1.39)	25	0.83 (0.44–1.55)	50	1.13 (0.65–1.95)	37	0.88 (0.51–1.52)	42	0.86 (0.50–1.47)
3rd Quartile	342	245	1.05 (0.81–1.36)	21	0.82 (0.42–1.61)	67	0.84 (0.57–1.24)	30	0.96 (0.54–1.71)	78	1.63 (0.82–3.26)	35	0.82 (0.48–1.42)	32	1.06 (0.59–1.89)
4th Quartile	286	235	1.01 (0.76–1.35)	24	0.83 (0.31–2.21)	52	0.71 (0.45–1.14)	24	0.90 (0.46–1.77)	79	1.44 (0.89–2.34)	47	1.22 (0.68–2.19)	27	1.30 (0.24–7.11)
P-value for linear trend			0.55		0.90		0.15		0.77		0.13		0.88		0.63
P-value for heterogeneity			0.99		0.04		0.94		0.49		0.11		0.30		0.006
Free days during adulthood															
1st Quartile	387	320	Ref	22	Ref	109	Ref	44	Ref	81	Ref	29	Ref	52	Ref
2nd Quartile	493	301	0.79 (0.63–0.98)	22	0.71 (0.35–1.43)	86	0.63 (0.45–0.88)	45	0.78 (0.42–1.46)	76	0.81 (0.56–1.18)	51	1.45 (0.79–2.68)	45	0.63 (0.31–1.29)
3rd Quartile	540	421	0.93 (0.75–1.16)	35	0.97 (0.52–1.82)	109	0.70 (0.50–0.97)	71	1.17 (0.75–1.84)	105	0.95 (0.67–1.36)	76	1.55 (0.95–2.55)	46	0.60 (0.37–1.00)
4th Quartile	483	341	0.76 (0.61–0.95)	27	0.69 (0.34–1.38)	97	0.62 (0.44–0.87)	45	0.78 (0.47–1.27)	90	0.76 (0.44–1.31)	66	1.49 (0.88–2.50)	48	0.75 (0.42–1.36)
P-value for linear trend			0.10		0.56		0.02		0.60		0.53		0.10		0.46
P-hetero			0.63		0.46		0.67		0.81		0.13		0.36		0.28

Workdays during adulthood																
1st Quartile	388	262	Ref	20	Ref	81	Ref	36	Ref	66	Ref	32	Ref	39	Ref	
2nd Quartile	318	275	1.21 (0.92–1.60)	24	1.16 (0.59–2.28)	90	1.28 (0.88–1.86)	36	1.25 (0.72–2.18)	69	1.22 (0.64–2.34)	48	1.69 (1.01–2.82)	41	1.52 (0.82–2.85)	
3rd Quartile	308	209	0.96 (0.74–1.24)	17	0.80 (0.32–1.95)	56	0.82 (0.55–1.23)	26	0.94 (0.44–1.99)	65	1.15 (0.75–1.75)	39	1.35 (0.79–2.30)	19	0.74 (0.38–1.44)	
4th Quartile	275	204	0.97 (0.73–1.29)	23	1.15 (0.53–2.50)	59	0.93 (0.60–1.43)	17	0.81 (0.37–1.77)	55	0.91 (0.47–1.73)	39	1.38 (0.77–2.50)	21	1.62 (0.38–6.95)	
P-value for linear trend			0.59		0.89		0.31		0.52		0.76		0.35		0.68	
P-value for heterogeneity			0.84		0.34		0.61		0.28		0.28		0.45		0.008	
Sunlamp use																
Never	1685	1281	Ref	100	Ref	387	Ref	178	Ref	323	Ref	206	Ref	189	Ref	
1–24 times	186	105	0.79 (0.59–1.04)	11	1.32 (0.64–2.74)	29	0.67 (0.43–1.06)	21	1.18 (0.68–2.04)	18	0.92 (0.53–1.59)	13	0.76 (0.41–1.41)	34	0.86 (0.53–1.39)	
25 times or more	180	95	0.69 (0.51–0.93)	8	1.86 (0.39–8.81)	25	0.63 (0.38–1.03)	21	0.71 (0.41–1.24)	20	0.99 (0.58–1.70)	16	1.10 (0.59–2.05)	42	0.93 (0.57–1.50)	
P-value for linear trend			0.004		0.97		0.01		0.36		0.80		0.74		0.82	
P-value for heterogeneity			0.61		0.58		0.71		0.27		0.73		0.82		0.99	

n, number of subjects; OR, odds ratio adjusted for age, sex, centre, education, skin reaction to sun (several exposures) and questionnaire type; CI, confidence interval.

Table 4 OR* of lymphoma for indicators of occupational exposure to UV radiation

		NHL													
	Controls		All NHL		T-cell lymphoma		Diffuse large B-cell lymphoma		Follicular lymphoma		Chronic lymphocytic leukaemia/small lymphocytic lymphoma		**Multiple myeloma**		**Hodgkin lymphoma**
	n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
UV natural															
Never	1320	931	Ref	68	Ref	316	Ref	160	Ref	194	Ref	136	Ref	191	Ref
Ever	756	562	1.02 (0.81–1.29)	52	1.23 (0.73–2.07)	128	0.72 (0.54–0.97)	61	0.79 (0.55–1.14)	171	1.22 (0.86–1.73)	100	1.03 (0.72–1.47)	76	0.99 (0.70–1.41)
P-value for heterogeneity			0.13		0.31		0.31		0.66		0.20		0.36		0.48
Duration (years)															
Never exposed	1320	931	Ref	68	Ref	316	Ref	160	Ref	194	Ref	136	Ref	191	Ref
1st Tertile	253	180	0.99 (0.79–1.25)	24	2.06 (1.14–3.74)	40	0.68 (0.46–0.99)	25	1.10 (0.66–1.83)	46	1.19 (0.80–1.78)	18	0.74 (0.37–1.47)	35	0.91 (0.58–1.44)
2nd Tertile	248	173	1.07 (0.69–1.66)	16	1.21 (0.65–2.28)	48	0.81 (0.56–1.17)	18	0.74 (0.42–1.29)	50	1.27 (0.65–2.47)	34	1.21 (0.77–1.91)	22	1.04 (0.50–2.15)
3rd Tertile	243	192	0.97 (0.73–1.30)	12	0.81 (0.40–1.65)	35	0.63 (0.37–1.04)	15	0.61 (0.33–1.11)	71	1.27 (0.89–1.82)	42	1.17 (0.76–1.82)	16	1.35 (0.67–2.70)
P-value for linear trend			0.82		0.73		0.13		0.04		0.26		0.47		0.94
P-value for heterogeneity			0.03		0.53		0.12		0.63		0.16		0.63		0.12
Weighted duration (years)															
Never exposed	1320	931	Ref	68	Ref	316	Ref	160	Ref	194	Ref	136	Ref	191	Ref
1st Tertile	261	176	0.92 (0.73–1.16)	23	1.56 (0.86–2.84)	38	0.62 (0.42–0.92)	26	1.05 (0.64–1.72)	44	1.08 (0.72–1.63)	19	0.76 (0.42–1.38)	35	0.84 (0.53–1.33)
2nd Tertile	235	168	1.00 (0.71–1.43)	14	1.40 (0.72–2.75)	44	0.82 (0.50–1.33)	18	0.80 (0.46–1.40)	51	1.22 (0.79–1.88)	34	1.28 (0.81–2.03)	18	0.84 (0.47–1.50)
3rd Tertile	248	199	1.08 (0.74–1.56)	15	1.14 (0.59–2.21)	39	0.69 (0.42–1.15)	14	0.57 (0.31–1.06)	72	1.36 (0.86–2.14)	41	1.13 (0.73–1.76)	20	1.62 (0.62–4.27)
P-value for linear trend			0.65		0.86		0.21		0.03		0.22		0.52		0.79
P-value for heterogeneity			0.02		0.22		0.06		0.71		0.10		0.65		0.09
UV artificial															
Never	1951	1384	Ref	112	Ref	418	Ref	203	Ref	339	Ref	222	Ref	254	Ref
Ever	125	109	1.30 (0.78–2.16)	8	0.98 (0.24–4.10)	26	1.14 (0.56–2.28)	18	1.58 (0.88–2.83)	26	1.29 (0.53–3.15)	14	1.06 (0.57–1.97)	13	0.82 (0.42–1.63)
P-value for heterogeneity			0.04		0.18		0.13		0.83		0.02		0.72		0.95

Duration (years)																
Never exposed	1951	1384	Ref	112	Ref	418	Ref	203	Ref	339	Ref	222	Ref	254	Ref	
⩽median	64	52	1.29 (0.67–2.49)	3	0.92 (0.27–3.19)	15	1.69 (0.65–4.42)	9	1.57 (0.73–3.37)	13	1.47 (0.39–5.59)	6	1.01 (0.41–2.48)	7	0.69 (0.29–1.66)	
>median	61	54	1.14 (0.77–1.70)	5	4.48 (1.39–14.37)	11	0.90 (0.45–1.79)	9	1.92 (0.85–4.31)	12	0.90 (0.45–1.78)	6	1.00 (0.39–2.55)	6	1.27 (0.46–3.50)	
P-value for linear trend			0.40		0.87		1.00		0.13		0.78		0.72		0.82	
P-value for heterogeneity			0.18		0.17		0.42		0.79		0.16		0.75		0.87	
Weighted duration (years)																
Never exposed	1951	1384	Ref	112	Ref	418	Ref	203	Ref	339	Ref	222	Ref	254	Ref	
⩽median	64	61	1.27 (0.86–1.88)	6	1.24 (0.50–3.11)	17	1.86 (0.33–10.69)	6	0.52 (0.15–1.79)	14	0.97 (0.30–3.15)	5	0.44 (0.17–1.18)	8	0.60 (0.48–0.74)	
>median	60	45	1.05 (0.58–1.89)	2	1.87 (0.38–9.14)	9	0.73 (0.34–1.59)	12	2.53 (1.23–5.23)	11	0.80 (0.39–1.66)	7	0.90 (0.39–2.10)	5	1.30 (0.43–3.95)	
P-value for linear trend			0.49		0.88		0.92		0.03		0.65		0.73		0.74	
P-value for heterogeneity			0.05		0.28		0.16		0.74		0.05		0.95		0.83	
Intensity																
Never exposed	1951	1384	Ref	112	Ref	418	Ref	203	Ref	339	Ref	222	Ref	254	Ref	
Low	43	49	1.81 (0.75–4.36)	3	1.42 (0.39–5.17)	7	0.85 (0.37–1.98)	7	1.96 (0.81–4.77)	12	1.43 (0.42–4.92)	5	1.49 (0.54–4.10)	4	0.53 (0.17–1.69)	
Medium	69	43	0.79 (0.53–1.19)	5	2.95 (0.98–8.90)	10	0.74 (0.36–1.53)	10	2.21 (1.00–4.84)	10	0.65 (0.22–1.91)	7	0.83 (0.36–1.92)	9	1.22 (0.54–2.76)	
High	13	16	1.74 (0.78–3.86)	0	0.98 (0.71–1.37)	8	4.96 (2.30–10.70)	1	0.29 (0.23–0.36)	4	0.89 (0.33–2.36)	1	0.47 (0.08–2.90)	0	0.54 (0.45–0.65)	
P-value for linear trend			0.51		0.88		0.57		0.12		0.89		0.97		0.94	
P-value for heterogeneity			0.24		0.22		0.24		0.70		0.14		0.72		0.92	

n, number of subjects; OR, odds ratio adjusted for age, sex, centre, education, skin reaction to sun (several exposures) and questionnaire type; CI, confidence interval.

Table 5 ORs of NHL for personal indicators of UV radiation exposure by type of controls

Study variable	OR (95% CI) Population based	Hospital based	*P*-hetero**
Free days childhood			
1st Quartile	Ref	Ref	
2nd Quartile	0.98 (0.71–1.35)	1.17 (0.82–1.66)	
3rd Quartile	1.22 (0.88–1.68)	1.02 (0.74–1.42)	
4th Quartile	1.31 (0.96–1.79)	0.87 (0.62–1.23)	
P-trend	0.21	0.95	0.39
School days childhood			
1st Quartile	Ref	Ref	
2nd Quartile	0.72 (0.42–1.23)	1.09 (0.80–1.49)	
3rd Quartile	0.93 (0.54–1.61)	1.09 (0.82–1.45)	
4th Quartile	1.01 (0.57–1.77)	1.01 (0.72–1.42)	
P-trend	0.64	0.68	0.85
Free days adulthood			
1st Quartile	Ref	Ref	
2nd Quartile	0.77 (0.57–1.05)	0.81 (0.58–1.11)	
3rd Quartile	0.83 (0.61–1.12)	1.05 (0.78–1.41)	
4th Quartile	0.78 (0.57–1.05)	0.75 (0.52–1.07)	
P-trend	0.18	0.32	0.88
Work days adulthood			
1st Quartile	Ref	Ref	
2nd Quartile	0.90 (0.53–1.55)	1.31 (0.98–1.77)	
3rd Quartile	1.01 (0.59–1.72)	0.94 (0.70–1.27)	
4th Quartile	1.02 (0.59–1.77)	0.95 (0.68–1.33)	
P-trend	0.83	0.45	0.57
Sunlamp use			
Never	Ref	Ref	
1–24 times	0.90 (0.63–1.29)	0.62 (0.39–0.99)	
25 times or more	0.73 (0.53–1.00)	0.49 (0.22–1.10)	
P-trend	0.06	0.01	0.15

OR adjusted for age, sex, centre, education, skin reaction to sun (several exposures) and questionnaire type; CI, confidence interval.
***P*-value for heterogeneity of trend effect between types of controls.

exposure made with high confidence by the experts resulted in risk estimates similar to those reported in Table 4.

Results of the analysis on personal UV radiation exposure stratified by type of controls are presented in Table 5. For none of the main exposure variables there was evidence of heterogeneity in the results according to this characteristic of the study.

The results of the analysis on personal UV radiation exposure and risk of B-cell NHL, an entity proposed by the recent World Health Organization classification[24] and encompassing diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma and unspecified B-cell lymphoma, are presented in Table 6. Since this group comprises the majority of NHLs, the results are very similar to those presented in Table 2 for NHL as a whole.

Discussion

This study adds evidence to the hypothesis of a protective effect of UV radiation on NHL risk, which is based on the results of recent case–control studies from

Table 6 ORs of B-cell lymphoma[a] for personal indicators of UV radiation exposure

Sun exposure	Controls	Cases	OR (95% CI)	*P*-trend	*P*-hetero**
Free days childhood					
1st Quartile	408	232	Ref		
2nd Quartile	414	260	1.11 (0.87–1.41)		
3rd Quartile	529	330	1.18 (0.93–1.50)		
4th Quartile	610	443	1.11 (0.84–1.46)	0.40	0.05
School days childhood					
1st Quartile	377	212	Ref		
2nd Quartile	334	225	1.06 (0.80–1.40)		
3rd Quartile	342	224	1.09 (0.84–1.42)		
4th Quartile	286	211	1.04 (0.78–1.41)	0.50	0.98
Free days adulthood					
1st Quartile	387	298	Ref		
2nd Quartile	493	279	0.79 (0.63–0.99)		
3rd Quartile	540	386	0.93 (0.75–1.16)		
4th Quartile	483	313	0.76 (0.60–0.96)	0.11	0.65
Work days adulthood					
1st Quartile	388	242	Ref		
2nd Quartile	318	251	1.21 (0.93–1.59)		
3rd Quartile	308	192	0.97 (0.74–1.26)		
4th Quartile	275	180	0.93 (0.70–1.25)	0.49	0.89
Sunlamp use					
Never	1685	1179	Ref		
1–24 times	186	94	0.75 (0.56–1.00)		
25 times or more	180	87	0.69 (0.51–0.93)	0.008	0.38

OR adjusted for age (10-year intervals), sex, centre, education, skin reaction to sun (several exposures) and questionnaire type; CI, confidence interval.
[a]Includes DLBCL, Follicular, CLL/SLL and B-cell NOS.
***P*-value for heterogeneity of trend effect between countries.

Australia,[18] Denmark and Sweden[19] and the United States,[20] as well as a pooled analysis that included these data.[21] This hypothesis does not necessarily contradict the evidence of a direct association between NHL and UV-related neoplasms such as melanoma, that has been found in ecological comparisons.[4,5] We have detected a relatively weak but consistent association between sensitivity to the carcinogenic effect of UV radiation on the skin and risk of lymphoma, and particularly diffuse large B-cell and follicular lymphoma, thus confirming the findings of recent studies from Australia[27] and Scandinavia[19] (we did not collect information on personal history of skin cancer, a variable that was also associated with increased lymphoma risk in these studies), as well as the pooled analysis.[21] The link between skin cancer and NHL can be real and explained by shared mechanisms, such as alterations in DNA repair or immunocompetence, different from the direct carcinogenic effect of UV radiation. While the aetiologic role of solar radiation on skin carcinogenesis (both melanoma and non-melanoma) has been established beyond doubt,[28] its mechanisms, primarily involving direct DNA damage,[29] might not be relevant to lymphomagenesis. A beneficial effect of UV radiation exposure in reducing cancer risk might be explained either by modulation of the immune system (e.g. a suppression of immunoresponse[3]), or by a protective effect exerted by vitamin D. A number of genes are known to be regulated by the active form of vitamin D, 1,25-dihydroxyvitamin D_3, including genes involved in the regulation of the cell cycle and humoral mechanisms.[30] Furthermore, 1,25-dihydroxyvitamin D_3 has been suggested to reduce proliferation on lymphoma cell lines.[31] The role of vitamin D in carcinogenesis is an area of active research and strong controversy,[32] and it is plausible that the effect depends on the target organ: in

the case of lymphoma, the evidence accumulated so far is compatible with the hypothesis of a protective effect.

Our results suggest that a protective effect of UV radiation, whatever its mechanism, might be particularly relevant for diffuse large B-cell lymphoma. The other studies addressing the risk of specific types of NHL identified an effect for all major B-cell lymphoma types,[19,20,21] as well as Hodgkin lymphoma.[19] Although broadly consistent with this previous evidence, our findings are limited by the relatively small number of cases of individual subtypes. The results on sun lamp use replicate those of a smaller study from the United States.[20]

This is the first study addressing the risk of multiple myeloma on the basis of personal UV exposure data: our results are consistent with an increased risk of this neoplasm for increasing exposure. A previous study of occupational UV exposure did not detect such an association, but the assessment of the exposure in this study was limited to a reclassification of job titles.[16] Little is known about the aetiology of multiple myeloma:[33] there are no environmental factors that have been definitely associated with it. However, an increased risk has been detected in several groups of workers employed in outdoor occupations, such as farmers and seamen.[33,34] Our results suggest that UV radiation might act via pathways similar to those involved in skin carcinogenesis, since the increased risk of myeloma was present for both variables related to skin sensitivity to sun and variable aimed to measure directly UV exposure. Clearly, our results need replication before any inference can be made on their possible aetiological significance.

Our study has a number of strengths over previous similar investigations. First, the assessment of sun sensitivity and UV radiation exposure, both personal and occupational, was based on a questionnaire that has been successfully used in studies of NHL and other malignancies,[18,35,36] and has been tested for reproducibility with good results.[37] Second, the large size of the study and the pathological verification of the cases made it possible to investigate the risk of major subtypes of NHL. Third, we included in the analysis also Hodgkin lymphoma and multiple myeloma. Finally, the rapid ascertainment of cases, the high response rate of cases and hospital controls, the central pathology review of a subset of cases and the fact that all interviews were done in person represent additional methodological strengths.

On the other hand, the relatively low response rates among population controls are a limitation of the study and could have introduced selection bias, if participation in the study was associated with determinants of UV radiation exposure (e.g. social class). The use of hospital controls in some of the centres is also a matter of concern since they might not represent the study base. However, diseases of controls included a broad range of conditions, unlikely to be linked to UV radiation. A comparison of results between centres using hospital or population controls (Table 5) did not reveal any heterogeneity for the variables linked to an increased or decreased risk of one of the malignancies under study; furthermore, any bias in the selection of controls would have equally affected the comparisons for all groups of cases, and would not have generated the pattern of results observed across different types of malignancies. Residual confounding by factors associated with the exposures under study (e.g. sun lamps) cannot be completely excluded.

Some misclassification of exposure is inevitable, and may be more prominent for circumstances of exposures more subject to recall errors (i.e. childhood rather than adult exposure), but this should have likely affected cases and controls in a comparable manner (non-differential misclassification, resulting in a general attenuation of risk estimates). In fact, it is unlikely that patients with lymphoma had reported their UV radiation exposure in a different way than controls (either over- or under-reporting), as the hypothesis of an association between UV radiation and lymphoma is not widespread. In any case, this bias would hardly have affected only selected types of lymphoma. Furthermore, occupational exposure to UV was not self-reported, but assessed by experts on the basis of the individuals' employment histories, and recall of sun lamp use, a circumstance of exposure associated with a decreased risk of diffuse large B-cell lymphoma and follicular lymphoma, may be more salient than everyday sun exposure, and thus recalled more accurately.

Our study adds to recently generated evidence that exposure to UV radiation might decrease the risk of some types of lymphoma. This is not in contradiction with the association between lymphoma and skin cancer (both melanoma and non-melanoma), as the pathways linking UV radiation to these malignancies might be different. These findings, however, do not contribute to the understanding of the reasons behind the increasing incidence of lymphoma that has been reported in many countries. Finally, we have also detected a direct association between UV radiation exposure and risk of myeloma, which deserves further investigation.

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Conflict of interest: None declared.

KEY MESSAGES

- This study supports the hypothesis that exposure to UV light might protect against development of NHL.
- The protective effect might be specific to diffuse large B-cell lymphoma.
- An association between exposure to UV light and increased risk of multiple myeloma was suggested.

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