

## Sun Exposure and Non-Hodgkin Lymphoma

Bruce K. Armstrong<sup>1,2</sup> and Anne Kricker<sup>2</sup>

<sup>1</sup>Sydney Cancer Centre, Royal Prince Alfred Hospital and <sup>2</sup>School of Public Health, The University of Sydney, Sydney, New South Wales, Australia

### Abstract

It was initially hypothesized that sun exposure might cause non-Hodgkin lymphoma (NHL) on the following grounds: its incidence was increasing in parallel with that of cutaneous melanoma; its risk was increased in those with a history of melanoma or other skin cancer; sun exposure causes immune suppression; and immunosuppression for other reasons is associated with an increased risk of NHL. The association of NHL with prior skin cancer has been found consistently in subsequent studies, but results of ecological analyses have only partially supported this hypothesis. Contrary to it, three recent studies of NHL in individuals found that risk decreased,

generally by 25% to 40%, across categories of increasing total or recreational, but not occupational, sun exposure. One study, thus far reported only in abstract, showed the opposite. Production of vitamin D from sun exposure offers a plausible mechanism for protection against NHL by sun exposure. A recent study has found a reduced risk of NHL in people with a high dietary intake of vitamin D. Results of additional studies in individuals and a planned original-data meta-analysis of case-control studies should help to resolve the present conflicting results on sun exposure and NHL. (Cancer Epidemiol Biomarkers Prev 2007;16(3):396–400)

### Introduction

Zheng et al. (1) first suggested that sun exposure might increase risk of non-Hodgkin lymphoma (NHL) on the following grounds: its incidence had increased in parallel with that of cutaneous melanoma in Connecticut from 1935 to 1939 to 1985 to 1988; risk of NHL had been reported to be increased in people with a history of skin cancer; sun exposure had been shown to have immune suppressant effects; and risk of NHL was increased in people with AIDS or receiving immune suppressant therapy. Support for this hypothesis was soon offered by Cartwright et al. (2) who reported a significant positive correlation between incidence of NHL and incidence of nonmelanocytic skin cancer in nine cancer registries worldwide that recorded both, and a weaker correlation between temporal trends in both.

With publication since 2004 of results in individuals that suggest that sun exposure might protect against NHL (3), a review of the relevant literature is timely.

were found in the bibliographies of relevant articles found in the initial search. Only studies dealing with NHL as a whole were reviewed; a small literature on UV radiation and cutaneous lymphoma has not been reviewed. Because of the brief communication format of this study, not all relevant studies are referred to.

### Results

**NHL Risk Higher with a History of Skin Cancer.** In 1995, Adami et al. (4) reported that the relative risk for NHL was 2.0 [95% confidence interval (95% CI), 1.7–2.4] in those with a prior Danish Cancer Registry record of nonmelanocytic skin cancer; it was rather less in those with a prior cutaneous melanoma (relative risk, 1.4; 95% CI, 1.1–1.7). These associations had been observed in some smaller, preceding studies and have been consistently found in subsequent similar studies (see, e.g., ref. 5), including a meta-analysis that found a relative risk of 2.01 (95% CI, 1.79–2.24) for NHL following melanoma (6). Although the risk for NHL is significantly increased following diagnosis of any cancer, it is particularly increased following UV-related cancers (7). Shared genetic or environmental risk factors, particularly sun exposure, might explain associations between skin cancer and NHL; it has also been suggested that persistent suppressor T-cell activity or some other immunologic change initiated by the first tumor might increase risk of the second, independently of any shared etiology (6).

**NHL Risk Varies with Ambient UV Irradiance.** In response to Adami et al.'s article, Newton pointed out that incidence of NHL fell with increasing measured ambient UV in six U.S. populations for which data on both NHL and UV were available, the opposite of what would be expected if exposure to the sun increased NHL risk (8). Similar results were reported for NHL mortality and estimated UV irradiance in the United States (9). Findings inconsistent with these, however, were reported more or less simultaneously: Bentham

### Materials and Methods

The National Center for Biotechnology Information PubMed online index of biomedical articles was searched for relevant publications using the following syntax: ("lymphoma/epidemiology" [MeSH Terms] OR "lymphoma/etiology" [MeSH Terms]) AND ("ultraviolet rays" [MeSH Terms] OR "sunlight" [MeSH Terms]). Additional informative publications

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**Requests for reprints:** Bruce Konrad Armstrong, Sydney Cancer Centre, Royal Prince Alfred Hospital, Missenden Road, Camperdown 2050, Sydney, New South Wales, Australia. E-mail: brucea@health.usyd.edu.au

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reported that incidence of NHL increased significantly with increasing UV irradiance in 59 counties of England and Wales (10), and McMichael and Giles reported a significant overall positive correlation of NHL incidence in 1978 to 1987, with estimated ambient solar UVB in 49 populations of European origin in Europe, North America, and Oceania (11).

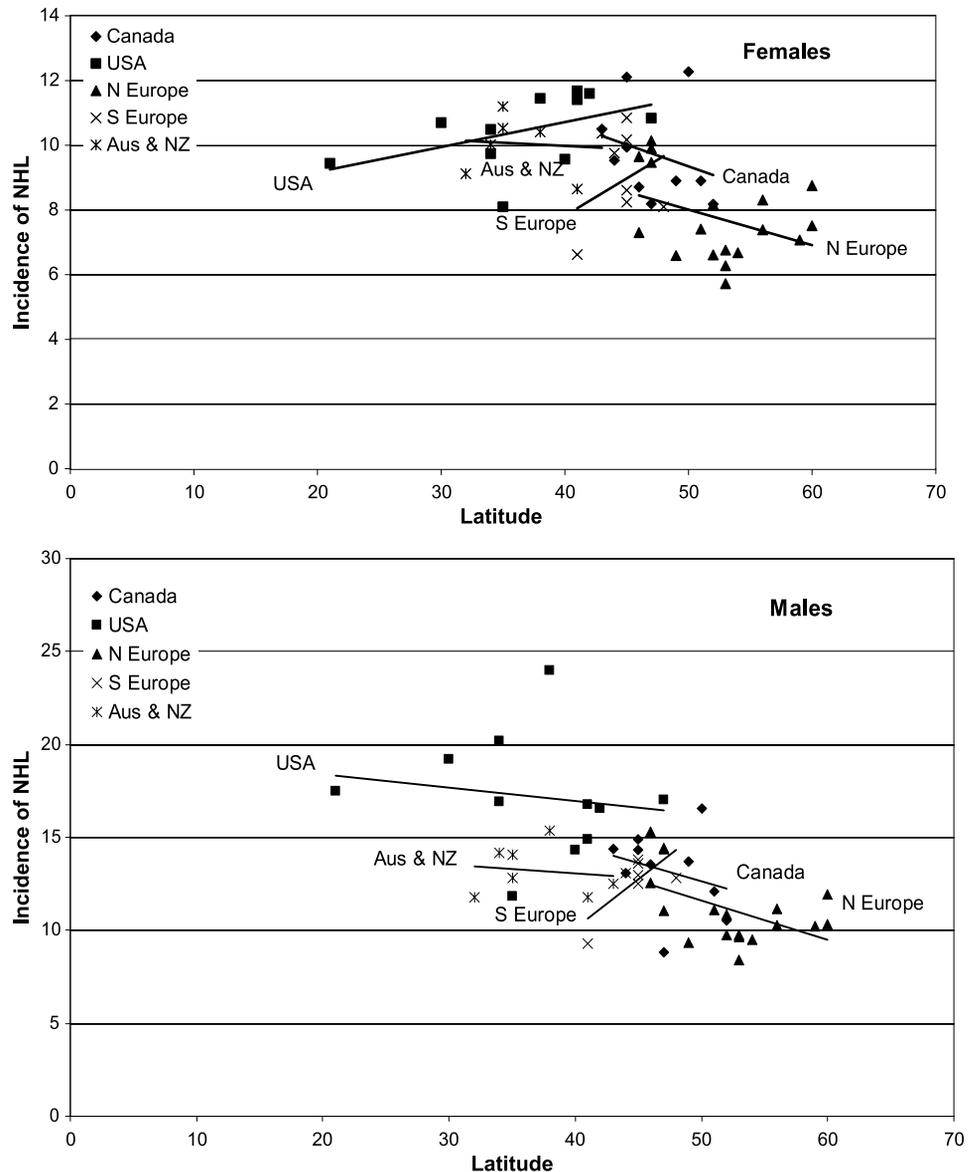
Figure 1 presents an up-to-date picture of these global geographic gradients based on data for 1993 to 1997 from 53 cancer registries with mainly European origin populations that had at least 500 incident cases of NHL in each sex in the period. Although an overall downtrend can be seen with increasing latitude (decreasing UV irradiance) in both sexes, this seems to be largely due to the relative positions of the United States (i.e., lower latitudes and higher NHL incidence rates) and Northern Europe (i.e., higher latitudes and lower NHL rates). The trends in NHL incidence with latitude varied among the five broad geographic regions shown. In females, uptrends and downtrends with latitude are more or less evenly balanced, whereas in males, there is a more, but not wholly, consistent downtrend with increasing latitude. It thus seems probable that ambient

UV irradiance is not the main determinant of these trends, if a determinant at all.

**NHL Risk Varies with Race and Migration.** McMichael and Giles (11) reported that NHL risk on migration to Australia, a region of high ambient UV, from the United Kingdom, a region of low ambient UV, showed a similar but less pronounced pattern to that of melanoma. That is, risk was higher in people born in Australia than in those resident in the United Kingdom and risk in migrants lay between the two. The age-standardized incidence of NHL in Blacks in the United States is from 59% to 100% of that in Whites living in the same geographic region, depending on registry and sex. This pattern too is similar to that for melanoma but much less marked (Blacks, 3-16% of corresponding rates in Whites; ref. 12).

**NHL Risk with Inferred Occupational Sun Exposure.** Several studies in the United States and Sweden have examined incidence or mortality of NHL in relation to occupational sun exposure, generally classified from the job title and only in men (13-16). We did a simple, fixed-effects meta-analysis of the results in men treating "low" and

**Figure 1.** Age-standardized (to World population) incidence of NHL plotted against latitude in 53 populations of mainly European origin (incidence data from ref. 26). Cancer registry populations included are Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, Quebec, Saskatchewan), United States (Los Angeles non-Hispanic White, San Francisco White, Connecticut White, Atlanta White, Hawaii White, Iowa, New Orleans White, Detroit White, New Mexico, Utah, Seattle), Northern Europe (Denmark, Finland, Germany Saarland, Norway, Sweden; Switzerland: Basel, Geneva, St Gall-Appenzell, Vaud, Zurich; The Netherlands Eindhoven; England: Mersey, North Western, Oxford, South Thames, West Midlands, Yorkshire; Scotland), Southern Europe (France; Bas-Rhin, Isere; Italy: Florence, Parma, Torino, Varese; Spain Zaragoza), Australia (New South Wales, South Australia, Tasmania, Victoria, Western Australia, Australian Capital Territory), and New Zealand.



## Sun Exposure and Non-Hodgkin Lymphoma

**Table 1. Sun sensitivity characteristics and NHL in the NSW, SCALE and NCI-SEER case-control studies (3, 18)**

| Sun sensitivity characteristics*                 | OR (95% CI) for highest exposure category |               |                  |
|--|---|---------------|------------------|
|  | NSW                                       | SCALE         | NCI-SEER         |
| Blue or gray eyes                                | 1.02 (0.79-1.31)                          |               |                  |
| Blue, gray, green, or "mix" eyes <sup>†</sup>    |   | 1.2 (1.1-1.4) | 0.54 (0.41-0.71) |
| Blonde, fair, or red hair                        | 0.89 (0.67-1.17)                          |               | —                |
| Blond or red hair                                |   | 1.0 (0.8-1.1) |                  |
| Very fair skin                                   | 1.44 (1.01-2.07)                          | —             |                  |
| Light complexion                                 |   |               | 0.75 (0.41-1.40) |
| Severe burn with blisters on acute sun exposure  | 1.53 (0.95-2.45)                          |               | 1.36 (0.63-2.94) |
| Always burns on acute sun exposure               |   | 1.0 (0.9-1.2) |                  |
| No tan or freckles only on repeated sun exposure | 1.70 (1.06-2.71)                          | —             | —                |
| Heavy facial freckling as a child                | 1.19 (0.88-1.60)                          | —             | —                |

\*Reference categories in order from top to bottom were - NSW: brown, dark brown, brown or olive, very brown, none; SCALE: brown or black, dark brown or black, seldom burns; NCI-SEER: dark brown, dark, no change; OR for "tan no sunburn" on acute exposure in NCI-SEER was 1.06 (0.53-2.14).

<sup>†</sup>This describes the SCALE category; NCI-SEER OR is for combination of blue and blue-green.

"indoor," "medium" and "mixed," and "high" and "outdoor" as equivalent and combining the second and third exposure categories of van Wijngaarden and Savitz (16) as medium and the fourth and fifth as high. Relative to 1 for low occupational sun exposure, the relative risk for medium exposure was 0.98 (95% CI, 0.94-1.01) and that for high was 0.92 (95% CI, 0.88-0.96).

**NHL Risk and Recalled Sun Sensitivity and Personal Sun Exposure.** Three case-control studies initiated in the late 1990s and early 2000s have tested the hypothesis that sun sensitivity or sun exposure alters NHL risk: Hughes et al. reported results from an Australian population (refs. 3, 17; the New South Wales or NSW study); Smedby et al. reported from a large study in Sweden and Denmark (the Scandinavian Lymphoma Etiology or SCALE study; ref. 18, 19); and Hartge et al. reported from a U.S. study (the National Cancer Institute/Surveillance, Epidemiology, and End Results or NCI-SEER study; ref. 20).

Only in the NCI-SEER study was there a strong association between a sun-sensitivity characteristic and NHL (Table 1);

risk was about 50% less in those with blue or blue-green eyes than in those with dark brown eyes. This result is statistically incompatible with weakly increased risks with roughly corresponding eye colors in the other two studies. The NSW study found increases in risk of about 50% for very fair skin, severe burn with blisters on acute sun exposure, and no tan or freckles only on repeated sun exposure, whereas the SCALE study found no increase in risk in people who always burn on acute sun exposure, and the NCI-SEER study reported a 25% reduction in risk with fair complexion, but with a wide confidence interval.

All three studies found significant inverse associations between NHL risk and sun exposure (Table 2). Risk of NHL fell significantly with total sun exposure in the NSW study (estimated from recall of usual daytime outdoor hours on working and nonworking days in a typical week in the warmer and cooler months in decade years of age from age 10 to 60), and there was a similar but weaker and nonsignificant trend in the NCI-SEER study estimated in a similar way in several different periods of life. The NSW study trend was due entirely to a strong trend with exposure on nonworking days (Table 2).

**Table 2. Sun exposure and NHL in the NSW and SCALE case-control studies (3, 18)**

| Sun exposure   | Exposure categories, OR (95% CI): NSW study |                  |                  |                  | <i>P</i> <sub>trend</sub> |
|--|---|------------------|------------------|------------------|---------------------------|
|  | 1st quarter                                 | 2nd quarter      | 3rd quarter      | 4th quarter      |                           |
| Total exposure   | 1   | 0.72 (0.53-0.98) | 0.66 (0.48-0.91) | 0.65 (0.46-0.91) | 0.01                      |
| Nonworking days exposure                                       | 1   | 0.83 (0.61-1.11) | 0.57 (0.42-0.79) | 0.47 (0.34-0.66) | 0.0001                    |
| Working days exposure  | 1   | 0.98 (0.73-1.33) | 0.91 (0.66-1.25) | 0.95 (0.68-1.33) | 0.68                      |
| Vacation exposure in warmer months*                            | 1   | 0.78 (0.57-1.05) | 0.81 (0.59-1.10) | 0.65 (0.47-0.91) | 0.02                      |
| Sun exposure   | Exposure categories, OR (95% CI)            |                  |                  |                  | <i>P</i> <sub>trend</sub> |
| <i>SCALE study</i>   |   |                  |                  |                  |                           |
| Sunbathing at age 20   | Never                                       | <1/wk            | 2-3/wk           | ≥4/wk            | 0.001                     |
|  | 1   | 0.8 (0.7-0.9)    | 0.7 (0.6-0.9)    | 0.7 (0.6-0.9)    |                           |
| Sunny vacations abroad   | Never                                       | 1-5              | 6-20             | >20              | <0.001                    |
|  | 1   | 1.0 (0.9-1.1)    | 0.9 (0.8-1.0)    | 0.7 (0.6-0.8)    |                           |
| Sunburns at age 20   | Never                                       | <1/y             | 1/y              | ≥2/y             | <0.001                    |
|  | 1   | 1.0 (0.9-1.2)    | 0.8 (0.7-0.9)    | 0.6 (0.5-0.8)    |                           |
| <i>NCI-SEER study</i>  |   |                  |                  |                  |                           |
| Hours per week in the midday sun in the last 10 y <sup>†</sup> | <7  | 7-13             | 14-27            | ≥28              | 0.07                      |
|  | 1   | 0.85 (0.62-1.18) | 0.75 (0.54-1.05) | 0.73 (0.46-1.15) |                           |
| History of blistering sunburns                                 | None  | 1                | 2-4              | ≥5               | 0.10                      |
|  | 1   | 0.87 (0.62-1.23) | 1.02 (0.72-1.46) | 0.68 (0.47-0.97) |                           |

\*Pattern for vacations in cooler months was similar but more consistently downwards and with a smaller *P*.

<sup>†</sup>Results were also presented for hours per week in the midday sun during teens, during twenties, and during thirties. The results were similar with ORs trending down to 0.75, 0.75, and 0.78 with ≥28 h of exposure, and *P*s are somewhat higher.

Apparently, protective effects of recreational or intermittent sun exposure are also indicated by results of the NSW and SCALE studies for vacation sun exposure: the SCALE study for sunbathing at 20 years of age and the SCALE and NCI studies for sunburn (Table 2). Neither exposure on working days (Table 2) nor exposure in all jobs held from 15 years of age (data not shown) was significantly associated with NHL risk in the NSW study. Risk of NHL in the SCALE study was increased slightly but significantly with occupational sun exposure [odds ratio (OR), 1.1; 95% CI, 1.0-1.2]. The NCI-SEER study found an inverse association with increasing ambient UV at all places of residence (OR, 0.76; 95% CI, 0.50-1.15; per 50 Robertson-Berger units increase in UV; ref. 20) as did the NSW study, with an OR of 0.76 (95% CI, 0.45-1.26) for the highest quarter of estimated lifetime average annual solar UVB irradiance,<sup>3</sup> but neither was statistically significant. The apparent protective effect of sun exposure in the NSW study was greater in women than men and with exposure in early life, but the statistical significance of these apparent differences was not tested formally. Sun exposure effects in the NCI-SEER study were reported to be similar between the sexes and with different ages at exposure.

Results of analyses of effects of sun exposure in another case-control study of NHL have been reported in abstract only. Increased risks of NHL were reported for the highest category of time spent in strong sunlight between 9 a.m. and 3 p.m. in summer (OR, 1.7; 95% CI, 1.2-2.5) and with having an outdoor occupation (OR, 1.8; 95% CI, 1.0-3.5). No protective effects of sun exposure were observed (21).

## Discussion

Ecological evidence on the association between ambient UV irradiance and risk of NHL provides weak support for a causal rather than a protective relationship. Although incidence of NHL has increased in parallel with that of melanoma, for which the evidence of a causal connection to sun exposure is strong (19), factors other than a shared cause could produce such parallel trends. Studies of incidence by area of residence have produced conflicting patterns. Although increasing risk with migration from an area of low to one of high ambient UV is consistent with a causal effect of sun exposure, there is limited evidence of this pattern, and other explanations for it are possible, including selection for migration and health service factors that lead to differences in probability of diagnosis between the two areas. Ethnic differentials in risk in the United States are also compatible with a causal effect, but lifestyle and health service access differences are possible alternative explanations for them.

The evidence for a positive relationship between risk of skin cancer and risk of NHL is much more consistent than the evidence for a positive relationship between ambient UV and risk of NHL. An inference of causation from this association, however, is quite indirect. Other explanations are possible, but none have been proven or ruled out.

The data on individual sun exposure and risk of NHL are more consistent with a protective than a causal effect of sun exposure. There is, though, inconsistency in this evidence too. Specific occupational studies suggest a weak protective effect of sun exposure, but this has not been observed in studies that have included measures of both occupational and recreational

sun exposure. Although recreational sun exposure was significantly protective in two studies, one incompletely reported study suggests the opposite. Moreover, there have been limited attempts thus far to rule out confounding as an explanation for the apparently protective associations. The SCALE results were adjusted for occupational exposure to pesticides, smoking, body mass, and history of autoimmune disorders, which have been reported as associated with NHL, but other possible confounders, such as diet, physical activity, and hormone use, and reproductive variables in women (the NSW association was stronger in women than men) have not been addressed. It would be wise, therefore, to reserve judgement on the current evidence for protective effects of recreational sun exposure until more results from studies in individuals are available, and possible confounding has been more thoroughly considered.

Is there any mechanism whereby sun exposure might protect against NHL? There is: vitamin D, the main source of which (said to be as much as 90% ref. 22) is cutaneous synthesis of the pro-vitamin under the influence of incident UVB radiation. There is some limited evidence that vitamin D can induce regression of low-grade NHL (23), and it has been shown to have antiproliferative and pro-differentiating effects in lymphoma cell lines, although at above physiologic concentrations (24). A recent study found a significant 40% reduction in risk of NHL from the lowest to the highest third of dietary intake of vitamin D (25). There was little evidence of this association, however, in the NCI-SEER study (20). Any certainty as to it must probably await results from studies of serum vitamin D and NHL nested in one or more of the large cohort studies.

As yet, there is inconsistent evidence for either a causal effect of sun exposure for, or a protective effect against, NHL. There are plausible biological mechanisms for either. In addition, if there is a protective effect, as three of four case-control studies suggest, it may not be large. For example, in the NCI-SEER data, 65% of controls had  $\geq 7$  h a week of sun exposure in the preceding 10 years, and the OR of NHL for this exposure was 0.78, which suggests a prevented fraction of 14%. There are complete but not yet published studies available, and there is an InterLymph<sup>4</sup> initiative to pool their results with those that have been published already. The statistical power available from these studies, thorough consideration of confounding, and future possibilities of studying gene and environment interactions may help to reach a more certain position on sun exposure and NHL.

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<sup>3</sup> Unpublished data.

<sup>4</sup> <http://epi.grants.cancer.gov/InterLymph/>

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