An association between cutaneous melanoma and non-Hodgkin’s lymphoma: pooled analysis of published data with a review

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Background: Several epidemiological studies have suggested an association between cutaneous melanoma and non-Hodgkin’s lymphoma.

Methods: We pooled the data from seven cohort studies and calculated the risk of secondary occurrence of cutaneous melanoma after non-Hodgkin’s lymphoma, and of non-Hodgkin’s lymphoma subsequent to the occurrence of cutaneous melanoma.

Results: There were 137,612 patients with primary non-Hodgkin’s lymphoma and 109,532 patients with primary cutaneous melanoma. We found a statistically significant increased risk of non-Hodgkin’s lymphoma among cutaneous melanoma survivors (standardised incidence ratio (SIR) 2.01, 95% confidence interval (CI) 1.79–2.24) and cutaneous melanoma among non-Hodgkin’s lymphoma survivors (SIR 1.41, 95% CI 1.26–1.58).

Conclusion: Our study confirmed an association between cutaneous melanoma and non-Hodgkin’s lymphoma occurring in the same patient indicative of a need to examine further the role of the common risk factors.

Key words: association, cutaneous melanoma, non-Hodgkin’s lymphoma

Introduction

The incidences of cutaneous melanoma and non-Hodgkin’s lymphoma have increased over the past several decades in all parts of the world. However, the rate of increase has been greater for cutaneous melanoma. In the last two decades the incidence of non-Hodgkin’s lymphoma has almost doubled, increasing at an average rate of 3%–4% per year, while the incidence rate for cutaneous melanoma has more than trebled in the same period with an annual increase rate of 3%–7% [1, 2]. The sharp increase in cutaneous melanoma has been considered to be due to sun exposure [3], whereas the increase in non-Hodgkin’s lymphoma has remained unexplained. Several large population-based epidemiological studies have furthermore suggested an association between melanoma and lymphoproliferative malignancies in individual patients (particularly non-Hodgkin’s lymphoma and chronic lymphatic leukaemia) [4]. Patients with lymphoid neoplasia were reported to have an increased risk of developing skin cancers and, vice versa, an increased risk of developing lymphoproliferative malignancy has been reported in patients with skin cancers [5]. This interesting possible association between the two tumours is of interest in terms of understanding their aetiology, which is likely to be multifactorial.

This study examines the occurrence of cutaneous melanoma and non-Hodgkin’s lymphoma in the same patient. We pooled the data from several studies and calculated the risk of secondary occurrence of cutaneous melanoma after non-Hodgkin’s lymphoma, and of non-Hodgkin’s lymphoma subsequent to the occurrence of cutaneous melanoma.

Methods

The aim was to identify all relevant papers evaluating an association between cutaneous melanoma and non-Hodgkin’s lymphoma available for review by September 2004.

Inclusion criteria

All studies that met the following criteria were included: cohort studies examining an association between cutaneous melanoma and non-Hodgkin’s lymphoma; cohorts comprising patients registered with cutaneous melanoma under the 7th revision of the International Classification of Diseases (ICD-7) code 190 and patients with non-Hodgkin’s lymphoma under ICD-7 codes 200 and 202; patients with an index cancer (first primary tumour) who were followed through the population-based data set to identify a subsequent cancer (second primary tumour). The standardised incidence ratio (SIR) of cutaneous melanoma following non-Hodgkin’s lymphoma and/or the SIR of non-Hodgkin’s lymphoma following cutaneous melanoma was determined. The SIR was defined as the ratio of the observed to expected number of cases.
Search strategy
A sensitive electronic search of Medline (from 1966 to September 2004) and Embase (1974 to September 2004) was performed to identify all published articles. The recommended Cochrane Collaboration search strategy with MeSH headings ‘melanoma’ and ‘non-Hodgkin’s lymphoma’ including all subheadings was applied. The references of all relevant papers found in the search were reviewed to identify other eligible studies not found through the computerised database searching. Where possible, the authors of the studies were contacted to verify the data and obtain additional information. No language restrictions were applied.

Data extraction
The following data were extracted from each included study: total number of patients with index cancer (first primary cutaneous melanoma and/or first primary non-Hodgkin’s lymphoma), gender distribution of the cohort, mean age at the diagnosis of the primary tumour, number of person-years of follow-up, median years of follow-up, number of observed and expected cases of second primary malignancy, SIR with 95% confidence interval (CI).

Statistical analysis
In studying the pairs of tumours, two relevant statistics are the SIR of cutaneous melanoma following non-Hodgkin’s lymphoma (SIRCMLNHL) and/or the SIR of non-Hodgkin’s lymphoma following cutaneous melanoma (SIRNLCMLM). The data from individual studies were combined and an analysis was performed calculating pooled SIRs with 95% CI. SIR was calculated as the ratio of observed to expected number of cases. The 95% CI was estimated assuming that the observed number of cases followed a Poisson distribution. In evaluating the SIR of the two malignancies, a benchmark for the interpretation of two observed SIRs was the hypothesis that the SIRCMLNHL is equal to the SIRNLCMLM [6].

The analysis was performed using the Confidence Interval Analysis software (BMJ Bookshop, London, UK).

Results
Ten retrospective cohort studies assessing an association between cutaneous melanoma and non-Hodgkin’s lymphoma published in 12 papers were retrieved [7–18]. Seven studies published in eight papers fulfilled our inclusion criteria [7, 8, 10–12, 14, 15, 18]. Three studies published in four papers [9, 13, 16, 17] were excluded from our analysis. Two excluded studies were conducted in Sweden: one study used the data from the Swedish Family Cancer Register [9] while one used the data from the Swedish Regional Cancer Register (Stockholm-Gotland) [13]. These two studies were excluded in order to avoid overlapping of the data with the included study with a higher number of enrolled patients [12]. One study conducted in Denmark and published in two papers [16, 17] was excluded because authors reported the incidence of multiple cancers in patients from Denmark in the period from 1943 to 1980. One included study already covered a longer period including a higher number of patients with longer follow-up (1943–1989) [12].

Four included studies were conducted in Europe: one study used the data from the Scottish National Cancer Register [7], one study used the data from the Cancer Registries of the Swiss Cantons of Vaud and Neuchatel [11], one study used the data from the Danish and Swedish Cancer Registries [12] and another used the data from the Finish Cancer Registry [18]. Two studies were conducted in the US: one study used the data from nine SEER (Surveillance, Epidemiology and End Results) Cancer Registries [8], another study published in two papers used the data from the Connecticut Tumor Registry [14, 15]. One study was conducted in Australia using the data from the New South Wales Central Cancer Registry [10]. This study has reported only the data on the second primary cutaneous melanoma following an initial diagnosis of primary non-Hodgkin’s lymphoma.

We contacted the authors to obtain additional data from the included studies but no further information was provided.

Characteristics of the patients with first primary non-Hodgkin’s lymphoma and patients with first primary cutaneous melanoma are presented in Tables 1 and 2, respectively.

The data on the number of observed and expected cases with subsequent melanoma, and SIRs of melanoma after an initial diagnosis of primary non-Hodgkin’s lymphoma are given in Table 3. The data on the number of observed and expected cases with subsequent primary non-Hodgkin’s lymphoma, and SIRs of primary non-Hodgkin’s lymphoma after

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Men n (%)</th>
<th>Women n (%)</th>
<th>Person-years of follow-up</th>
<th>Mean age at diagnosis (years)</th>
<th>Median follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKenna et al. [23]</td>
<td>2003</td>
<td>13 857</td>
<td>6760 (48.8)</td>
<td>7097 (51.2)</td>
<td>44 999</td>
<td>67.0\a</td>
<td>–</td>
</tr>
<tr>
<td>Goggins et al. [8]</td>
<td>2001</td>
<td>62 597</td>
<td>33 459 (53.5)</td>
<td>29 138 (46.5)</td>
<td>121 288</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brennan et al. [10]</td>
<td>2000</td>
<td>12 452</td>
<td>6724 (54.0)</td>
<td>5728 (46.0)</td>
<td>54 308</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Levi et al. [11]</td>
<td>1996</td>
<td>17 67</td>
<td>962 (54.4)</td>
<td>805 (45.6)</td>
<td>74 888</td>
<td>63.5</td>
<td>4.2\b</td>
</tr>
<tr>
<td>Adami et al. [12]</td>
<td>1995</td>
<td>34 641</td>
<td>19 219 (55.5)</td>
<td>15 422 (44.5)</td>
<td>114 423</td>
<td>63.0</td>
<td>3.3\c</td>
</tr>
<tr>
<td>Greene et al. [14]</td>
<td>1985</td>
<td>6734</td>
<td>3539 (52.6)</td>
<td>3195 (47.4)</td>
<td>27 231</td>
<td>58</td>
<td>4.0</td>
</tr>
<tr>
<td>Teppo et al. [18]</td>
<td>1985</td>
<td>5564</td>
<td>3057 (54.9)</td>
<td>2507 (45.1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\aMedian.
\bMean.
\n, number of patients; –, not reported.
an initial diagnosis of primary melanoma from four included studies are presented in Table 4.

In a pooled analysis combining the data from seven cohort studies examining the incidence of primary cutaneous melanoma after primary non-Hodgkin’s lymphoma a total of 137,612 patients (73,720 men and 63,892 women, 53.6% and 46.4%, respectively) were included. There were 310 observed cases of cutaneous melanoma compared with 154.47 expected cases. Pooled SIR was 2.01 (95% CI 1.79–2.24).

In all, 109,532 patients (52,869 men and 56,663 women, 48.3% and 51.7%, respectively) were registered with first primary cutaneous melanoma in a pooled analysis combining the data from six studies examining the incidence of primary non-Hodgkin’s lymphoma after primary cutaneous melanoma. There were 296 observed cases of non-Hodgkin’s lymphoma compared with 209.53 expected cases. Pooled SIR was 1.41 (95% CI 1.26–1.58).

Results from the pooled analysis are presented in Table 3 and Table 4. It seems that the SIRCM/NHL and SIRNHL/CM are of a similar magnitude, which may confirm that the results are grossly consistent with the equivalence model. The fact that the confidence intervals do not overlap is not evidence of the lack of equality between SIRCM/NHL and SIRNHL/CM, rather the similarity of their exceptional magnitude.

In the analysis of the data aggregated by gender, it emerges that although both SIRCM/NHL and SIRNHL/CM are statistically significant in both sexes, they are higher for males than for females.

Three of the included studies [7, 8, 12] showed that the relative risk of cutaneous melanoma following diagnosis of non-Hodgkin’s lymphoma and, vice versa, the relative risk of non-Hodgkin’s lymphoma following diagnosis of cutaneous melanoma, were higher in the first 3 years following the diagnosis of the first primary tumour (Table 5). Other studies did not have the data to establish the relative risk of the occurrence of the second primary tumour in relationship with time.

**Discussion**

The incidence of cutaneous melanoma and non-Hodgkin’s lymphoma has increased substantially in many countries over recent decades. This study has shown, under fairly general assumptions about the prevalences of the common risk factors and their influences on the incidence rates of cutaneous melanoma and non-Hodgkin’s lymphoma, that the SIRCM/NHL and SIRNHL/CM are similar. Thus, our pooled analysis has confirmed an increased risk of cutaneous melanoma following a diagnosis of non-Hodgkin’s lymphoma and, vice versa, for
non-Hodgkin’s lymphoma following a diagnosis of cutaneous melanoma.

The equivalence model used in this study predicts the SIRs on the basis of known relative risks of the common risk factors and their population prevalences. However, an aetiological link between cutaneous melanoma and non-Hodgkin’s lymphoma is still not proven. Several mechanisms could be responsible for the association between cutaneous melanoma and non-Hodgkin’s lymphoma.

One possible explanation for this relationship might be a shared environmental cause for both tumours. Exposure to sunlight is established as the major environmental cause of melanoma. There is also clearly an interaction between exposures and heredity, in that CDKN2A gene penetrance in melanoma families is higher in Australia than in Europe [19], and inheritance of variants in the MC1R gene, which governs hair colour, tendency to sunburn and freckling, is a common cause of genetic predisposition to melanoma [20]. However, several studies have found that gene mutations (BRAF mutations) are significantly more common in melanoma arising in sun exposed sites in contract to melanoma arising in non-exposed sun sites [21, 22]. Further research on gene–environment interactions is required to elucidate the relationship between distinct genetic alterations and risk factors and behavioural patterns.

In addition to its mutagenic effects, UV radiation impairs the immune system both systemically and locally in the skin [23, 24]. UVB light (UV light 270–320 nm) has the capacity to damage the cutaneous immune system by the alteration of the antigen-presenting activity of cells in the skin and draining lymph nodes, decreasing the contact hypersensitivity response and decreasing the activity of T-cells [25, 26].

There is some evidence that UV exposure might also be an aetiological factor for non-Hodgkin’s lymphoma, although results from the studies evaluating the association between the incidence of non-Hodgkin’s lymphoma and the level of solar radiation are conflicting. A study using the data presented in the Atlas of Cancer Incidence in England and Wales found that the incidence of the non-Hodgkin’s lymphoma in 59 counties of England and Wales for the period 1968–1985 was positively associated with the level of UV radiation ($P = 0.004$) [27]. If sun exposure is important in the aetiology of non-Hodgkin’s lymphoma then skin colour may have an effect. The data collected by the SEER Program of the National Cancer Institute showed that in the period from 1978 to 1995 among the 60 057 patients diagnosed with non-Hodgkin’s lymphoma, total incidence (per 100 000 person-years) was 17.1 and 11.5 among white males and females, respectively, and 12.6 and 7.4 among black males and females, respectively [28]. There is, therefore, some weak support for the theory that sunlight may have a role

### Table 4. SIRs of the second primary non-Hodgkin’s lymphoma after an initial diagnosis of the first primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall</th>
<th>Overall</th>
<th>Overall</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>SIR with 95% CI</td>
<td>Obs</td>
</tr>
<tr>
<td>McKenna et al. [23]</td>
<td>18</td>
<td>12.2</td>
<td>1.48 (0.87–2.33)</td>
<td>9</td>
</tr>
<tr>
<td>Goggins et al. [8]</td>
<td>198</td>
<td>139</td>
<td>1.42 (1.26–1.60)</td>
<td>124</td>
</tr>
<tr>
<td>Levi et al. [11]</td>
<td>4</td>
<td>2</td>
<td>2.00 (0.55–5.12)</td>
<td>NR</td>
</tr>
<tr>
<td>Adami et al. [12]</td>
<td>67</td>
<td>49.1</td>
<td>1.36 (1.06–1.73)</td>
<td>31</td>
</tr>
<tr>
<td>Greene et al. [14]</td>
<td>3</td>
<td>5.3</td>
<td>0.57 (0.15–1.46)</td>
<td>2</td>
</tr>
<tr>
<td>Teppo et al. [18]</td>
<td>6</td>
<td>1.93</td>
<td>3.11 (1.14–6.77)</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>296</td>
<td>209.53</td>
<td>1.41 (1.26–1.58)</td>
<td>170</td>
</tr>
</tbody>
</table>

Obs, observed number of cases; Exp, expected number of cases; SIR, standardised incidence ratio; CI, confidence interval; NR, not reported.

### Table 5. SIRs according to the time from the diagnosis of the first primary tumour

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>&lt;3 years</th>
<th>&gt;3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>SIR with 95% CI</td>
</tr>
<tr>
<td>McKenna et al. [23]</td>
<td>4</td>
<td>2.6</td>
<td>2.31 (1.01–4.56)</td>
</tr>
<tr>
<td>Goggins et al. [8]</td>
<td>10</td>
<td>3.6</td>
<td>2.78 (1.51–4.71)</td>
</tr>
<tr>
<td>Adami et al. [12]</td>
<td>34</td>
<td>12.2</td>
<td>3.53 (2.69–4.55)</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>48.9</td>
<td>2.19 (1.85–2.57)</td>
</tr>
</tbody>
</table>

Obs, observed number of cases; Exp, expected number of cases; SIR, standardised incidence ratio; CI, confidence interval.
in causing non-Hodgkin’s lymphoma. Looking at the subtypes of non-Hodgkin’s lymphoma, however, black people demonstrated a much higher incidence than whites for peripheral T-cell non-Hodgkin’s lymphoma, while the incidence of the follicular non-Hodgkin’s lymphoma was two to three times greater among whites than among blacks. In contrast, a study from the US observing six geographical areas over a 5-year period failed to find a significant association between non-Hodgkin’s lymphoma and UV radiation [29]. The results from the recently conducted study in Sweden did not support a causal relationship between non-Hodgkin’s lymphoma and UV radiation [30]. Furthermore, a case–control study conducted in Australia found an inverse association between non-Hodgkin’s lymphoma and UV radiation, suggesting that there is increasing evidence that vitamin D protects against cancer, making UV-mediated synthesis of vitamin D a plausible mechanism whereby sun exposure might protect against non-Hodgkin’s lymphoma [31].

Chronic immunosuppression is suggested as a risk factor for the development of both cutaneous melanoma and non-Hodgkin’s lymphoma [23]. The increased risk of cutaneous melanoma after non-Hodgkin’s lymphoma could arise from immunodeficiency as a result of the disease itself or the drugs used to treat it. Cytotoxic chemotherapy has an immunosuppressive effect and could explain the increased risk of a subsequent cutaneous melanoma among patients with non-Hodgkin’s lymphoma treated with chemotherapy [32]. Also, it is known that patients with non-Hodgkin’s lymphoma have different immunological disorders that may also elevate the risk for the development of cutaneous melanoma in the absence of any treatment effect. Although the SIRCM/NHL and SIR_{NHL/CNM} are similar, there is a slightly higher SIR_{NHL/CNM}, which may support the hypothesis that chemotherapy regimens in patients with primary non-Hodgkin’s lymphoma may cause subsequent primary cutaneous melanoma (SIR_{CM/NHL} is higher than SIR_{NHL/CNM}) since surgery is the main treatment for patients with non-metastatic cutaneous melanoma rather than chemotherapy [4].

There is a hypothesis that the aetiologic link between cutaneous melanoma and non-Hodgkin’s lymphoma can be explained by immunodeficiency mechanisms mediated by the tumour itself. It has been demonstrated that in patients with cutaneous melanoma, persistent suppressor T-cell activity appears after the surgical removal of the tumour, while the same activity has been detected in long-term survivors with lymphoma [33, 34].

The association of melanoma and non-Hodgkin’s lymphoma in a significant number of patients might suggest a hereditary susceptibility to both, although there are some data from Utah that lymphoma is less hereditary than melanoma [35]. One study evaluated familial aggregation of non-Hodgkin’s lymphoma with other cancers and found that the risk of non-Hodgkin’s lymphoma was elevated in relatives of non-Hodgkin’s lymphoma cases while evaluation of family history of other cancers showed modest evidence for an increased risk of melanoma of the skin [36]. The most common germline mutations that predispose to melanoma occur in the CDKN2A gene, but there are no data to suggest that CDKN2A mutation carriers are at increased risk of lymphoma. Less common germline mutations in the CDK4 gene or at the CDKN2A locus but coding for p14ARF [37, 38] underlie susceptibility in other families. More recently a fourth putative susceptibility gene was proposed in a linkage study at 1p22 [39]. It is possible that mutations in one of these genes, or indeed in other genes, may explain susceptibility to both melanoma and non-Hodgkin’s lymphoma but there are no data to support or refute this view at present.

Since the association between cutaneous melanoma and non-Hodgkin’s lymphoma appears to be more pronounced in recent years it has been suggested that the increase in the occurrence of either cutaneous melanoma or non-Hodgkin’s lymphoma after the other initial tumour, is partially due to the improvements in clinical surveillance and awareness as well as the improvements in cancer registration [5]. Our data showed that the short-term incidence is higher than the long-term incidence of the cutaneous melanoma following non-Hodgkin’s lymphoma and, vice versa, non-Hodgkin’s lymphoma following cutaneous melanoma. This observation may provide the evidence that the incidence rates are influenced by ascertainment bias (systematic distortion in measuring the true frequency of a phenomenon due to the difference in surveillance) caused by increased surveillance and careful clinical check-up of patients with recently diagnosed malignancy.

Our pooled analysis confirmed an association between cutaneous melanoma and non-Hodgkin’s lymphoma and an increased risk of cutaneous melanoma following non-Hodgkin’s lymphoma and vice versa. However, our data did not provide information on specific aetiological risk factors and their influence on patients. Thus, further research is necessary to elucidate the role of different common aetiological factors responsible for this association. In addition, an evaluation of the diagnostic bias and its influence on the cancer incidence rates is required.

References

7. McKenna DB, Stockton D, Brewster DH, Doherty VR. Evidence for an association between cutaneous melanoma and lymphoid