Abstract

Although thus far no occupational agents have been classified as established causes of non-Hodgkin lymphoma (NHL) by the IARC Monograph program. Therefore, the fraction of NHL attributable to occupation is, strictly speaking, zero. However, a number of jobs and industries have been suggested as entailing an increased risk of NHL. In particular, reviews and meta-analyses (1) have associated the risk of NHL with employment as farmer (2), teacher (3), dry cleaner, meat worker, printer, and wood worker. Except for dry cleaners, where the risk for NHL is ascribed to trichloroethylene exposure (covered in an accompanying study in CEBP), this review describes the results of key studies; new or updated meta-analyses are done. In addition, there are a number of other jobs and industries that have been suggested to entail an increased risk of NHL, including metal workers, painters, electrical engineers, and health care workers (4-6). However, the database for these jobs is very limited, and they are not reviewed in detail.

Materials and Methods

Articles on NHL in relation to farming, teaching, wood working, printing and typesetting, and employment in the meat industry were searched for in the MEDLINE database. The search started for articles published after the meta-analysis for NHL risk among farmers by Khuder et al. (2) and among teachers after the meta-analysis by Baker et al. (3) and ended on August 1, 2006 for all occupations.

Studies were excluded from the meta-analyses when (a) the disease was not limited to NHL or subtypes, (b) risk estimates were calculated for specific exposures and no overall risk was estimated for the occupation, (c) risk estimates were stratified by years of employment in the industry, and (d) risk estimates for the specific occupations were not provided, but only for related or grouped occupations.

After selecting the groups of studies for the specific occupations, a series of meta- and sensitivity analyses was conducted. Heterogeneity among study-specific relative risks (RR; odds ratios in case-control studies and standardized mortality or incidence ratios in cohort studies) was tested using Cochran Q statistics. If statistically significant between-study heterogeneity was detected, a random-effects model was used to obtain the summary risk ratio and SE (7), in contrast to a fixed-effects model if the Q statistics test revealed homogeneity within the group of studies. Possible publication bias was assessed using Begg’s funnel plots and associated test and Egger’s test (8, 9).

Results

Results of the meta-analyses are reported in Table 1. Results of the studies included in the meta-analyses are summarized in Supplementary Tables S2 to S7.
Farming. An increased risk of NHL among farmers has been reported in several publications. Khuder et al. (2) did a meta-analysis of 36 studies, which resulted in an overall RR of 1.10 [95% confidence interval (95% CI), 1.03-1.19]. The RR was higher among men than women in studies conducted in the United States more than other countries and in case-control studies than cohort studies. There was strong heterogeneity in the risk estimates of the different studies, which may reflect both differences in study design (e.g., classification of NHL and sources of bias) and differences in exposure circumstances (e.g., exposure to pesticides or viruses).

Twenty-six additional studies published after the meta-analysis were identified. After exclusion of six studies (10-15) that did not match the inclusion criteria, 11 studies (6, 16-25), providing a total of 14 risk estimates, were added to the 36 studies from the 1998 meta-analysis (Supplementary Table S2). Four studies reported an association with NHL; seven reported no association; and none reported an inverse association. Results for employment in farming of specific crops and livestock breeding were analyzed separately: four risk estimates for crop farming (5, 26-28) and six (4, 5, 23, 26-28) for animal breeding (Supplementary Table S3). Only one of the studies on crop farming reported an association with NHL, whereas four of six studies on animal breeding reported an association with NHL.

Diagnostic analyses did not indicate the presence of publication bias, but there was strong heterogeneity (P < 0.01) in RR estimates among the different studies in all three meta-analyses (Table 1). Implementation of random effects models yielded a combined RR for farming of 1.11 (95% CI, 1.05-1.17), which was similar to the estimate from the meta-analysis by Khuder et al. (2). The suggestion of a concentration of the risk in animal breeding (RR, 1.31; 95% CI, 1.08-1.60) rather than crop farming (RR, 0.96; 95% CI, 0.83-1.09) points towards a viral rather than chemical etiology, although farmers involved in animal breeding may also be exposed to organic chemicals such as insecticides.

The evidence for an association of NHL with duration of employment as farmer was weak and often contradictory (17-29). The analyses of the three main NHL types revealed a higher risk of small lymphocytic leukemia/chronic lymphocytic lymphoma (RR, 5.0; 95% CI, 2.9-8.8) than of follicular lymphoma (RR, 1.3; 95% CI, 0.8-2.0) and diffuse lymphoma (RR, 1.2; 95% CI, 0.8-1.7; ref. 6). More specifically, an increased risk of small lymphocytic leukemia has been associated with livestock farming (RR, 5.81; 95% CI, 2.01-16.8; ref. 4). A subsequent analysis of archival biopsy material available for 182 cases resulted in an increased farming-related RR for cases positives for the t(14;18) translocation (RR, 1.4; 95% CI, 0.9-2.3) but not for cases negative for the translocation (RR, 1.0; 95% CI, 0.8-1.4; ref. 22).

Overall, the available evidence supports the hypothesis of a weak association between farming and NHL risk. Although the quantitative summary estimate of the strength of the association is uncertain given the heterogeneity in exposure circumstances, it is unlikely that the excess risk in farmers is higher than 10% to 15%.

Teachers. An association between employment as a teacher and increased risk of NHL has been suggested in several epidemiologic studies. In a review of 13 studies published in 1999, Baker et al. provided a summary RR of 1.36 (95% CI, 1.13-1.62; ref. 3). Although most of the studies were small in size, and because the risk estimates suffered from random error, these additional results supported the hypothesis of an association between employment as teacher and increased NHL risk.

Five studies (5, 6, 17, 19, 28) of school teachers published after the meta-analysis were identified (Supplementary Table S4), of which three reported an association with NHL. These five new studies were analyzed together with the 13 studies included in the meta-analysis (Table 1). Diagnostic analyses suggested that similar to the results from the initial meta-analysis, publication bias could not be ruled out, although graphical analysis of the funnel plot did not suggest any directional bias. The RRs showed considerable heterogeneity between studies. The combined RR estimated using the random-effects model was 1.47 (95% CI, 1.34-1.61), showing that the inclusion of the more recent studies increased the estimate for the summary RR compared with the meta-analysis by Baker et al. (3). No statistically significant differences were found between teachers in primary or secondary education (6, 17), nor between teachers in theoretical subjects, teachers of music, arts and crafts, or headmasters and principals (5).

Although these results support an association between teaching and elevated risk for NHL, evidence of publication bias might have inflated the actual summary RR, and large heterogeneity was present in the RRs from the individual studies. Nonetheless, the association with employment as a teacher would support the hypothesis of a viral etiology of NHL.

Meat Workers. Employment in the meat industry has been associated with increased risk of NHL since the early studies in New Zealand abattoir workers (32). Thirteen studies were identified that addressed risk of NHL among meat workers, including butchers and meat-processing, meat-packing, and abattoir workers (Supplementary Table S5). In three studies, an association with NHL was found, of which one showed an inverse association between risk and working as a butcher. Five studies (33-37) were excluded from the meta-analysis because they did not fit the inclusion criteria. Diagnostic analyses did not suggest the presence of publication bias, but the risk estimates showed strong heterogeneity among the studies (6, 23, 28, 38-43).

No overall association was detected between employment in the meat industry and NHL, with a summary RR of 0.99

Table 1. Results of meta-analyses on NHL risk and employment in selected occupations

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No. studies</th>
<th>Q statistic (P)</th>
<th>RR (95% CI)</th>
<th>Test for publication bias (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Begg’s test</td>
</tr>
<tr>
<td>Farming</td>
<td>50</td>
<td>&lt;0.001</td>
<td>1.11 (1.05-1.17)</td>
<td>0.18</td>
</tr>
<tr>
<td>Crop farming</td>
<td>4</td>
<td>&lt;0.001</td>
<td>0.96 (0.83-1.09)</td>
<td>0.46</td>
</tr>
<tr>
<td>Livestock</td>
<td>6</td>
<td>&lt;0.001</td>
<td>1.31 (1.08-1.60)</td>
<td>0.71</td>
</tr>
<tr>
<td>Meat workers</td>
<td>9</td>
<td>&lt;0.001</td>
<td>0.99 (0.77-1.29)</td>
<td>0.81</td>
</tr>
<tr>
<td>Teachers</td>
<td>19</td>
<td>&lt;0.001</td>
<td>1.47 (1.34-1.61)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Printers</td>
<td>6</td>
<td>0.563</td>
<td>1.86 (1.37-2.52)</td>
<td>0.54</td>
</tr>
<tr>
<td>Wood workers</td>
<td>11</td>
<td>0.211</td>
<td>1.15 (1.00-1.31)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

NOTE: Summary RR based on fixed-effects model if P of Q statistics is >0.05, based on random-effects models otherwise.
likely candidates (52). Present in the printing industry, with organic solvents being association, if real, can be explained by exposure to chemicals than for small cell lymphocytic leukemia (RR, 1.2; 95% CI, 0.66-2.10), large cell lymphoma (RR, 0.6; 95% CI, 0.36-0.96), or diffuse lymphoma (RR, 0.5; 95% CI, 0.1-3.9; ref. 41). Because exposure circumstances included were highly heterogeneous, which was reflected in large heterogeneity in RR between studies, it is premature to decide on the presence or absence of risk of NHL among meat workers.

Wood Workers. Occupations in the wood industry are very diverse and range from sawmill operators and forestry workers to paper pulp workers and carpenters. Fourteen studies were identified that assessed employment in these industries and risk of NHL. Three studies (41, 44, 45) were excluded from the meta-analysis, resulting in 11 studies (4, 5, 17, 19, 24, 26, 36, 46-49), with 23 risk estimates for different occupational groups within the wood processing industry (Supplementary Table S6). Increased risk of NHL was found in several of these studies; diagnostic analyses provided evidence of publication bias, and visual analysis of the funnel plot showed a skewed pattern with an absence of smaller null studies. However, despite the differences in exposure circumstances, the risk estimates from the different studies were relatively homogeneous (PQ = 0.21), and a summary RR of 1.15 (95% CI, 1.00-1.31) was estimated using a fixed-effects model (Table 1). Nonetheless, taking into account that the summary RR might be inflated because of publication bias, these results suggest that any association between employment in the wood industry and risk of NHL is likely to be weak.

Workers in the Printing Industry. Only a relatively limited number of studies have been conducted to address the association between NHL and employment in the printing industry. Eight studies were identified, of which seven were included in the meta-analysis (refs. 4, 5, 19, 24, 29, 36, 50; Supplementary Table S7). One study (51) was excluded because it assessed exposure to printing ink in relation to NHL instead of employment in the printing industry. These studies were relatively small, but significant associations with NHL risk were found in some of them. In particular, the study by Mester et al. (29) suggested that risk might be higher for follicular lymphoma than for other types, and that it increases with duration of employment as a printer.

The risk estimates from the different studies did not show any significant heterogeneity, and no evidence of publication bias was found; the summary RR of NHL for employment in the printing industry was 1.86 (95% CI, 1.37-2.52). This association, if real, can be explained by exposure to chemicals present in the printing industry, with organic solvents being likely candidates (52).

Discussion

The meta-analyses described in this review are based on a literature search for studies on NHL and occupations in MEDLINE only and should therefore not be regarded as complete systematic reviews of the published and unpublished literature. Nonetheless, these meta-analyses provide an overview of key studies addressing employment in specific occupations and industries and risk for NHL.

The summary RRs presented in the review suggest an increased risk for NHL among farmers (especially animal breeders), teachers, and workers in the printing industry. Nonetheless, for no job or industry is there, at present, conclusive evidence of a causal association. This might be due to methodologic problems in studying the link between NHL risk and occupation, including heterogeneity of disease, heterogeneity of exposure circumstances (i.e., the same job entailing exposure to different agents in different regions and periods), and low statistical power, in particular for NHL subtypes. Despite these methodologic problems, however, these results suggest that it is unlikely that occupation represents a major risk factor for NHL in most populations.

Further research on jobs and industries possibly associated with NHL risk might provide clues on possible causal agents, as in the case of trichloroethylene among dry cleaners. Future studies on NHL and occupation should have sufficient statistical power to analyze etiologically relevant NHL subtypes. They should also include state-of-the-art exposure assessment technologies, including biomarker-based assessment, and aim to identify susceptible subgroups. These goals can be best attained within the framework or large-scale, international collaborative projects, such as the InterLymph collaboration.²

References


² http://epi.grants.cancer.gov/InterLymph/