CEBP Focus: Update on Lymphoma

Occupation and the Risk of Non-Hodgkin Lymphoma

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Abstract

Although thus far no occupational agents have been classified as established causes of non-Hodgkin lymphoma (NHL), employment as a farmer, teacher, dry cleaner, meat worker, printer, or wood worker has been associated with elevated risk in the peer-reviewed literature. We conducted several meta-analyses to assess risk in these occupations and industries from articles published in MEDLINE up to August 1, 2006. The summary risk estimates suggest a homogeneous excess risk for NHL among workers in the printing industry [relative risk (RR), 1.86; 95% confidence interval (95% CI), 1.37-2.52] and wood workers (RR, 1.15; 95% CI, 1.00-1.31). Considerable heterogeneity but elevated risks were found for farmers (RR, 1.11; 95% CI, 1.05-1.17), especially in animal husbandry (RR, 1.31; 95% CI, 1.08-1.60), and teaching (RR, 1.47; 95% CI, 1.34-1.61). An increased risk was absent for employment in the meat processing industry (RR, 0.99; 95% CI, 0.77-1.29). These results suggest that although excess risk is found for employment in the printing industry, wood processing industry, teaching, and farming, it is unlikely that occupation represents a major risk factor for NHL in most populations. At present, no conclusive evidence of causal relations between occupations and increased NHL risk exists; this can be ascribed to methodologic problems in studying the link between NHL risk and occupation, including heterogeneity of disease and exposure circumstances and low statistical power. Implementing state-of-the-art exposure assessment technologies, including biomarker-based assessment, and aiming to identify susceptible subgroups can increase the statistical power enough to analyze etiologically relevant NHL subtypes and provide clues on possible causal agents in future studies. These goals can be best attained within the framework of large-scale, international collaborative projects. (Cancer Epidemiol Biomarkers Prev 2007;16(3):369–72)

Introduction

No occupational agents have been classified as established causes of non-Hodgkin lymphoma (NHL) by the IARC Monograph program.[1] 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.

Received 12/15/06; accepted 12/20/06.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi:10.1158/1055-9965.EPI-06-1055

[1] http://monographs.iarc.fr/

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

Occupation	No. studies	*Q* statistic (*P*)	RR (95% CI)	Test for publication bias (*P*)	
				Begg's test	Egger's test
Farming	50	<0.001	1.11 (1.05-1.17)	0.18	0.77
Crop farming	4	<0.001	0.96 (0.83-1.09)	0.46	0.60
Livestock	6	<0.001	1.31 (1.08-1.60)	0.71	0.45
Meat workers	9	<0.001	0.99 (0.77-1.29)	0.81	0.77
Teachers	19	<0.001	1.47 (1.34-1.61)	<0.05	<0.05
Printers	6	0.563	1.86 (1.37-2.52)	0.54	0.24
Wood workers	11	0.211	1.15 (1.00-1.31)	0.08	0.02

NOTE: Summary RR based on fixed-effects model if *P* of *Q* statistics is >0.05, based on random-effects models otherwise.

Farming. An increased risk of NHL among farmers has been reported in several populations. 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 risk 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, 29-31). 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 nor 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

(95% CI, 0.77-1.29; Table 1). Analyses of subtypes of NHL suggest that the risk may be higher for follicular lymphoma [RR, 1.6; 95% CI, 0.99-2.60 (41) and RR, 4.6; 95% CI, 1.5-15.0 (6)] 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 (P_Q = 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]

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

References

1. Descatha A, Jenebian A, Conso F, Ameille J. Occupational exposures and haematological malignancies: overview on human recent data. Cancer Causes Control 2005;16:939–53.
2. Khuder SA, Schaub EA, Keller-Byrne J. Meta-analyses of non-Hodgkin lymphoma and farming. Scand J Work Environ Health 1998;24:255–61.
3. Baker P, Inskip H, Coggon D. Lymphatic and hematopoietic cancer in teachers. Scand J Work Environ Health 1999;25:5–17.
4. Band PR, Le ND, Fang R, Gallagher R. Identification of occupational cancer risks in British Columbia: a population-based case-control study of 769 cases of non-Hodgkin lymphoma analyzed by histopathology subtypes. J Occup Environ Med 2004;46:479–89.
5. Cano MI, Pollan M. non-Hodgkin lymphomas and occupation in Sweden. Int Arch Occup Environ Health 2001;74:443–9.
6. Zheng, T, Blair A, Zhang Y, Weisenburger DD, Zahm SH. Occupation and risk of non-Hodgkin lymphoma and chronic lymphocytic leukemia. J Occup Environ Med 2002;44:469–74.
7. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1987;7:177–88.
8. Dear K, Begg C. An approach to assessing publication bias prior to performing a meta-analysis. Stat Sci 1992;7:237–45.
9. Egger M, Davey S, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
10. Chiu BCH, Weisenburger DD, Zahm SH, et al. Agricultural pesticide use, familial cancer, and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2004;13:525–31.
11. Fontana A, Picoco C, Masala G, Prastaro C, Vineis P. Incidence rates of lymphomas and environmental measurements of phenoxy herbicides: ecological analysis and case-control study. Arch Environ Health 1998;53:384–7.
12. Keller-Byrne J, Khuder SA, Schaub EA, McAfee O. A meta-analysis of non-Hodgkin lymphoma among farmers in the Central United States. Am J Ind Med 1997;31:442–4.
13. Miligi L, Seniori Costantini A, Bolejack V, et al. Non-Hodgkin lymphoma, leukemia, and exposures in agriculture: results from the Italian Multicenter Case-Control Study. Am J Ind Med 2003;44:627–36.
14. Mills PK, Yang R, Riordan D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. Cancer Causes Control 2005;16:823–30.
15. Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. J Occup Environ Med 2001;43:641–9.
16. Baris D, Zahm SH, Cantor KP, Blair A. Agricultural use of DDT and risk of non-Hodgkin lymphoma: pooled analysis of three case-control studies in the United States. J Occup Environ Med 1998;55:522–7.
17. Miligi L, Seniori Costantini A, Crosignani P, et al. Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. Am J Ind Med 1999;36:60–9.
18. Settimi L, Comba P, Carrieri P, et al. Cancer risk among female agricultural workers: a multi-center case-control study. Am J Ind Med 1999;36:135–41.
19. Seniori Costantini A, Miligi L, Kriebel D, et al. A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. Epidemiology 2001;12:78–87.

20. Waddell BL, Zahm SH, Baris D, et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin lymphoma among male farmers (United States). Cancer Causes Control 2001;12:509–17.
21. Fabbro-Peray P, Daures JP, Rossi JF. Environmental risk factors for non-Hodgkin lymphoma: a population-based case-control study in Languedoc-Roussillon, France. Cancer Causes Control 2001;12:201–12.
22. Schroeder JC, Olshan AF, Baric R, et al. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin lymphoma. Epidemiology 2001;12:701–9.
23. Fritschi L, Johnson KC, Kliewer EV, Fry R, and the Canadian Cancer Registries Epidemiology Research Group. Animal-related occupations and the risk of leukemia, myeloma, and non-Hodgkin lymphoma in Canada. Cancer Causes Control 2002;13:563–71.
24. Dryver E, Brandt L, Kauppinen T, Olsson H. Occupational exposures and non-Hodgkin lymphoma in Southern Sweden. Int J Occup Environ Health 2004;10:13–21.
25. Kelleher C, Newell J, MacDonagh-White C, et al. Incidence and occupational pattern of leukemias, lymphomas, and testicular tumours in western Ireland over an 11 year period. J Epidemiol Community Health 1998;52:651–6.
26. Amadori D, Nanni O, Falcini F, et al. Chronic lymphocytic leukemias and non-Hodgkin lymphomas by histological type in farming-animal breeding workers: a population case-control study based on job titles. Occup Environ Med 1995;52:374–9.
27. Lee E, Burnett CA, Lalich N, Cameron LL, Sestito JP. Proportionate mortality of crop and livestock farmers in the United States, 1984-1993. Am J Ind Med 2002;42:410–20.
28. Svec MA, Ward MH, Dosemeci M, Checkoway H, De Roos AJ. Risk of lymphatic or haematopoietic cancer mortality with occupational exposure to animals and the public. Occup Environ Med 2005;62:726–35.
29. Mester B, Nieters A, Deeg E, Elsner G, Becker N, Seidler A. Occupation and malignant lymphoma: a population based case control study in Germany. Occup Environ Med 2006;63:17–26.
30. Kato I, Watanabe-Meserve H, Koenig KL, et al. Pesticide product use and risk of non-Hodgkin lymphoma in women. Environ Health Perspect 2004;112:1275–81.
31. McDuffie HH, Pahwa P, Spinelli JJ, et al. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin lymphoma (NHL). Am J Ind Med 2002;Suppl 2:54–61.
32. Pearce N, Smith AH, Reif JS. Increased risks of soft tissue sarcoma, malignant lymphoma, and acute myeloid leukemia in abattoir workers. Am J Ind Med 1988;14:63–72.
33. Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA. Non-Hodgkin lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: a case-control study. Br J Ind Med 1986;43:75–83.
34. Johnson ES. Cancer mortality among workers in the meat department of supermarkets. Occup Environ Med 1994;51:541–7.
35. Johnson ES, Shorter C, Rider B, Jiles R. Mortality from cancer and other diseases in poultry slaughtering/processing plants. Int J Epidemiol 1997;26:1142–50.
36. Metayer C, Johnson ES, Rice JC. Nested case-control study of tumors of the hemopoietic and lymphatic systems among workers in the meat industry. Am J Epidemiol 1998;147:727–38.
37. Blair A, Linos A, Stewart PA, et al. Am J Ind Med 1993;23:301–12.
38. Pearce NE, Sheppard RA, Smith AH, Teague CA. Non-Hodgkin lymphoma and farming: an expanded case-control study. Int J Cancer 1987;39:155–61.
39. Reif JS, Pearce NE, Fraser J. Cancer risks among New Zealand meat workers. Scand J Work Environ Health 1989;15:24–9.
40. Coggon D, Pannett B, Pippard EC, Winter PD. Lung cancer in the meat industry. Br J Ind Med 1989;46:188–91.
41. Tatham L, Tolbert P, Kjeldsberg C. Occupational risk factors for subgroups of non-Hodgkin lymphoma. Epidemiology 1997;8:551–8.
42. Boffetta P, Gridley G, Gustavsson P, Brennan P, Blair A. Employment as butcher and cancer risk in a record-linkage study from Sweden. Cancer Causes Control 2000;11:627–33.
43. Besson H, Banks R, Boffetta P. Cancer mortality among butchers: a 24-state death certificate study. J Occup Environ Med 2006;48:289–93.
44. Mao Y, Hu J, Ugnat AM, White K for the Canadian Cancer Registries Epidemiology Research Group. Ann Oncol 2000;11:S69–73.
45. Fritschi L, Benke G, Hughes AM, et al. Risk of non-Hodgkin lymphoma associated with occupational exposure to solvents, metals, organic dusts and PCBs (Australia). Cancer Causes Control 2005;16:599–607.
46. Schumacher MC, Delzell E. A death-certificate case-control study of non-Hodgkin lymphoma and occupation in men in North Carolina. Am J Ind Med 1988;13:317–30.
47. Reif J, Pearce N, Kawachi I, Fraser J. Soft-tissue sarcoma, non-hodgkin lymphoma and other cancers in New Zealand forestry workers. Int J Cancer 1989;43:49–54.
48. Kawachi I, Pearce N, Fraser J. A New Zealand Cancer Registry-Based Study of Cancer in Wood Workers. Cancer 1989;64:2609–13.
49. Jappinen P, Pukkala E, Sakari T. Cancer incidence of workers in a Finnish sawmill. Scand J Work Environ Health 1989;15:18–23.
50. Rafnsson V. Incidence of cancer among bookbinders, printers, photoengravers, and typesetters. Occup Environ Med 2001;58:523–7.
51. Kato I, Koenig KL, Watanabe-Meserve H, et al. Personal and occupational exposure to organic solvents and risk of non-Hodgkin lymphoma (NHL) in women (United States). Cancer Causes Control 2005;16:1215–24.
52. Olsson H, Brandt L. Risk of non-Hodgkin lymphoma among men occupationally exposed to organic solvents. Scand J Work Environ Health 1988;14:246–51.

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Cancer Epidemiol Biomarkers Prev 2007;16:369-372.