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Asthma history, occupational exposure to pesticides and the risk of non-Hodgkin's lymphoma

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Abstract

We previously reported that, although asthma did not increase the risk of non-Hodgkin's lymphoma (NHL), the risk from pesticide exposures was higher among asthmatics than that among nonasthmatics. To further evaluate this finding, we analyzed data from a population-based case–control study of NHL conducted in Iowa, Detroit, Los Angeles and Seattle. Cases (n = 668) diagnosed with NHL from 1998 to 2000 and controls (n = 543) randomly selected from the same geographical areas as that of the cases were included in this analysis. Odds ratios (OR) for the risk of NHL from potential occupational exposure to pesticides tended to be higher among asthmatics (OR = 1.7; 95% CI 0.3–9.1) when compared with that among nonasthmatics (OR = 0.9; 95% CI 0.6–1.5). The risks of NHL associated with pesticide exposure were also higher among asthmatics who had history of hospitalization (OR = 2.1; 95% CI 0.2–29.0) or daily medication for asthma (OR = infinite) than those among asthmatics who did not have such histories. Our results support the previous finding that the risk of NHL from pesticide exposure may be greater among asthmatics.

Keywords

asthma; non-Hodgkin's lymphoma; pesticide exposure

Pesticides are the suspected risk factors for non-Hodgkin's lymphoma (NHL)[1–3] and immune system alterations.[4,5] Asthma, a chronic immune-related disease, has also been studied as a potential risk factor for NHL.[6,7] However there is an ongoing debate as to whether there is a link between a history of asthma and NHL risk.[8] Because both pesticide exposure and asthma may affect the risk of NHL through immunologic alterations, it has been hypothesized that the

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combination of these conditions might interact in putting individuals at special risk. A previous study of agricultural pesticide exposure, asthma and the risk of NHL found that the risk of NHL from pesticide exposure was higher among asthmatics than that among nonasthmatics.[9] However, the study population was small, and there was a need to investigate whether this interaction might be further influenced by asthma severity. Therefore, we examined the relation between NHL and pesticide exposure by correlation with asthma history in a population-based case–control study[10] conducted within the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI).

Material and methods

Study population

The NCI SEER case–control study of NHL has been described previously.[10,11] In brief, between July 1998 and June 2000, subjects were enrolled from 4 US SEER registry areas: Iowa State, Los Angeles County, Seattle and Detroit metropolitan area. Eligible cases were individuals 20–74 years old with incident NHL. Controls were selected from the general population in the 4 registry areas, stratified on the basis of: age in 5-year intervals, sex and race, to match the distribution in the cases. Trained interviewers administered a computer-assisted personal interview in the home, which covered a wide variety of topics, including demographic factors, diet, pesticide use, medical history, occupation and asthma history. The study was approved by the institutional review boards at the NCI, and the participating institutions and study participants provided informed consent. Among all eligible subjects who we were able to contact, 1,321 case patients (76%) and 1,057 control subjects (52%) participated in the study. Two self-administered questionnaires were used to gather additional information; each went to about 1 half of the participants. Information on asthma was obtained in 1 of these self-administered questionnaires, and 685 cases and 663 controls answered the questions about asthma. After excluding subjects for whom information on occupational history was unavailable (17 cases and 120 controls), the final study sample consisted of 668 cases and 543 controls.

Pesticide exposure assessment

We estimated the level of potential pesticide exposure for each occupation during the subject's lifetime using a job exposure matrix approach developed by an industrial hygienist (P. Stewart). Scores reflecting the relative probability of pesticide exposure, the relative level of exposure and the confidence of exposure coding were assigned (from 0 = lowest to 4 = highest for each of the 3 categories) for insecticides, herbicides and fungicides separately. If an individual reported, during the interview, to have handled pesticides in the workplace, the relative probability scores were changed to 4 and confidence of exposure coding scores of less than 3 were raised by 1. We divided the subjects into 3 levels of occupational pesticide exposure as belonging to: (*i*) "probably unexposed" (*i.e.*, individuals who were not working in an environment where there was a likelihood of pesticide exposure (probability and level equalled zero) to any pesticide class); (*ii*) "exposure uncertain" (*i.e.*, individuals who never worked in an environment that met the criteria for being classified as "probably unexposed" or "probably exposed"); and (*iii*) "probably exposed" (*i.e.*, individuals who have always been working in an environment that met the criteria for being assigned a probability of exposure ≥3, level of exposure ≥2 and a confidence of exposure coding ≥2 for any pesticide class).

Statistical analysis

We used unconditional logistic regression with Stata software (version 8.0)[12] to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for combinations of pesticide exposure and asthma history. The reference group was the nonasthmatics classified as "probably unexposed" to pesticides (*i.e.*, individuals who had no probable exposure to pesticides in any job, and who

did not have asthma). The baseline logistic model included age (<45, 45–64, ≥65), sex, race (black, white, others) and study center (Iowa, Detroit, Los Angeles and Seattle). We estimated the risk of NHL by level of pesticide exposure and by correlation with asthma history (such as hospitalization and daily medication). We also attempted to examine multiplicative interactions among asthma history, pesticide exposure and risk of NHL.

Results

Table I shows the distribution of the 668 cases and 543 controls by asthma history, age, sex, race and state of residence. Of the total, 123 (10.2%) subjects reported having been told by a physician that they had asthma. No significant differences were observed between cases and controls in the asthmatic group, but nonasthmatic NHL cases were significantly more likely (than nonasthmatic controls) to be white and to be living in Detroit.

We observed no effect on NHL risk of pesticide exposure among nonasthmatics (OR = 0.9; 95% CI 0.6–1.5) and no effect of asthma history among subjects unexposed to pesticides (OR = 0.9; 95% CI 0.5–1.6). Asthmatic subjects with probable pesticide exposure, however, had a higher risk of NHL (OR = 1.7; 95% CI 0.3–9.1) than nonasthmatics (OR = 0.9; 95% CI 0.6–1.5), although the interaction between asthma and pesticide exposure was not statistically significant ($p = 0.38$) (Table II). The risk of NHL associated with probable pesticide exposure appears to be increased when subjects had always hospitalized, or had taken daily medication for asthma. However, all results were based on a small number of asthmatic NHL cases.

Discussion

Although asthma alone does not appear to increase the risk of NHL in these data, asthmatics with potential exposure to pesticides had a higher relative risk of NHL than nonasthmatics exposed to pesticides. Although numbers are small and this could be a chance finding, these results are consistent with a previous study[9] and support the hypothesis of effect modification between asthma and pesticide exposure in the development of NHL. When asthma is regarded as a hyperactive state of the immune system, it is usually assumed to reflect a shift in the T-lymphocyte response away from the T-helper 1 towards a T-helper 2 dominated activity. This skewing of the immune response towards the T-helper 2 phenotype by conditions such as asthma could exacerbate the effects of pesticides, some of which are known to inhibit some aspects of the immune system.[13] There is no direct evidence, however, that pesticides skew the immune response toward the T-helper 2 phenotype. Asthmatics may also have increased susceptibility to carcinogens because of their impaired mucociliary system and pulmonary function.[14] Some organophosphorus pesticides also inhibit a different type of the immune response, *e.g.*, cytotoxic T lymphocytes or natural killer cells,[15] and these inhibitory effects impair immune surveillance and cytotoxic functions,[16] so that the combination of asthma and pesticide exposure eliminates more than 1 mechanism of immunosurveillance.

A limitation of our study is that asthma case definition was based on self report and misclassification is likely. Reported hospitalization or daily use of medications was used to define asthma in order to minimize this problem and to identify more severe cases. Although numbers were small, the excess of NHL among persons probably exposed to pesticides persisted in this group. It is possible, however, that the excess could be generated from medicines taken for asthma, which may facilitate development of NHL due to their cellular and humoral immunosuppression.[17,18] Assessment of pesticide exposure is also a limitation of our study. The job exposure matrix was based on job title and industry, which undoubtedly leads to misclassification due to differing tasks within the same job and industry codes. This misclassification would probably be nondifferentional and would, thus, lead to an underestimation of the association between pesticide exposure and NHL risk.

An important strength of our study is its use of population-based sampling of NHL cases and controls, which allows a generalization of our results to the general population. The lifetime prevalence of asthmatics in this study (10.2%) is virtually identical to that reported in the United States in 2000 (10.4%).[19]

In summary, asthma and possible exposure to pesticides appears to increase the risk of NHL, which is consistent with a previous study. The excess risk among asthmatics with pesticide exposure were more pronounced when subjects had ever been hospitalization or taken daily medication for asthma. Numbers, however, are small, which underscores the need for further evaluation of the interplay between environmental exposures, immunologic conditions and risk of NHL.

References

1. Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 1992;52:5485s–8s. [PubMed: 1394159]
2. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10:1155–63. [PubMed: 11700263]
3. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 2002;43:1043–9. [PubMed: 12148884]
4. Colosio C, Corsini E, Barcellini W, Maroni M. Immune parameters in biological monitoring of pesticide exposure: current knowledge and perspectives. Toxicol Lett 1999;108:285–95. [PubMed: 10511273]
5. Voccia I, Blakley B, Brousseau P, Fournier M. Immunotoxicity of pesticides: a review. Toxicol Ind Health 1999;15:119–32. [PubMed: 10188195]
6. McWhorter WP. Allergy and risk of cancer. A prospective study using NHANESI follow up data. Cancer 1988;62:451–5. [PubMed: 3383143]
7. Mills PK, Beeson WL, Fraser GE, Phillips RL. Allergy and cancer: organ site-specific results from the Adventist Health Study. Am J Epidemiol 1992;136:287–95. [PubMed: 1415150]
8. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005;60:1098–111. [PubMed: 16076292]
9. Lee WJ, Cantor KP, Berzofsky JA, Zahm SH, Blair A. Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. Int J Cancer 2004;111:298–302. [PubMed: 15197786]
10. Engels EA, Chatterjee N, Cerhan JR, Davis S, Cozen W, Severson RK, Whitby D, Colt JS, Hartge P. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. Int J Cancer 2004;111:76–80. [PubMed: 15185346]
11. Hartge P, Colt JS, Severson RK, Cerhan JR, Cozen W, Camann D, Zahm SH, Davis S. Residential herbicide use and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2005;14:934–7. [PubMed: 15824166]
12. StataCorp. Stata reference manual release 8.0. Texas: Stata Press, 2003.
13. Thomas, PT.; Busse, WW.; Kerkvliet, NI.; Luster, MI.; Munson, AE.; Murry, M.; Roberts, D.; Robinson, M.; Silkworth, J.; Sjoblad, R.; Smialowicz, R. Immunologic effects of pesticides. In: Baker, SR.; Wilkinson, CF., editors. The effects of pesticides on human health. Princeton: Princeton Scientific Publishing; 1990. p. 261-99.
14. Santillan AA, Camargo CA Jr, Colditz GA. A meta-analysis of asthma and risk of lung cancer (United States). Cancer Causes Control 2003;14:327–34. [PubMed: 12846363]
15. Li Q, Nagahara N, Takahashi H, Takeda K, Okumura K, Minami M. Organophosphorus pesticides markedly inhibit the activities of natural killer, cytotoxic T lymphocyte and lymphokine-activated killer: a proposed inhibiting mechanism via granzyme inhibition. Toxicology 2002;172:181–90. [PubMed: 11893417]
16. Newcombe DS. Immune surveillance, organophosphorus exposure, and lymphomagenesis. Lancet 1992;339:539–41. [PubMed: 1346889]

17. Oehling AG, Akdis CA, Schapowal A, Blaser K, Schmitz M, Simon HU. Suppression of the immune system by oral glucocorticoid therapy in bronchial asthma. Allergy 1997;52:144–54. [PubMed: 9105518]

18. Gemou-Engesaeth V, Bush A, Kay AB, Hamid Q, Corrigan CJ. Inhaled glucocorticoid therapy of childhood asthma is associated with reduced peripheral blood T cell activation and 'Th2-type' cytokine mRNA expression. Pediatrics 1997;99:695–703. [PubMed: 9113946]

19. Center for Disease Control and Prevention. 2000 BRFSS summary data quality report. Atlanta, Geogia: National Center for Chronic Disease Prevention Health Program, 2001. http://www.cdc.gov/asthma/brfss/00/pdf/l1pdf2000

TABLE I

CHARACTERISTICS OF CASES AND CONTROLS BY ASTHMA HISTORY

Characteristics	Nonasthmatics (*n* = 1,088)		Asthmatics (*n* = 123)	
	Cases (*n* = 602)	Controls (*n* = 486)	Cases (*n* = 66)	Controls (*n* = 57)
Age				
<45	103 (17.1)	85 (17.5)	14 (21.2)	9 (15.8)
45–64	290 (48.2)	214 (44.0)	34 (51.5)	27 (47.4)
≥65	209 (34.7)	187 (38.5)	18 (27.3)	21 (36.8)
Gender				
Male	346 (57.5)	257 (52.9)	33 (50.0)	28 (49.1)
Female	256 (42.5)	229 (47.1)	33 (50.0)	29 (50.9)
Race				
Black	70 (11.6)	111 (22.8)	11 (16.7)	15 (26.3)
White	485 (80.6)	345 (71.0)	47 (71.2)	35 (61.4)
Other	47 (7.8)	30 (6.2)	8 (12.1)	7 (12.3)
State of residence				
Detroit	147 (24.4)	84 (17.3)	12 (18.2)	9 (15.8)
Iowa	154 (25.6)	119 (24.5)	12 (18.2)	5 (8.8)
Los Angeles	158 (26.3)	151 (31.1)	24 (36.4)	21 (36.8)
Seattle	143 (23.7)	132 (27.2)	18 (27.3)	22 (38.6)
Hospitalized for asthma				
No	—	—	35 (53.0)	36 (63.2)
Yes	—	—	31 (47.0)	21 (36.8)
Daily medication for asthma				
No	—	—	35 (53.0)	27 (47.4)
Yes	—	—	31 (47.0)	30 (52.6)

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TABLE II

RELATIVE RISKS OF NHL BY ASTHMA HISTORY AND EXPOSURE TO PESTICIDES

Asthma history	Occupational exposure to pesticides											
	Probably unexposed				Exposure uncertain				Probably exposed			
	Ca.	Co.	OR[1]	95% CI	Ca.	Co.	OR	95% CI	Ca.	Co.	OR	95% CI
Nonasthmatics	282	225	1.0	reference	253	202	1.1	0.8–1.4	67	59	0.9	0.6–1.5
Asthmatics	30	28	0.9	0.5–1.6	29	26	1.1	0.4–3.1	7	3	1.7	0.3–9.1 (p = 0.38[2])
Hospitalized for asthma												
No	16	16	0.9	0.4–1.8	15	18	0.8	0.2–2.9	4	2	1.5	0.2–11.9
Yes	14	12	1.0	0.4–2.2	14	8	2.0	0.5–9.0	3	1	2.1	0.2–29.0
Daily medication for asthma												
No	14	11	1.2	0.5–2.9	16	13	1.2	0.3–5.2	5	3	1.3	0.2–8.7
Yes	16	17	0.7	0.4–1.5	13	13	1.0	0.3–3.9	2	0	∞	0–∞

[1]Odds ratios adjusted for age, sex, race and study center.–

[2]Test for interaction between asthma and pesticide exposure.