Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study

Ola Landgren,[1,2] Robert A. Kyle,[3] Jane A. Hoppin,[4] Laura E. Beane Freeman,[1] James R. Cerhan,[3] Jerry A. Katzmann,[3] S. Vincent Rajkumar,[3] and Michael C. Alavanja[1]

[1]Division of Cancer Epidemiology and Genetics and [2]Center for Cancer Research, Medical Oncology Branch, National Cancer Institute, National Institutes of Health (NIH), Bethesda, MD; [3]College of Medicine, Mayo Clinic, Rochester, MN; and [4]National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC

Pesticides are associated with excess risk of multiple myeloma, albeit inconclusively. We included 678 men (30-94 years) from a well-characterized prospective cohort of restricted-use pesticide applicators to assess the risk of monoclonal gammopathy of undetermined significance (MGUS). Serum samples from all subjects were analyzed by electrophoresis performed on agarose gel; samples with a discrete or localized band were subjected to immunofixation. Age-adjusted prevalence estimates of MGUS were compared with MGUS prevalence in 9469 men from Minnesota. Associations between pesticide exposures and MGUS prevalence were assessed by logistic regression models adjusted for age and education level. Among study participants older than 50 years (n = 555), 38 were found to have MGUS, yielding a prevalence of 6.8% (95% CI, 5.0%-9.3%). Compared with men from Minnesota, the age-adjusted prevalence of MGUS was 1.9-fold (95% CI, 1.3- to 2.7-fold) higher among male pesticide applicators. Among applicators, a 5.6-fold (95% CI, 1.9- to 16.6-fold), 3.9-fold (95% CI, 1.5- to 10.0-fold), and 2.4-fold (95% CI, 1.1- to 5.3-fold) increased risk of MGUS prevalence was observed among users of the chlorinated insecticide dieldrin, the fumigant mixture carbon-tetrachloride/carbon disulfide, and the fungicide chlorothalonil, respectively. In summary, the prevalence of MGUS among pesticide applicators was twice that in a population-based sample of men from Minnesota, adding support to the hypothesis that specific pesticides are causatively linked to myelomagenesis. (Blood. 2009;113:6386-6391)

Introduction

Multiple myeloma is a clonal neoplasm of differentiated B cells (plasma cells) characterized by an overproduction of monoclonal immunoglobulins with evidence of hypercalcemia, renal insufficiency, anemia, or bone lesions.[1,2] According to the American Cancer Society, almost 19 900 new multiple myeloma cases and 10 700 multiple myeloma deaths are expected in the United States during 2008.[3] Multiple myeloma is usually preceded by the premalignant plasma cell disorder, monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined by a serum monoclonal immunoglobulin concentration less than 3 g/dL; a proportion of plasma cells in the bone marrow less than 10%[1]; and the absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the proliferation of monoclonal plasma cells. On average, MGUS progresses to multiple myeloma at a rate of 1% per year.[4]

Although the cause of MGUS and multiple myeloma remain largely unclear, previous cohort[5-12] and case-control studies[13-26] have reported an elevated risk of multiple myeloma among farmers and other agricultural workers. More specifically, pesticides (ie, insecticides, herbicides, fungicides) have been hypothesized as the basis for these associations.[27-30] However, most prior investigations have been hampered by small numbers and limited exposure assessment.[31] In the US Agricultural Health Study, in a prospective cohort of 57 310 private and commercial licensed applicators of restricted use of pesticides in Iowa and North Carolina, we found a 1.34-fold (95% confidence interval [CI], 0.97-1.81) excess risk of multiple myeloma among pesticide applicators compared with population rates in Iowa and North Carolina.[32] Several pesticides widely used on farms and in homes and gardens by the general public were associated with increased multiple myeloma risk in previous analyses coming from this cohort.[33-36] Currently, however, it is unclear whether the observed increased risk of multiple myeloma among persons exposed to pesticides might reflect a higher prevalence of MGUS or an increase in the rate of progression from MGUS to multiple myeloma.

We have conducted the first population-based study of MGUS in relation to pesticide exposure in a sample of 678 male pesticide applicators. The aims of our study were to estimate the age-specific prevalence of MGUS among pesticide applicators and to compare the prevalence to that in the general population as determined in a population-based screening study in Olmsted County, Minnesota.[37] In addition, we assessed the prevalence of MGUS in relation to specific pesticide reportedly used by these farmers.

Methods

Study subjects

The Agricultural Health Study is a prospective cohort study of 57 310 private and commercial applicators licensed to apply restricted-use pesticides who lived in Iowa or North Carolina and who were enrolled between

Submitted February 3, 2009; accepted April 16, 2009. Prepublished online as *Blood* First Edition paper, April 22, 2009; DOI 10.1182/blood-2009-02-203471.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Table 1. MGUS prevalence (%) among 678 men in the Agricultural Health Study and 9469 men in Olmsted County, MN

Age group, y	Agricultural Health Study Cohort			Olmsted County, MN[37]			P*
	Total, n	MGUS, n	Prevalence† (95% CI)	Total, n	MGUS, n	Prevalence† (95% CI)	
< 50	123	0	0	0	0	NA	
50-59	214	5	2.3 (1.0-5.4)	4038	82	2.0 (1.6-2.5)	
60-69	182	10	5.5 (3.0-9.9)	2864	105	3.7 (3.0-4.4)	
70-79	129	18	14.0 (9.0-21.1)	1858	104	5.6 (4.6-6.7)	
> 80	30	5	16.7 (7.1-34.3)	709	59	8.3 (6.5-10.6)	
Total‡	555	38	6.8 (5.0-9.3)	9469	350	3.7 (3.3-4.1)	< .001

CI indicates confidence interval; and NA, not applicable.

*χ^2 $P < .001$; logistic regression adjusted for age yields an odds ratio = 1.9 (95% CI, 1.3-2.7) comparing MGUS positive in the Agricultural Health Study versus Olmsted County, MN.[37]

†Per 100 persons.

‡Older than 50 years of age.

1993 and 1997.[38] Applicators completed a self-administered questionnaire at enrollment. Comprehensive occupational exposure information was obtained for 22 frequently used pesticides, and ever/never use was obtained for 28 additional pesticides for which more detailed exposure data were obtained in a take-home questionnaire. Detailed information included mean annual days of use of the individual pesticides, years of use, use of personal protective equipment while applying pesticides, pesticide application methods, how frequently the applicator mixed pesticides, and whether pesticide equipment was personally repaired by the study subject. For all participants, information was obtained on smoking and alcohol use, cancer history of first-degree relatives, and other basic demographic and health information.[38] Occupational exposures, medical histories, and lifestyle factors were updated at a 5-year follow-up interview. All questionnaires may be accessed at http://www.aghealth.org/questionnaires.html. Cancer incidence, mortality, and changes in address are monitored annually.[38]

A stratified random sample (based on lifetime organophosphate use) of 685 male study subjects, who completed all 3 phases of the Agricultural Health Study, were enrolled into a neurobehavioral study nested within the cohort and provided serum for analysis. For Iowa and North Carolina study subjects, phlebotomy was performed in 2006-2007 and 2008, respectively. Because of the low prevalence of women among the applicators in the cohort (2%), women were excluded from this study. On the basis of diagnostic criteria for MGUS,[1] persons with a prior history of a lymphoproliferative malignancy (ie, multiple myeloma or lymphoma) were excluded (n = 7) in our study. Thus, a total of 678 study subjects were included in this investigation. All participants provided signed informed consent at time of blood draw, in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Boards of the National Institutes of Health and its contractors.

Collection of biologic samples

Venous blood was collected from the antecubital vein with the use of standard aseptic techniques. Blood was processed in the field and stored in a secure −20°C freezer on the testing site.

Laboratory tests

All serum samples were processed and analyzed for MGUS in an identical fashion and in the same laboratory (Mayo Clinic Protein Immunology Laboratory, Rochester, MN) as the population-based study of MGUS in Olmsted County, Minnesota, to which the rates of MGUS in the Agricultural Health Study are compared.[37] Electrophoresis was performed on agarose gel (REP; Helena Laboratories, Beaumont, TX). The agarose strip was inspected by a technician and by 2 of the authors (R.A.K. and J.A.K.). Any serum with a discrete band or thought to have a localized band was subjected to immunofixation (Hydrasys and Hydragel; Sebia, Norcross, GA).[39] MGUS was defined in accordance with previous definition, which was identical to the definition used in the Olmsted County prevalence study.[37,39]

Statistical analysis

Age-specific prevalence rates for pesticide applicators and Olmsted County men were calculated by dividing the number of persons with MGUS in each age stratum by the number of subjects in that stratum. Associations of MGUS prevalence with pesticide exposures, demographics, and subject characteristics were assessed in logistic regression models (PROC LOGISTIC, SAS 9.1; SAS Institute, Cary, NC) adjusted for age and education level. All *P* values are 2-sided. For every significant association between a specific pesticide and MGUS, we evaluated the 5 most highly correlated pesticides with the pesticide of interest as a potential source of confounding. We also assessed the potential confounding effect of other pesticides that had a significant association with MGUS.

Results

The median age of study subjects was 60 years (range, 30-94 years). Ninety-five percent were white, 1.9% were African American, and the remaining 3.1% included all other racial groups and those with missing racial data. By design, 50% of the pesticide applicators were from North Carolina and 50% were from Iowa.

Prevalence of MGUS

MGUS was detected in the serum of 38 (5.6%) of the 678 participants, and the prevalence varied significantly by age ($P < .001$, χ^2 test; Table 1). The age-specific prevalence rate of MGUS among pesticide applicators aged 50 to 59 years, 60 to 69 years, 70 to 79 years, and 80 years or older was 2.3%, 5.5%, 14.0%, and 16.7%, respectively. No MGUS cases were observed among the 123 study subjects younger than 50 years, but the prevalence of MGUS was 6.8% (95% CI, 5.0%-9.3%) among Agricultural Health Study subjects who were 50 years of age or older. The results were similar when we stratified the analyses by state (data not shown).

The age-adjusted prevalence of MGUS was significantly higher ($P < .001$) in this study of Agricultural Health Study participants compared with the rate 3.7% (95% CI, 3.3%-4.1%) observed among 9469 Olmsted County men.[33] The age-adjusted prevalence ratio was 1.9 (95% CI, 1.3-2.7; Table 1).

Selected demographic factors and risk of MGUS prevalence

We explored age-specific prevalence patterns by demographic factors within the study. The increase in MGUS prevalence with age is shown in Table 2, and we found those with more than 12 years of formal education to have 60% nonsignificantly reduced prevalence of MGUS compared with those who did not graduate

Table 2. Risk of MGUS among male Agricultural Health Study participants stratified by selected demographic and lifestyle factors

Factor	Total, n	MGUS, n	OR (95% CI)*
Age, y			
< 65	452	13	1.0 (ref)
66-74	141	13	3.4 (1.6-7.6)
> 75	85	12	5.6 (2.4-12.6)
Race			
White	645	36	1.0 (ref)
Nonwhite	17	1	1.3 (0.2-10.4)
Missing	16	1	1.0 (0.1-8.3)
State			
Iowa	338	18	1.0 (ref)
North Carolina	340	20	1.0 (0.5-1.9)
Education			
< 12	37	5	1.0 (ref)
12	295	21	0.7 (0.2-2.1)
> 12	320	11	0.4 (0.1-1.1)
Other/missing	26	1	0.3 (0.1-2.8)
Smoking			
Never	374	22	1.0 (ref)
Current	223	16	1.1 (0.5-2.1)
First-degree relative with cancer			
No	296	16	1.0 (ref)
Yes	360	22	1.0 (0.5-2.0)

OR indicates odds ratio; CI, confidence interval; and NA, not applicable.
*Estimates are adjusted for age.

from high school. This inverse association was not explained by age disparities or any other demographic variable. There were too few African Americans in our cohort to evaluate racial differences in prevalence.

Specific pesticide exposures and risk of MGUS prevalence

To improve our understanding on the observed increased risk of MGUS prevalence among pesticide users, we evaluated the potential association for 50 specific pesticides for which we have usage data in the Agricultural Health Study.

As shown in Table 3, we found a 5.6-fold (95% CI, 1.9- to 16.6-fold), 3.9-fold (95% CI, 1.5- to 10.0-fold), and 2.6-fold (95% CI, 1.2- to 5.7-fold) significantly increased risk of MGUS prevalence among users of the chlorinated insecticide dieldrin, the fumigant mixture carbon-tetrachloride/carbon disulfide, and the fungicide chlorthalonil, respectively. Several other insecticides, herbicides, and fungicides were associated with MGUS, however, not significantly (Table 3).

The excess risk of MGUS prevalence with dieldrin and chlorthalonil use was not attenuated and remained significant after adjusting for the influence of the use of other pesticides with a potential for confounding (data not shown). Similarly, the excess risk of MGUS prevalence with the use of the mixture carbon-tetrachloride/carbon disulfide was virtually the same when we controlled for other pesticides; however, the 95% CIs on the adjusted risks estimates sometimes included one. Finally, in exploratory subanalysis, we assessed risk of MGUS prevalence by lifetime days (below/above median) of exposure for specific pesticides, but in general numbers were too small to be informative.

Discussion

Beyond age, sex, race, and a positive family history of MGUS/multiple myeloma, no consistent extrinsic risk factors have been clearly linked to multiple myeloma.[5-26,40,41] Previous studies from around the world suggest that agricultural work is associated with multiple myeloma risk, but specific agents have not been identified.[5-26,40] Compared with population rates in Iowa and North Carolina, a 1.3-fold excess risk of multiple myeloma was observed in the Agricultural Health Study.[32] Although there is no clear explanation for this excess, pesticide-specific analyses from the Agricultural Health Study have suggested associations with a few pesticides. In our survey of MGUS among a subset of Agricultural Health Study pesticide applicators ages 50 years and older, we found a prevalence of 6.8%, which is twice that of a group of a population-based sample of men from Minnesota of comparable age.[37]

Our analyses point to possible links with dieldrin, a chlorinated insecticide, which had a significant 5-fold excess risk of MGUS prevalence, and carbon tetrachloride/carbon disulfide mix, a fumigant, which had a significant 4-fold risk of MGUS prevalence. Several other chlorinated insecticides were associated, but not significantly, with MGUS (Table 3). Most of these chlorinated compounds have been taken off the market in the United States and most other developed nations, but their use persists in many developing nations. With a few exceptions, organochlorine pesticides are fat soluble and persist in adipose tissue of many persons.[42]

We also found a 3-fold significant excess of MGUS prevalence among users of chlorthalonil. Chlorthalonil is a fungicide with broad applications to fruits and vegetables. This pesticide has not been evaluated for the association with multiple myeloma in the Agricultural Health Study because of relatively small numbers of exposed cases.

Permethrin use has been linked to multiple myeloma in the Agricultural Health Study[32] and a nonsignificantly increased risk of multiple myeloma was seen among study participants using the widely used herbicides atrazine[35] and glyphosate[33] and the insecticide chlorpyrifos.[34] In the present study, we had only 4 MGUS-positive exposed cases, and we could not reliably evaluate the association between MGUS and permethrin exposure. Among users of chlorpyrifos and atrazine we observed a nonsignificant elevated risk of MGUS, whereas for users of glyphosate we found a nonsignificant decreased risk of MGUS. Chlorpyrifos, an organophosphorothioate insecticide, was previously used in home and garden applications; however, its use is now restricted to agriculture.[34] Atrazine is used primarily on corn and soybean to control broadleaf and grassy weeds, and it is one of the most heavily used agricultural pesticides in the United States.[43]

The Agricultural Health Study has several important strengths. It is the largest study to date of private and commercial applicators licensed to apply restricted-use pesticides. Recall bias was minimized because exposure information was collected before blood draw and serum protein analysis. Furthermore, it has been shown that farmers provide accurate and reliable information and considerable detail about their pesticide application history.[44]

Our study also has some limitations. For example, we did not have a control group from Iowa and North Carolina. Instead, we chose Olmsted County in Minnesota as a comparison group, given that the Mayo Clinic had available data from the largest population-based MGUS screening study to date. Although a control group from Iowa and North Carolina might have been better, we think that Olmsted County in Minnesota is a reasonable control group. In fact, the difference between the 2 groups (ie, Olmsted County and the Agricultural Health Study) are not particularly different by education attainment (90.3% of the Agricultural Health Study cohort have graduated from high school and 40.7% have some education beyond high school; in Olmsted County 91.1% were

Table 3. Specific pesticide use at enrollment and risk of MGUS IN 2008 among 678 male applicators in the Agricultural Health Study

Pesticide/category	Exposed	Total, n	MGUS, n	OR (95% CI)*
Chlorinated insecticides				
Dieldrin	Never	649	31	1.0 (reference)
	Ever	20	6	*5.6 (1.9-16.6)*
Lindane	Never	539	26	1.0 (reference)
	Ever	138	12	1.9 (0.9-3.9)
Aldrin	Never	546	24	1.0 (reference)
	Ever	124	13	1.7 (0.8-3.6)
Toxaphene	Never	525	24	1.0 (reference)
	Ever	150	14	1.6 (0.8-3.2)
DDT	Never	468	18	1.0 (reference)
	Ever	205	20	1.4 (0.7-3.1)
Chlordane	Never	486	24	1.0 (reference)
	Ever	185	14	1.3 (0.6-2.6)
Herbicides				
2,4-D	Never	139	5	1.0 (reference)
	Ever	537	33	1.8 (0.7-4.8)
Pendimethalin	Never	373	17	1.0 (reference)
	Ever	305	21	1.7 (0.8-3.3)
Imazethapyr	Never	478	25	1.0 (reference)
	Ever	192	13	1.6 (0.8-3.4)
Cyanazine	Never	370	18	1.0 (reference)
	Ever	301	20	1.4 (0.7-2.8)
Alachlor	Never	217	11	1.0 (reference)
	Ever	453	27	1.3 (0.6-2.8)
Butylate	Never	479	27	1.0 (reference)
	Ever	199	11	1.1 (0.5-2.4)
Atrazine	Never	151	8	1.0 (reference)
	Ever	525	30	1.1 (0.5-2.5)
Trifluralin	Never	390	22	1.0 (reference)
	Ever	279	16	1.1 (0.5-2.1)
Chlorimuron-ethyl	Never	442	24	1.0 (reference)
	Ever	236	14	1.1 (0.5-2.2)
Metribuzin	Never	456	25	1.0 (reference)
	Ever	222	13	1.0 (0.5-2.1)
Dicamba	Never	352	21	1.0 (reference)
	Ever	316	17	0.9 (0.5-1.8)
Metolachlor	Never	316	21	1.0 (reference)
	Ever	356	17	0.8 (0.4-1.5)
Glyphosate	Never	108	11	1.0 (reference)
	Ever	570	27	0.5 (0.2-1.0)
Fumigants				
Carbon-tetrachloride/carbon disulfide mix	Never	632	31	1.0 (reference)
	Ever	41	7	*3.9 (1.5-10.0)*
Fungicides				
Chlorthalonil	Never	561	28	1.0 (reference)
	Ever	115	10	*2.4 (1.1-5.3)*
Captan	Never	558	29	1.0 (reference)
	Ever	115	9	1.9 (0.8-4.2)
Metalaxyl	Never	476	25	1.0 (reference)
	Ever	202	13	1.4 (0.7-2.9)
Insecticides				
Diazinon	Never	435	19	1.0 (reference)
	Ever	242	19	1.8 (0.9-3.6)
Chlorpyrifos	Never	305	16	1.0 (reference)
	Ever	367	21	1.3 (0.7-2.7)
Phorate	Never	457	23	1.0 (reference)
	Ever	220	15	1.3 (0.6-2.5)
Carbofuran	Never	405	20	1.0 (reference)
	Ever	266	17	1.2 (0.6-2.5)
Fonofos	Never	489	26	1.0 (reference)
	Ever	181	11	1.2 (0.5-2.4)
Carbaryl	Never	281	15	1.0 (reference)
	Ever	396	23	1.0 (0.5-2.0)
Malathion	Never	161	11	1.0 (reference)
	Ever	516	27	0.7 (0.3-1.5)
Terbufos	Never	345	22	1.0 (reference)
	Ever	326	15	0.7 (0.3-1.4)

As described in "Methods," a total of 50 specific pesticides were evaluated in this study. Unless there was a significant association with MGUS/MM, we only provide information for specific pesticides with more than 10 MGUS cases in the "ever" exposed category.

OR indicates odds ratio; and CI, confidence interval.

Underlined, italicized entries are statistically significant ($P < 0.05$).

*Estimates are adjusted for age and education level.

high school graduates or higher). The populations of both groups are predominantly white, and the age structure is also similar as shown in Table 2. Two-thirds of the Agricultural Health Study participants are from the Midwest (ie, Iowa), as are all the Olmsted County participants. We evaluated only the male population in both locations. In the present study, only 2 demographic variables were associated with a higher prevalence of MGUS: age and education status. We used both of these as adjustment variables in our multivariate analyses. We think, therefore, that our evaluation of the prevalence of MGUS in each of the populations provides a meaningful comparison and that the analyses by individual pesticides suggest pesticides may play an important role in causing the excess in the Agricultural Health Study cohort. Finally, because we explored the potential association between MGUS and 50 specific pesticides for which we have usage data in the Agricultural Health Study, one has to interpret detected associations for specific pesticides with caution. Future larger studies are needed to replicate our findings.

In summary, several million Americans use pesticides for which we have found an association with MGUS in the Agricultural Health Study. Some of these same chemicals have been associated with excess multiple myeloma risk. Importantly, a recent investigation based on 77 469 healthy adults enrolled in a US nationwide population-based prospective cancer screening trial identified 71 persons who developed multiple myeloma during the course of the study. With the use of serially collected prediagnostic serum samples obtained up to almost 10 years before multiple myeloma diagnosis, all multiple myeloma cases were found to be preceded by MGUS.[45] This finding establishes a key role for MGUS in the pathway to multiple myeloma. In turn, it suggests that our present observation of pesticide exposure being associated with excess MGUS risk might be an underlying explanation of the previously observed excess multiple myeloma risk among persons exposed to pesticides.[32-36] Future studies are needed to improve our knowledge on the role of pesticide exposure in the pathogenesis of MGUS, as well as the potential role in progression from MGUS to multiple myeloma. Identifying specific exposures responsible for myelomagenesis will be important to better understand chemical carcinogenesis in humans and to reduce the risk of disease by taking appropriate public health action.

Acknowledgments

We thank Dr Dale Sandler, National Institute of Environmental Health Sciences (NIEHS); Drs Aaron Blair, Joseph Coble, and Jay Lubin, National Cancer Institute (NCI); and Dr L. Joseph Melton III, Mayo Clinic, for scientific input; Dr Fredric Gerr and Ms Sarah Starks, University of Iowa, for providing us with blood samples from their Neurobehavioral Study that was nested within the Agricultural Cohort Study cohort; and Mr Stuart Long at Westat, and Mr Joe Barker at IMS, Inc, for computer programming.

This work was supported by NCI (research grants CA 62242 and CA 107476); the Intramural Research Program of the NIH, NCI, Division of Cancer Epidemiology and Genetics (DCEG); the NIEHS (Z01-ES049030); and the NCI (Z01-CP010119).

Authorship

Contribution: O.L. and M.C.A. initiated this work and wrote the report. All authors were involved in the design of the study; obtained and analyzed data; were involved in the interpretation of the results; read, gave comments, and approved the final version of the manuscript; had full access to the data in the study; and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Ola Landgren, National Cancer Institute, National Institutes of Health, Center for Cancer Research, Medical Oncology Branch, 9000 Rockville Pike, Bldg 10/Rm 13N240, Bethesda, MD, 20892; e-mail: landgreo@mail.nih.gov.

References

1. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121:749-757.
2. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351:1860-1873.
3. American Cancer Society. Cancer Facts and Figures 2008. Atlanta, GA: American Cancer Society; 2008.
4. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002;346:564-569.
5. Alavanja MC, Blair A, Merkle S, Teske J, Eaton B. Mortality among agricultural extension agents. Am J Ind Med. 1988;14:167-176.
6. Baris D, Silverman DT, Brown LM, et al. Occupation, pesticide exposure and risk of multiple myeloma. Scand J Work Environ Health. 2004;30:215-222.
7. Cerhan JR, Cantor KP, Williamson K, Lynch CF, Torner JC, Burmeister LF. Cancer mortality among Iowa farmers: recent results, time trends, and lifestyle factors (United States). Cancer Causes Control. 1998;9:311-319.
8. 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;42:410-420.
9. Nandakumar A, English DR, Dougan LE, Armstrong BK. Incidence and outcome of multiple myeloma in Western Australia, 1960 to 1984. Aust N Z J Med. 1988;18:774-779.
10. Pukkala E, Notkola V. Cancer incidence among Finnish farmers, 1979-93. Cancer Causes Control. 1997;8:25-33.
11. Stark AD, Chang HG, Fitzgerald EF, Riccardi K, Stone RR. A retrospective cohort study of cancer incidence among New York State Farm Bureau members. Arch Environ Health. 1990;45:155-162.
12. Steineck G, Wiklund K. Multiple myeloma in Swedish agricultural workers. Int J Epidemiol. 1986;15:321-325.
13. Boffetta P, Stellman SD, Garfinkel L. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer. 1989;43:554-559.
14. Brownson RC, Reif JS, Chang JC, Davis JR. Cancer risks among Missouri farmers. Cancer. 1989;64:2381-2386.
15. Burmeister LF. Cancer in Iowa farmers: recent results. Am J Ind Med. 1990;18:295-301.
16. Cantor KP, Blair A. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. J Natl Cancer Inst. 1984;72:251-255.
17. Costantini AS, Miligi L, Kriebel D, et al. A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. Epidemiology. 2001;12:78-87.
18. Cuzick J, De Stavola B. Multiple myeloma–a case-control study. Br J Cancer. 1988;57:516-520.
19. Demers PA, Vaughan TL, Koepsell TD, et al. A case-control study of multiple myeloma and occupation. Am J Ind Med. 1993;23:629-639.
20. Eriksson M, Karlsson M. Occupational and other environmental factors and multiple myeloma: a population based case-control study. Br J Ind Med. 1992;49:95-103.
21. Figgs LW, Dosemeci M, Blair A. Risk of multiple myeloma by occupation and industry among men and women: a 24-state death certificate study. J Occup Med. 1994;36:1210-1221.
22. Franceschi S, Barbone F, Bidoli E, et al. Cancer risk in farmers: results from a multi-site case-control study in north-eastern Italy. Int J Cancer. 1993;53:740-745.
23. Heineman EF, Olsen JH, Pottern LM, Gomez M, Raffn E, Blair A. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control. 1992;3:555-568.
24. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Occupation and lymphoid neoplasms. Br J Cancer. 1989;60:385-388.
25. Milham S Jr. Leukemia and multiple myeloma in farmers. Am J Epidemiol. 1971;94:507-510.

26. Pearce N, Reif JS. Epidemiologic studies of cancer in agricultural workers. Am J Ind Med. 1990; 18:133-148.
27. Blair A, Dosemeci M, Heineman EF. Cancer and other causes of death among male and female farmers from twenty-three states. Am J Ind Med. 1993;23:729-742.
28. Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni JF Jr. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health. 1992;18:209-215.
29. Brown LM, Burmeister LF, Everett GD, Blair A. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control. 1993;4:153-156.
30. Khuder SA, Mutgi AB. Meta-analyses of multiple myeloma and farming. Am J Ind Med. 1997;32: 510-516.
31. Alavanja MC, Hoppin JA, Kamel F. Health effects of chronic pesticide exposure: cancer and neurotoxicity. Annu Rev Public Health. 2004;25:155-197.
32. Alavanja MC, Sandler DP, Lynch CF, et al. Cancer incidence in the agricultural health study. Scand J Work Environ Health. 2005;31(suppl 1): 39-45; discussion 5-7.
33. De Roos AJ, Blair A, Rusiecki JA, et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect. 2005;113:49-54.
34. Lee WJ, Blair A, Hoppin JA, et al. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst. 2004;96:1781-1789.
35. Rusiecki JA, De Roos A, Lee WJ, et al. Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J Natl Cancer Inst. 2004;96:1375-1382.
36. Rusiecki JA, Patel R, Koutros S, et al. Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. Environ Health Perspect. 2009;117:581-586.
37. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354: 1362-1369.
38. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. Environ Health Perspect. 1996;104:362-369.
39. Kyle RA, Katzmann JA, Lust JA, Dispenzieri A. Immunochemical characterization of immunoglobulins. In: Rose NR, Hamilton RG, Detrik B, eds. Manual of Clinical Laboratory Immunology. Washington, DC: ASM Press; 2002:71-91.
40. De Roos AJ, Baris D, Weiss NS, Herrington LJ. Multiple myeloma. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer Epidemiology and Prevention. New York, NY: Oxford University Press; 2006: 946-970.
41. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma-cell and lymphoproliferative disorders among 14,621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance (MGUS) in Sweden. Blood. Prepublished on January 30, 2009, as DOI 10.1182/blood-2008-12-191676.
42. Centers for Disease Control and Prevention. Third National Report on Human Exposure to Environmental Chemicals. Atlanta, GA: CDC; 2005.
43. US Environmental Protection Agency. Pesticides: Topical and Chemical Fact Sheets. Vol 2008. Washington, DC: EPA; 2008. http://www.epa.gov/opp00001/factsheets/. Accessed April 2009.
44. Blair A, Tarone R, Sandler D, et al. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology. 2002;13:94-99.
45. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) precedes multiple myeloma: a prospective study. Blood. 2009;113:5412-5417.

2009 113: 6386-6391
doi:10.1182/blood-2009-02-203471 originally published online April 22, 2009

Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study

Ola Landgren, Robert A. Kyle, Jane A. Hoppin, Laura E. Beane Freeman, James R. Cerhan, Jerry A. Katzmann, S. Vincent Rajkumar and Michael C. Alavanja

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.