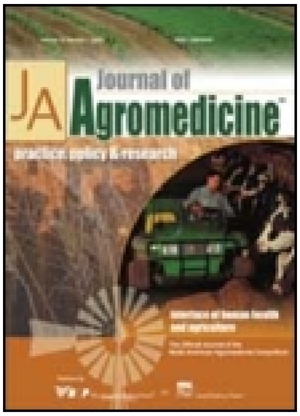

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Multiple Myeloma and Exposure to Pesticides: A Canadian Case-Control Study

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ABSTRACT. The objective of this study was to investigate the putative associations of specific pesticides with multiple myeloma. A matched, population-based, case-control study was conducted among men residing in six Canadian provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia). Data were collected on 342 multiple myelome cases and 1506 age and province of residence matched controls. Data were collected by mailed questionnaires to capture demographic characteristics, antecedent medical history, detailed lifetime occupational history, smoking history, family history of cancer, and exposure to broadly characterized pesticides at home, work, and practicing hobbies. Details of pesticide exposures were collected by telephone interview for those who reported 10 hours or more per year of exposure. Exposure to pesticides grouped into major chemical classes resulted in increased risk being detected only for carbamate insecticides [odds ratio (OR) and 95%

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confidence interval (CI) 1.90 (1.11, 3.27) adjusted for potential confounders]. An exposure to fungicide captan [2.35 (1.03, 5.35)] was positively associated with the incidence of multiple myeloma. While an exposure to carbaryl [1.89 (0.98, 3.67)] was associated with the incidence of multiple myelome with borderline significance. The authors further suggest that certain pesticide exposures may have a role in multiple myeloma etiology, and identify specific factors warranting investigation in other populations.

KEYWORDS. Multiple myeloma, pesticides, herbicides, insecticides, fungicides, captan, carbaryl

BACKGROUND

Multiple myeloma (MM) is a clonal tumor of slowly proliferating plasma cells, which are mature lymphocytes that are specialized for monoclonal antibody (M-protein) production within the bone marrow.[1,2] MM is the second most common blood malignancy (after non-Hodgkin lymphoma) and accounts for 1% of all reported neoplasms.[2] The disease primarily affects older individuals, with a median age of diagnosis of 71 years of age, and is slightly more common in males.[3] The 5-year relative survival after diagnosis of MM is 38%, hence identification of causal factors is extremely important.[3]

The incidence rates vary greatly worldwide, with the highest incidence observed in African-Americans and lowest in Asians.[4] The incidence of MM has increased slowly since 1975.[5] Some of the worldwide variation in rates and increase in incidence can be explained by differences in the awareness and ascertainment of the disease, including the increased availability of serum electrophoresis and other sensitive diagnostic methods.[6]

Little is known about etiologic factors for MM. Ionizing radiation, antigenic stimulation, and the presence of monoclonal gammopathy of unknown significance (MGUS) have been clearly associated with MM, and several other factors have been suggested; these include lifestyle, environmental, and occupational factors.[7–14] Agricultural occupations have been consistently found to be associated with an increased risk of MM,[8–14] and although pesticides have been hypothesized as the causal agent, few studies have identified risk related to exposure to specific pesticides.

In this report the authors explore the hypothesis that non-trivial exposure to selected chemical classes of pesticides and individual pesticides will increase the risk of a diagnosis of MM in comparisons of newly diagnosed male cases (ICD-O M 9732/3)[15] and control subjects with the similar age distribution.

METHODOLOGY

Details of the study design and methodology have been published elsewhere.[16,17] Briefly, researchers conducted a matched, population-based, case-control study of men residing in six Canadian provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia) to test whether there are associations between pesticide exposure and four rare tumors: MM, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and soft-tissue sarcoma (STS).

Incident cases were men, ages 19 years or over, with a first diagnosis of MM (ICD-O M 9732/3) from September 1, 1991 to December 31, 1994. Cases were ascertained from provincial cancer registries, except in Quebec where hospital ascertainment was used. After physician consent was received, postal questionnaires and informed consent forms were mailed to potential cases. Control subjects were matched by age ±2 years to be comparable with the age distribution of the entire case group (MM, HL, NHL, and STS) within each province of residence. Potential controls (men, 19 years or over) were selected at random within age constraints from provincial health insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia). Postal questionnaires and informed consent forms were mailed to potential controls, and information collected from all of the participating control subjects was used in the statistical analyses of each cancer site. Deceased subjects were ineligible as either cases or controls.

A total of 1528 cases diagnosed with the four types of tumors (MM = 342, HL = 316, NHL = 513, and STS = 357) under investigation participated. The total number of control participants was 1506, and to analyze data for each specific tumor type, all controls were used. In this report, statistical analysis is based on 342 (58.0% of those contacted) MM cases and all 1506 (48.0% of those contacted) controls, which gave an average of four to five matched controls for each MM case. A reference pathologist reviewed pathology reports and tumor tissue slides for 36.5% (125/342) of MM cases for which specimens could be obtained. The most common reasons for non-participation for both cases and control participants were death, change of address, and refusal. Some important definitions used in this article are given below:

Pesticide

In this article pesticide refers primarily to herbicides, insecticides, fumigants, and fungicides. Pesticide is a generic term that refers to a host of compounds of diverse chemical structure and biological modes of action.[17]

Pesticide Exposure

A pilot study was conducted to test questionnaires and to determine a working definition of pesticide exposure to distinguish between environmental (which includes bystander and incidental) and more intensive exposure. Information on non-occupational use of pesticides (such as at home, in garden, and as a hobby) was also included. Based on the statistical analysis of pilot study data, it was decided that the most efficient definition of pesticide exposure, which discriminated (a) between incidental, bystander, and environmental exposure as compared with more intensive exposure, and (b) between cases and controls, was a cumulative exposure $\geq$10 hrs/year to any combination of pesticides. The screening questions in the postal questionnaire were used to select study participants for telephone interviews among those with cumulative exposure of $\geq$10 hrs/year to any combination of herbicides, insecticides, fungicides, fumigants, and/or algicides. Cumulative exposure was derived multiplying two quantitative indices of extent of exposure number of days/year and number of hours/day.[17]

Medical History

Information on medical history including family history of cancer, infectious disease (bacterial and viral), allergies, acne, and immune disorders (which include autoimmune and inflammatory disorders), and asthma was collected via postal questionnaire.[17]

Exposure Assessment

Data were collected in two stages: by self-administered postal questionnaire in Stage 1, and detailed pesticide exposure information via telephone interview in Stage 2. The pesticide exposure questionnaire developed by Hoar et al.[18] was modified (with permission) for use in Canadian context.[16] In Stage 1, information was collected on demographic details, personal medical history, cigarette smoking history, lifetime occupational history, and specific occupational exposures of interest. Each subject who had reported $\geq$10 hours/year of exposure to pesticides (in any combination of compounds) as defined by the screening questions in the postal questionnaire, and a 15% random sample of the remainder, were mailed a list of pesticides (both chemical and brand names) along with an explanatory letter a week prior to the telephone interview. All subjects who had $<$10 hours/year of exposure based on the screening questions and were not part of the 15% random sample were considered as having "no exposure to the individual chemicals listed in the telephone questionnaire."[17]

The telephone questionnaire was used as a source of information to characterize exposure to individual pesticides. The listed pesticides in the telephone questionnaire were chosen for inclusion for the following reasons: (a) if the compound was ever registered for use in Canada and reviewed by the International Agency for Research on Cancer (IARC);[19–21] or (b) if the pesticide was recently banned or restricted in Canada by the federal licensing agency; or (c) if the pesticide was commonly used in Canada for specific purposes.[17]

STATISTICAL ANALYSIS

Merged data from the postal and telephone interview questionnaires for all provinces were analyzed using SAS (Statistical Analysis System) version 9.2,[22] with the primary results being reported as odds ratios (OR) and 95% confidence intervals (CI) derived from conditional logistic regression analyses, stratifying by age groups and province of residence. ORs were calculated for categorical variables related to medical history, pesticides exposure, smoking history, educational level, and chemical exposure other than pesticides. Further, ORs were calculated for individual active chemicals and for major chemical classes of herbicides, insecticides, fungicides, and fumigants.

RESULTS

Data from postal questionnaires based on 342 MM cases and 1506 controls were analyzed. Comparisons between MM cases and control subjects indicated that cases and controls were similar in their smoking patterns, whereas cases were less likely than controls to have a history of measles, mumps, or allergies, but more likely than controls to have history of shingles, or a first-degree relative with cancer (Table 1). Cases and controls were similar in their

TABLE 1. Comparison of Demographic, Antecedent Personal Medical, General Pesticide Exposures, and Cigarette Smoking History between Cases of MM and Control Subjects Based on the Postal Questionnaire

	MM ($n = 342$)		Controls ($n = 1506$)		OR_{adj} [a] (95% CI)
Age, yr	*n*	%	*n*	%	
≤40	9	26.3	356	23.6	
40–49	24	8.8	221	14.7	
49–59	59	18.1	248	16.5	
59–69	116	34.5	362	24.0	
>69	134	36.0	319	21.2	
Age (mean ± SD, years)	64.7 ± 11.1		54.1 ± 16.4		
Education Level					
Elementary/high school (reference)	200	58.8	723	48.6	1.00
University	50	14.7	310	20.9	0.75 (0.52, 1.08)
Technical/vocational	74	21.8	358	24.1	0.96 (0.70, 1.33)
University and technical/vocational	16	4.7	96	6.5	0.96 (0.53, 1.75)
Smoking History					
Nonsmoker (reference)	87	25.8	526	35.7	1.00
Ex-smoker	197	58.5	648	44.0	1.30 (0.97, 1.73)
Current smoker	53	15.7	298	20.2	1.25 (0.85, 1.85)
Personal medical history[b]					
Measles (yes)	166	48.5	888	59.0	0.55 (0.42, 0.71)
Mumps (yes)	141	41.2	661	43.9	0.75 (0.60, 0.96)
Allergies (yes)	60	17.5	378	25.1	0.69 (0.50, 0.95)
Rheumatoid arthritis (yes)	16	4.7	88	5.8	0.57 (0.32, 0.99)
Shingles (yes)	49	14.3	87	5.8	2.21 (1.49, 3.29)
Other type of cancer (yes)	61	17.8	87	5.8	2.35 (1.62, 3.42)
Family history of cancer					
Any first degree relative (yes)	164	49.3	497	33.0	1.38 (1.07, 1.78)
Pesticide exposure (screening questions)					
<10 hrs/yr (reference)	257	75.2	1142	75.8	1.00
≥10 hrs/yr	85	24.8	364	24.2	1.12 (0.84, 1.50)
Chemical exposure (excluding pesticides)	273	79.8	1137	75.5	1.53 (1.13, 2.08)

Note. [a]Odds Ratio (OR) and 95% confidence interval (CI) stratified by age group and province of residence.
[b]Also tested and found to be not associated; acne, asthma, celiac disease, chickenpox, diabetes, hay fever, mononucleosis, rheumatic fever, ringworm, syphilis, urinating tract infections, whooping cough, drug treatment for overactive thyroid, treatment for head lice, body lice or scabies, medical implants, drug treatment for epilepsy, tonsillectomy.

cumulative exposure to pesticides of ≥10 hours per year.

Analyses of the relationship between MM risk and specific pesticides (as obtained in the telephone interview) focused on the type of pesticide, major chemical classes (Table 2) and individual compounds for which at least 1% respondents reported exposure. All ORs were adjusted for age group and province, plus analyses assessed whether there was confounding by the factors identified in Table 1 (e.g., medical history variables). Mecoprop herbicide was associated with a significantly increased risk of MM [OR_{adj} (95% CI) = 1.89 (1.15, 3.12)] (Table 3). The risk of MM was not significantly associated with exposure to major herbicide classes (Table 3) of phenoxyherbicides [OR_{adj} (95% CI) = 1.32 (0.97,1.80)] and dicamba [OR_{adj} (95% CI) = 1.33 (0.98,1.80)]. Carbamate—a chemical class of insecticides and individual insecticides, carbaryl, and lindane (an organochlorine) were associated with increased risk (OR's$_{adj}$ of 1.90, 2.43 and 2.13, respectively), while other agents including DDT [OR_{adj} (95% CI) = 1.58 (0.93, 2.67)] were not significantly associated with MM risk (Table 4). Except for captan (an individual fungicide) [OR_{adj} (95% CI) = 3.11 (1.45, 6.69)] (Table 5), none of the fungicides and/or fumigants were significantly associated with MM risk.

TABLE 2. Major Chemical Classes in Terms of Combination of Individual Compounds

HERBICIDES
Phenoxyherbicides
Individual phenoxyherbicides: 2,4-D, Mecoprop, MCPA, Diclofopmethyl
Phosphonic acid
Individual phosphonic herbicides: Glyphosate (Round-up)
Thiocarbamates
Individual thiocarbamate herbicides: Diallate, Phenols: Bromoxynil
Dicamba
Individual dicamba herbicites: Dicamba (Banvel or Target)
Dinitroaniline
Individual dinitroanilinc herbicides: Trifluralin
INSECTICIDES
Carbamates
Individual carbamate insecticides: Carbaryl, Carbofuran, Methomyl
Organochlorine
Individual organochlorine (1) insecticides: Chlordane, Lindane, Aldrin
Organochlorine diphenylchlorides
Individual organochlorine (2) diphenylchlorides: Methoxychlor, DDT
Organophosphorus
Individual organophosphorus insecticides: Malathion, Dimethoate
FUNGICIDES
Amide
Individual amide fungicides: Captan, Vitavax
Aldehyde
Individual aldehyde fungicides: Formaldehyde
Mercury Containing
Mercury-containing fungicides: Mercury dust, Mercury liquid
Sulphur Compounds
FUMIGANTS
Malathion
Carbon tetrachloride
Malathion

Table 6 and Table 7 depict the results for the most parsimonious, multivariable model obtained by including all potential confounding factors that were significant at 0.20 p-value and pesticide variables significant at $p < 0.1$, for pesticide classes and individual pesticides, respectively. Based on the most parsimonious model involving major chemical classes: (1) a personal history of measles [OR_{adj} (95% CI) = 0.51 (0.39,0.67)], allergies [OR_{adj} (95% CI) = 0.67 (0.48, 0.93)], or of rheumatoid arthritis [OR_{adj} (95% CI) = 0.52 (0.29,0.93)] were significantly negatively associated with the incidence of MM; and (2) the medical history of shingles [OR_{adj} (95% CI) = 2.25 (1.47, 3.43)], a positive family history of cancer among first-degree relatives [OR_{adj} (95% CI) = 1.40 (1.07, 1.82)] were associated with a significant increase in MM risk; and (3) exposure to chemicals other than pesticides [OR_{adj} (95% CI) = 1.55 (1.13, 2.14)] and the carbamates class of chemicals [OR_{adj} (95% CI) = 1.81 (1.05, 3.12)] were associated with an increased risk of MM (Table 6). Carbaryl [OR_{adj} (95% CI) = 1.89 (0.98, 3.67)] with borderline significance, and captan [OR_{adj} (95% CI) = 2.35 (1.03, 5.35)] were associated with an increased risk of MM (Table 7).

Analyses to explore whether the associations reported in Table 7 varied by frequency of exposure (Table 8), found that for carbaryl the

TABLE 3. Herbicides: Frequency of Exposure to Herbicides Classified into Major Chemical Classes and as Individual Compounds (reported by 1% or more of responders)

Major chemical classes	MM $n = 342$		Controls $n = 1506$		OR$_{adj}$ ^{a} (95% CI)
	n exposed	% exposed	*n* exposed	% exposed	
Phenoxyherbicides, exposed	87	25.6	321	21.2	1.32 (0.97, 1.80)
Individual phenoxyherbicides					
2,4-D	80	23.4	293	19.5	1.28 (0.93, 1.76)
Mecoprop	27	7.9	81	5.4	**1.89 (1.15, 3.12)**
MCPA	8	2.3	46	3.1	0.68 (0.30, 1.53)
Diclofopmethyl	8	2.3	25	1.7	1.49 (0.60, 3.72)
Phosphonic acid, exposed	37	11.0	147	9.8	1.27 (0.82, 1.95)
Individual phosphonic herbicides					
Glyphosate (Round-up)	32	9.4	133	8.8	1.22 (0.77, 1.93)
Thiocarbamates, exposed	13	4.0	49	3.3	1.23 (0.61, 2.50)
Individual thiocarbamate herbicides					
Diallate	8	2.3	29	1.9	1.37 (0.59, 3.35)
Phenols: Bromoxynil, exposed	11	3.2	48	3.2	1.03 (0.48, 2.20)
Dicamba, exposed	38	11.1	131	8.7	1.33 (0.98, 1.80)
Individual dicamba herbicides					
Dicamba (Banvel or Target)	14	4.1	50	3.3	1.24 (0.64, 2.42)
Dinitroaniline, exposed	7	2.1	31	2.1	0.98 (0.39, 2.54)
Individual dinitroaniline herbicides					
Trifluralin	7	2.1	31	2.1	0.98 (0.39, 2.45)

Note. [a]ORs adjusted for statistically significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence.
Statistically significant results are bold.

TABLE 4. Insecticides: Frequency of Exposure to Insecticides Classified into Major Chemical Classes and as Individual Compounds (reported by 1% or more of responders)

Major chemical classes	MM $n = 342$		Controls $n = 1506$		OR$_{adj}$ ^{a} (95% CI)
	n exposed	% exposed	*n* exposed	% exposed	
Carbamates, exposed	25	7.3	60	4.0	1**.90 (1.11, 3.27)**
Individual carbamate insecticides					
Carbaryl	21	6.1	34	2.3	**2.43 (1.31, 4.49)**
Carbofuran	3	0.9	18	1.2	0.79 (0.21, 2.99)
Methomyl	3	0.9	13	0.9	1.42 (0.35, 5.78)
Organochlorine, (1) exposed	33	9.7	125	8.3	1.23 (0.79, 1.91)
Individual organochlorine (1) insecticides					
Chlordane	25	7.3	105	7.0	1.18 (0.72, 1.93)
Lindane	12	3.5	23	1.5	**2.13 (0.96, 4.74)**
Aldrin	2	0.6	6	0.4	0.82 (0.15, 4.41)
Organochlorine (2) diphenylchlorides, exposed	52	15.2	233	15.5	1.05 (0.73, 1.51)
Individual organochlorine (2) diphenylchlorides					
Methoxychlor	43	12.6	201	13.4	1.13 (0.76, 1.67)
DDT	25	7.3	59	3.9	1.58 (0.93, 2.67)
Organophosphorus, **exposed**	42	12.3	159	10.6	1.05 (0.70, 1.57)
Individual organophosphorus insecticides					
Malathion	32	9.4	127	8.4	0.97 (0.62, 1.53)
Dimethoate	9	2.6	50	3.3	0.68 (0.32, 1.46)
Diazinon	9	2.6	28	1.9	1.33 (0.59, 3.01)

Note. [a]ORs adjusted for statistically significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence.
Statistically significant results are bold.

TABLE 5. Fungicides and Fumigants: Frequency of Exposure to Fungicides Classified into Major Chemical Classes and as Individual Compounds (reported by 1% or more of responders)

Major chemical classes	MM $n = 342$		Controls $n = 1506$		OR_{adj} [a] (95% CI)
	n exposed	% exposed	*n* exposed	% exposed	
Fungicides					
Amide, exposed	20	5.9	58	3.9	1.68 (0.93, 3.04)
Individual amide fungicides					
Captan	14	4.1	24	1.6	3.11 (1.45, 6.69)
Vitavax	8	2.3	39	2.6	0.98 (0.42, 2.30)
Aldehyde, exposed	12	3.5	25	1.7	1.39 (0.62, 3.11)
Individual aldehyde fungicides					
Formaldehyde	12	3.5	25	1.7	1.39 (0.62, 3.11)
Mercury Containing, exposed	17	5.0	48	3.2	1.02 (0.54, 1.91)
Mercury-containing fungicides					
Mercury dust (n exposed)	17	5.0	39	2.6	1.22 (0.64, 2.34)
Mercury liquid (n exposed)	6	1.8	22	1.5	1.00 (0.39, 2.60)
Sulphur Compounds	6	1.8	21	1.4	1.39 (0.51, 3.78)
Fumigants					
Carbon tetrachloride	8	2.3	18	1.2	1.96 (0.79, 4.88)
Malathion	6	1.8	23	1.5	1.16 (0.44, 3.11)

Note. [a]ORs adjusted for statistically significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence.

TABLE 6. Most Parsimonious Model: Conditional Logistic Regression Analyses that Contained Major Chemical Classes of Pesticides and Statistically Significant Covariates

Variable	OR_{adj} [a] (95% CI)
Measles	0.51 (0.39, 0.67)
Allergies	0.67 (0.48, 0.93)
Arthritis	0.52 (0.29, 0.93)
Shingles	2.25 (1.47, 3.43)
Positive family history of cancer	1.40 (1.07, 1.82)
Exposure to chemicals (other than pesticides)	1.55 (1.13, 2.14)
Carbamate	1.81 (1.05, 3.12)

Note. [a]Odds Ratio (OR) and 95% confidence interval (CI) stratified by age group and province of residence.

TABLE 7. Most Parsimonious Model: Conditional Logistic Regression Analyses that Contained Individual Pesticide Compounds and Statistically Significant Covariates

Variable	OR_{adj} [a] (95% CI)
Measles	0.51 (0.39, 0.67)
Allergies	0.65 (0.47, 0.92)
Arthritis	0.50 (0.28, 0.90)
Shingles	2.27 (1.49, 3.48)
Positive family history of cancer	1.39 (1.07, 1.81)
Exposure to chemicals (other than pesticides)	1.57 (1.14, 2.17)
Carbaryl	1.89 (0.98, 3.67)
Captan	2.35 (1.03, 5.35)

Note. [a]Odds Ratio (OR) and 95% confidence interval (CI) stratified by age group and province of residence.

OR was highest with more than 2 days of use per year [OR_{adj} (95% CI) = 3.26 (1.25, 8.48)], whereas paradoxically for captan the OR was highest among those who used it less frequently.

DISCUSSION

Overall, this Canadian study detected risk factor patterns for MM consistent with several previous studies. The large number of participants enabled the effects of multiple variables to be examined simultaneously, which showed that a personal history of measles, allergies, or arthritis were associated with reduced risk, while a medical history of shingles or a family history of cancer were associated with increased risk. After accounting for these personal factors in multivariable models, significant

TABLE 8. Frequency of Exposure to Selected Insecticides and Fungicides Stratified by the Number of Days per Year of Exposure

Individual compound	Days/yr	MM		Controls		OR_{adj} [a] (95% CI)
		n	%	*n*	%	
Insecticide						
Carbaryl	Unexposed	321	93.9	1472	97.7	1.00
	>0 and ≤2	12	3.5	21	1.4	2.01 (0.92, 4.39)
	>2	9	3.6	13	0.9	3.26 (1.25, 8.48)
Fungicide						
Captan	Unexposed	328	95.9	1482	98.4	1.00
	>0 and ≤2	9	2.6	11	0.7	3.91 (1.47, 10.42)
	>2	5	1.5	13	1.9	2.22 (0.66, 7.44)

Note. [a]ORs adjusted for statistically significant medical variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for age group and province of residence.

associations were detected for mecoprop (a phenoxyherbicide), carbaryl (which accounted for the association with the carbamate class of insecticides), lindane (an organochlorine insecticide), and captan (a fungicide). When multiple pesticides were considered together, the only pesticide class that remained significant was the carbamate—a chemical class of insecticides [OR_{adj} (95% CI) = 1.81 (1.05, 3.12)], whereas the remaining associations were for individual insecticide carbaryl [OR_{adj} (95% CI) = 1.89 (0.98, 3.67)] with borderline significance and individual fungicide captan [OR_{adj} (95% CI) = 2.35 (1.03, 5.35)].

Although relatively few previous reports were able to examine the role of specific pesticides, these results are generally consistent with several previous studies that explored whether pesticides are involved in MM etiology.[6, 23–30] Regarding insecticides, Nanni et al.[24] reported a significant association with chlorinated insecticides among Italian agriculture workers [OR_{adj} (95% CI) = 2.4 (1.0, 5.9) for agricultural workers], with DDT being one of the specific agents (OR_{adj} = 2.6, not significant). In this Canadian study there was no overall association with the organochlorine classes of insecticides, however, lindane, an individual insecticide, was associated with increased risk [OR_{adj} (95% CI) = 2.13 (0.96, 4.74)], and similar to the Italian study, a non-significant relationship was seen for DDT (OR_{adj} = 1.6). Results were also similar regarding exposure to the carbamate class of insecticides, for which a recent study in France[31] detected a significant increase in risk [OR_{adj} (95% CI) = 2.9 (1.0, 8.6)] as did this Canadian study (OR_{adj} = 1.9), whereas this relationship was not statistically significant in the Italian study (OR = 1.7 among agriculture workers).[24] Consistency between studies is in part affected by statistical power and regional variation in pesticide usage. For example, even though the Canadian study was larger than the studies in Italy and France (342, 46, and 56 MM cases, respectively), the difference in prevalence such as for DDT exposure (3.9% vs. 10% among controls in Canada and Italy, respectively) would account partly for differences in results.

Herbicides, and in particular, phenoxyherbicide exposures, have been studied in several settings regarding both MM and other hematopoietic cancers (e.g., Canadian results for NHL were previously reported).[16] In the current study, 2,4-D was the most frequently used phenoxyherbicide, thus results were similar for both this chemical and the class of compounds (OR_{adj} = 1.3, not significant). Mecoprop phenoxyherbicide was significantly associated with MM (OR_{adj} = 1.9), however, this relationship did not remain significant in the final analyses that included multiple pesticides. The OR here was similar to that of Erikson and Karlsson who reported an increased risk of MM with exposure to phenoxyherbicides [OR (95% CI) = 1.9 (0.8, 4.4)].[11] Similarly, an occupational cohort study in New Zealand reported higher myeloma mortality among phenoxyherbicide producers, but not sprayers.[25]

Fungicides as a group have been considered in previous studies of MM, and similar to this study, no significant associations have been reported.[24,31] However, previous studies have not reported individual chemicals in this class, thus the association detected here for captan is a first-report that requires confirmation in other settings.

Several studies reported an elevated MM risk among workers in occupations with an increased likelihood of using pesticides. A meta-analysis reported in 2007 examined studies of hematopoietic cancers and was able to combine results from two studies of MM to obtain an OR of 1.16 (95% CI = 0.99, 1.30)[26] for pesticide-related occupations. Several studies detected elevated MM risks among agricultural workers, including increasing levels of risk with increasing duration of farming,[12,27] however, not all studies observed this effect.[6] The Agricultural Health Study (AHS) followed a cohort of pesticide applicators in which, with 71 MM cases, incidence higher than expected occurred in one of the two states covered.[28,32] Analyses of specific chemicals within this cohort found that workers in the highest category of exposure to permethrin (a pyrethroid insecticide) had a five-fold increase in MM incidence.[29] Within a cohort of pesticide applicators of the AHS, Waggoner et al.[14] observed a significant elevated relative standardized mortality ratio for MM (1.89 and 95% CI:1.44, 2.48).

The study had several strengths and limitations, which have been outlined previously.[16, 17] Briefly, some of the strengths include: (1) testing of all study procedures via a pilot study conducted prior to the main case-control study; (2) relatively large sample size and the availability of extensive data collected from each participant, such as collection of lifetime occupational history and detailed information on pesticides use; and (3) review of tumor slides by a reference pathologist. The availability of extensive data collected from each participant provided researchers with the opportunity to examine the individual and combined effects of specific chemicals, and to account for the potential confounding by a wide range of factors. For example, it was possible to adjust (at least partially) for potential confounding by exposures that pesticide users can have to other high-risk compounds, which overcomes a limitation identified in previous studies.[11,23] The pan-Canadian approach also enabled a wide range of occupational settings and agricultural practices to be represented, which permitted direct comparisons of multiple pesticides within a single study. Like any other epidemiological case-control study, this study had some limitations, such as potential for recall bias and misclassification of pesticides exposure, and low response rates. [16, 17] As with any case-control study there was a potential for selection bias. To minimize selection bias, incident cases were identified sequentially from population-based cancer registries in five provinces except Quebec and every effort was made to contact cases while they were alive by using the initial reports to the cancer registries.

With MGUS being a premalignant disorder that precedes MM,[33] the biological plausibility of a role for pesticides in MM etiology can be assessed in part by examining pesticide–MGUS relationships. Within the AHS, MGUS was associated with several pesticides, but for the chemicals identified in this study, an increased risk that did not reach statistical significance was seen for lindane (OR = 1.9) and captan (OR = 1.9), while for carbaryl (OR = 1.0) there was no association.[34] Results related to the association between a first-degree family history of cancer, and antecedent medical conditions (e.g., shingles) and MM occurrence support previously published results,[6] but also raise interesting concepts for future studies, such as whether family history is indicative of shared genes or environmental factors.

For carbaryl and captan, the two chemicals found here to be most strongly and independently associated with MM risk, few human cancer-related data are available, and accordingly both have been listed as "not classifiable as to its carcinogenicity to humans (group 3)" by the IARC.[20,35] Having been licensed for approximately 50 years, the toxicology of each is well understood (carbaryl is a cholinesterase inhibitor that is toxic to invertebrates; captan is an alkylating agent that is an effective fungicide), and with both having relatively short half-lives they do not persist or accumulate in the environment. The rarity of these exposures (e.g., 1%–2% prevalence in controls) also makes these agents difficult to study, yet the finding here of a gradient of effect for carbaryl provides some support for this not being a chance finding. Reviews of the global epidemiological, toxicological, and basic science literature resulted in mecoprop (a phenoxyherbicide) and lindane (a hexachloro-cyclohexane insecticide) being classified as possibly carcinogenic to humans "(group 2B)".[20] In addition to pesticides having diverse and complex toxicology, biological modes of action, targets, and modes of exposure, interpretation of such results is further challenged by the mixtures that are used as active ingredients are combined with emulsifiers, carriers, and dispersants.

Even though this study was conducted in 1991–1994, most of the pesticides discussed are still for sale and in use. Some of the pesticides were restricted or banned due to the concern over their environmental persistence and possible health effects to humans.[36] DDT and chlordane were widely used in Canada and the United States in the 1970s. DDT was banned[37] in the 1980s and chlordane was completely banned[38] in 1995 in both countries. Registration of aldrin and dieldrin in Canada was discontinued in December 1990.[39] After a re-evaluation of the insecticide carbaryl, Health Canada's Pest Management Regulatory Agency, under the authority of the Pest Control Products Act, proposed the continued registration of carbaryl products for sale and use in Canada.[40] The fungicide captan is also in use in Canada but banned in several other countries.[41]

While these findings are generally consistent with previous studies, suggesting that certain pesticide exposures may increase the risk of MM, there is still great uncertainty about which specific agents, how and at what doses these act, and who would be most affected. Few studies have been able to examine the specific chemicals identified here as potential risk factors for MM (e.g., carbaryl). Thus, there is need for additional large studies, more comprehensive exposure assessment, and harmonized methods between diverse populations that permit studies to be pooled. In addition, by incorporating these improvements into study designs that assess precursor lesions, greater clarity regarding environmental causes of MM will emerge that will have direct potential to prevent cancer before it occurs.

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