Multiple Myeloma and Occupational Exposures

A Population-Based Case–Control Study

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Objective: The present study aims to identify occupational exposures associated with incidence of multiple myeloma (MM). **Methods:** A population-based case-control study of MM (ICD-9 203) was conducted among Canadian males, with a total of 342 cases and 1506 controls contributing to the final analyses. Conditional logistic regression was used to estimate odds ratios (OR) and confidence intervals (CI), stratifying by age groups and province of residence. **Results:** Based on the most parsimonious multivariable model, the following variables were significantly associated with an increased incidence of MM: exposure to coal dust (OR 1.7, 95% CI 1.2-2.4), long-held occupations as a carpenter (OR 3.2, 95% CI 1.4-7.1) or a machinist (OR 2.4, 95% CI 1.0-5.8); and immediate family member having been previously diagnosed with certain cancers (OR 1.4, 95% CI 1.1-1.8). **Conclusion:** In this study of Canadian men, a higher risk of MM may be associated with exposure to coal dust, long-held occupations as a carpenter or machinist, and a positive family history of cancer.

Multiple myeloma (MM), also known as plasma cell myeloma, is a cancer of white blood cells.[1] Plasma cells, which are a type of B cells that are produced in the bone marrow, are important in the production of antibodies.[1] Multiple myeloma occurs when there is abnormal production of plasma cells. Due to the fundamental nature of the affected system, MM is very difficult to diagnose. MM is one of the most common types of blood cancer and accounts for nearly 1% of all forms of cancer.[1]

The incidence and mortality of MM is higher among men than women,[2–6] and the disease primarily affects older individuals with median age of diagnosis of 71 years of age. Furthermore, African ancestry is also known to be a risk factor of multiple myeloma.[5,7–9] A large number of epidemiological studies have also associated occupational exposures with multiple myeloma.[9–15] Certain occupations such as railroad workers, precision metalworkers, and workers in the transportation and communication industries have been associated with increased risk of MM.[8] In addition, the duration of employment in some other occupations such as the production of synthetic yarns, plastic packaging, and miscellaneous compounds have been found to be associated with an elevated risk of MM.[12] Another study reported an increased risk of MM for men, who were agricultural, horticultural, and forestry workers, bakers and pastry cooks, dental technicians, and stone cutters/carvers.[13]

A career in the petroleum industry,[10,15] and exposure to pesticides,[11,14,16] and certain farm animals[17] have been associated with MM.

This article aims to identify the occupational risk factors associated with the elevated risk of MM among Canadian men.

METHODS

Details of the study design and methodology have been previously published.[18–20] Briefly, we conducted a six province Canadian population-based case–control study of men with an incident first diagnosis of MM between 1991 and 1994; control subjects were frequency matched by age ± 3 years to be comparable with the age distribution of the entire case group (MM, soft tissue sarcoma (STS), Hodgkin disease (HD), and non-Hodgkin lymphoma (NHL)) within each province of residence. The study had approximately four matched controls for each MM case. Deceased subjects were not included. All participating control subjects were used in the statistical analysis for MM. Cases were identified from provincial cancer registries—except in Quebec where hospital records were used—and were coded using ICD-O 2nd edition except Quebec which used ICD-O 1st edition. Control subjects were identified through provincial health insurance programs except in Ontario (telephone listing) and British Columbia (voter's lists), as generally described.[17–19] The study design consisted of two stages: stage 1 was a self-administered postal questionnaire; and stage 2 was detailed pesticide exposure information collected via telephone interview. The results in this manuscript are based on the stage 1 postal questionnaire only. The postal questionnaire collected information on demographic details, personal medical history, lifetime occupational history and specific occupational exposures of interest. Occupational information included a list of all full time jobs held by the respondent for at least 1 year. For each job held, information was collected on job titles, business organization—whether service or industry—as well as the duration of employment. Occupational exposures were grouped into those with exposure to dusts, coal products, printing products, paints, metals, pesticides, radiation and miscellaneous. Ever held jobs were defined as full time jobs at which a person has worked for at least 1 year.

Statistical Analysis

Occupations were defined as long held occupation if respondents worked for 10 years or more in that occupation. Duration of employment is the total of number of years in each long held occupation. Conditional logistic regression models were used to conduct bivariate (to select variables for multivariable model) and multivariable analyses by adjusting for age and province of residence (matching variables) to determine the association between each explanatory variable and the MM outcome. Statistically significant variables with $P < 0.20$ level became candidate for the multivariate model. All variables that were statistically significant ($P < 0.05$) as well as biologically important were retained in the final multivariate model. The adjusted odds ratios (OR) and the corresponding 95% confidence

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TABLE 1. Descriptive Characteristics of Multiple Myeloma (MM) Cases and Controls

Variables	MM (N = 342)	Controls (N = 1506)
Demographics		
Age, y		
<40	9 (26.3)	356 (23.6)
40–49	24 (8.8)	221 (14.7)
50–59	59 (18.1)	248 (16.5)
60–69	116 (34.5)	362 (24.0)
≥70	134 (36.0)	319 (21.2)
Age (Mean ± SD, y)	64.7 ± 11.1	54.1 ± 16.0
Education level		
University and Vocational	16 (4.7)	96 (6.5)
University	50 (14.7)	310 (20.8)
Vocational	74 (21.8)	358 (24.1)
Elementary and High School	200 (58.8)	723 (48.6)
Ever Lived/Worked on a farm		
Yes	176 (51.5)	673 (44.7)
No	166 (48.5)	833 (55.3)
Smoking status		
Current smoker	53 (15.7)	298 (20.2)
Ex-smoker	197 (58.5)	648 (44.0)
Nonsmoker	87 (25.8)	526 (35.7)
Medical History		
Immediate Family Member		
Diagnosed with Leukemia or Lymphoma		
Yes	164 (49.3)	497 (33.0)
No	169 (50.8)	973 (66.2)

intervals (95% CI) were reported for the logistic regression. All statistical analysis was conducted using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

Ethics

The letters of informed consent, questionnaires, and all other correspondence with study participants were approved by the relevant ethics agencies in each province. All of the information that could be used to identify study participants remained within each province of origin under the supervision of the provincial principal investigators.

RESULTS

A total of 342 cases and 1506 controls were included in the final analysis. The mean age ± SD was 64.7 ± 11.1 years and, for controls, it was 54.1 ± 16.0 years, thus the MM cases on average were 10 years older than the combined control series. Table 1 provides demographics information stratified according to MM cases and controls. On the basis of education level, the control subjects were had higher education (educational and/or vocational) compared to the cases. A higher percentage of controls belonged to current smoker and nonsmoker category whereas a higher percentage of cases were exsmokers. Almost 52% of cases lived or worked on a farm compared to 45% of the controls. Nevertheless, approximately 18% of the cases had previous diagnoses of cancer as compared to 6% of the controls group.

Table 2 provides the odds ratio for occupations adjusted for age and province. Ever-held and longest-held occupations are reported along with their occupation code. Ever-held occupation as a carpenter or farmer showed that these categories yielded an increased risk of MM, and the increase in risk was statistically significant. The long-held occupation includes cases and controls among them who worked for 10 years or more in one particular occupation. Longest held occupation as a farmers or machinists for more than 10 years was also found to be at an increased risk for MM with farmers having

TABLE 2. Odds Ratio (OR) and Corresponding 95% Confidence Interval for Relationship Between Multiple Myeloma (MM) Incidence and Different Occupations, Adjusted for Age and Province of Residence

Occupation (Code No.)	MM Cases N (%)	Controls N (%)	OR (95% CI)
Ever held occupation*			
Accountant (1)	8 (2.3)	54 (3.6)	0.6 (0.3–1.3)
Administrator (2)	9 (2.6)	30 (2.0)	1.1 (0.5–2.5)
Carpenter (12)	13 (3.8)	23 (1.5)	2.5 (1.1–5.4)
Clerk (17)	3 (0.9)	41 (2.7)	0.4 (0.1–1.3)
Constructor (19)	5 (1.5)	36 (2.4)	0.6 (0.2–1.6)
Driver (25)	18 (5.3)	60 (4.0)	1.4 (0.8–2.5)
Electrician (26)	7 (2.1)	23 (1.5)	1.5 (0.6–3.7)
Engineer (27)	6 (1.8)	47 (3.1)	0.6 (0.3–1.4)
Farmer (31, 33, 89)	41 (11.9)	106 (7.0)	1.3 (0.9–2.0)
Laborer (44)	7 (2.1)	30 (2.0)	4.0 (0.4–2.6)
Machinist (47)	9 (2.6)	25 (1.7)	1.9 (0.8–4.5)
Manager (48)	23 (6.7)	110 (7.3)	1.0 (0.6–1.6)
Mechanic (49)	13 (3.8)	44 (2.9)	1.3 (0.6–2.6)
Salesman (73)	7 (2.1)	63 (4.2)	0.5 (0.2–1.1)
School teacher (74)	11 (3.2)	60 (4.0)	0.8 (0.4–1.6)
Technician (79)	2 (0.6)	27 (1.8)	0.3 (0.1–1.3)
Office worker (97)	5 (1.5)	26 (1.7)	0.8 (0.3–2.2)
Long-held occupations†			
Accountant (1)	8 (2.3)	44 (2.9)	0.6 (0.3–1.3)
Carpenter (12)	13 (3.8)	17 (1.1)	2.8 (1.2–6.1)
Driver (25)	17 (5.0)	50 (3.3)	1.4 (0.8–2.5)
Farmer (31, 32, 89)	41 (11.9)	100 (6.6)	1.3 (0.9–2.1)
Machinist (47)	9 (2.6)	17 (1.1)	2.0 (0.8–4.6)
Manager (48)	22 (6.4)	95 (6.3)	0.9 (0.6–1.5)
Mechanic (49)	12 (3.5)	33 (2.2)	1.0 (0.9–1.0)

*Full time jobs at which a person has worked for at least 1 year.
†Derived from the ever held occupation and included cases and controls who had worked for 10 years or more in one particular occupation.

TABLE 3. Duration of Exposure as a Machinist and Carpenter Among Multiple Myeloma (MM) Cases and Control, and Odds Ratio (OR) and 95% Confidence Interval (CI) Adjusted for Age and Province of Residence

Duration (in years)	MM (N = 342) N (%)	Controls (N = 1506) N (%)	OR (95% CI)
Machinist			
No exposure	333 (97.4)	1489 (98.9)	1.0
<30 years	3 (0.9)	13 (0.9)	0.9 (0.3–3.4)
≥30 years	6 (1.7)	4 (0.3)	4.7 (1.3–17.0)
Carpenter			
No exposure	329 (97.4)	1489 (98.9)	1.0
<30 years	6 (1.8)	11 (0.7)	2.4 (0.8–7.0)
?30 years	7 (2.1)	6 (0.4)	3.3 (1.0–11.0)

an OR 1.5 (95% CI: 0.9–2.2) times, and machinists an OR of 1.8 (95% CI: 0.8–4.2).

To further explore the relationship of long-term exposure and working as farmer, machinist, or carpenter, we grouped the number of years of exposure into three categories (Table 3). The categories included no exposure, exposure for less than 30 years, and exposure for 30 years or more. No gradient of effect was seen between MM and long-held job as a farmer. However, occupation as a machinist for 30 or more years is associated with 4.7 (95% CI: 1.3–17.0) fold increased risk of MM in comparison to participants who had not worked in this job (Table 3). A similar trend was observed between carpentry experience for 30 or more years and risk of MM (OR 3.3, 95% CI 1.0, 11.0).

Specific occupational exposures were classified into six subgroups: with exposures to dusts, coal products, printing, paints, metals, and miscellaneous. Exposure to coal dust, coke dust, crude petroleum, iron, lubricants, and solvents were found to be positively associated with a statistically significant higher risk of MM (Table 4). Ever having been exposed to sources of ionizing radiations, such as uranium (OR = 2.0) and radium (OR = 1.8), were associated with an increased risk that was not statistically significant, while there was no association with non-ionizing radiation.

The significant variables (with $P < 0.20$) from the bivariate models (Tables 2–4) were included in the multivariate conditional logistic regression model to assess whether they confounded the effects of occupational factors, and of these only immediate family history of a cancer diagnosis remained in the final model. The explanatory variables with $P < 0.05$ were retained in the final model and results are presented in Table 5. Exposure to coal dust, ever-held occupation as a carpenter, and immediate family member diagnosed with leukemia or lymphoma were significantly associated with an increased risk for MM. A long-held occupation as a machinist, showed border line significance at the 5% level, and was suggestive of an increased risk for MM.

DISCUSSION

In our population-based study, we found that work that involved exposure to coal dust, a long-held occupation as a machinist, and as a carpenter were found to be associated with an increased risk for MM. Having an immediate family member diagnosed with leukemia or lymphoma was also associated with an increased risk of MM. The outcome of our study was consistent with other previous research, but a major point of difference was that our data did not reveal an association between farming and MM in the multivariable model, however it was observed that farming as an ever held job (OR 1.3, 95% CI 0.9, 2.0) or as a long-held job (OR 1.3, 95% CI (0.9, 2.1) was associated with increased risk of MM with borderline significance (Table 2). Similar findings were observed by Eriksson et al[11] in their population-based study. A few other studies also found that orchard farmers were at a higher risk of MM.[21,22] The possible reason for farmers' increased risk of MM could be attributed to their contact with various fertilizers, pesticides, and animals. Alternatively, Blair et al[25] suggested that farmers who often serve in the roles of mechanic, carpenter, welder, pesticide applicator, and veterinarian may be especially exposed to many potentially hazardous substances.[23]

Many studies have shown a positive association between pesticide use and MM.[13,16-17,24–25] Nanni et al reported a significant association between specific pesticides and increased risk of MM among Italian agriculture workers.[6] A recent meta-analysis based on studies of hematopoietic cancers reported a positive association between MM and pesticides related occupations with an OR of 1.16 (95% CI = 0.99–1.30).[26] An agricultural health study conducted in Iowa and North Carolina that researched the pesticide applicator profession found that such individuals faced a higher risk of being diagnosed with MM.[27] In the AHS, follow-up of a cohort of pesticide applicators revealed 77 MM cases having occurred, indicating incidence higher than expected in one of the four states covered.[28] In-depth analyses of our Canadian data to examine specific types of farm-work (not fully presented here), revealed that short-term occupation as a pesticide applicator was positively associated with MM at the bivariate level of analysis (OR = 2.77, 95% CI = 0.98–7.83), but the association was not significant in the multivariate analysis. However, overall there is considerable consistency in these results regarding MM risk among pesticide applicators.

Subjects in our study who were exposed to coal dust were 1.7 times more likely to have MM (95% CI: 1.1–2.3). Our result was similar to those of Sonoda et al[15] who determined that coal miners were 1.8 times more likely to have MM. Work in coal mines can be associated with exposure to coal dust. Demers et al[17] in their population-based case–control study of MM and various occupations and industries, found an association between working in a coal-product manufacturing industry and MM.[16] The carpentry profession was also found to be associated with MM in our study (OR = 2.8). Our results are similar to a case-control study by Brownson and Rief,[29] who found that those who worked as a carpenter were 3.1 times more likely to be diagnosed with MM.[29] A few other studies also showed that occupation as a carpenter was associated with an increased risk of MM.[30-32]

In addition to associations being detected for ever having worked in various occupations, we found that certain associations became stronger with longer term employment, such as for work as a machinist. This was consistent with other studies, such as by Sonoda et al.[15] who found that machinists were 1.4 times more likely to develop MM, which was similar to findings of Demers et al,[16] while Brownson and Rief found an even stronger association (OR = 4.9).[29] Consistency was also demonstrated in several other studies which found that machinists had an increased risk of MM.[33-34]

Also consistent with other studies was our finding that having an immediate family member diagnosed with cancer was associated with increased risk of MM. In a hospital-based case-control study, a family history of hematologic malignancy (ICD 200-208) was associated with a 2.4-fold elevated risk of MM.[8] Our study determined that a family history of leukemia, lymphoma, or Hodgkin's disease was associated with an OR of about 1.4 times.

Major strength of our study included the large sample size and that our in-depth questionnaire detailed occupation history allowed us to collect information about an individual's long-held jobs, and enabled acquisition also of information about non-occupational factors. In addition, diagnoses were confirmed a reference pathologist, which was feasible for approximately 60% of the MM cases.

However, our study did have some limitations, such as the fact that occupational exposure were self-reported which could lead to some recall bias. The study was also limited to male workers. The rate of response was approximately 67% for cases and 48% for controls, and although this is likely to be independent of the occupational categories explored in this report, there is still potential for slight selection bias that would cause the reported associations to be slightly weaker than true values. Since we did not have any information on the nonresponders, we could not determine if there were any differences between responders and nonresponders. However, we did compare the nonresponders to responders, according to their postal code, and confirmed that nonresponse was primarily due to death, a change of address, and the refusal to participate in the study. Another factor that should be considered while interpreting these findings is the possibility of false-positive findings that could arise from the large number of jobs and exposures assessed; however, the review of consistency with other studies is one way to address this limitation.

TABLE 4. Odds Ratio (OR) and 95% Confidence Interval (CI) for the Relationship Between Multiple Myeloma (MM) Incidence and Different Occupational Exposures (Ever Exposed at Work), Adjusted for Age and Province of Residence

	MM (N = 342)		Control (N = 1506)		
Exposure	**N**	**%**	**N**	**%**	**OR (95% CI)**
Dusts					
Cement dust	92	26.9	432	28.7	1.2 (0.9–1.6)
Fiberglass dust	72	21.1	319	21.2	1.3 (0.9–1.7)
Coal dust	62	18.1	149	9.9	1.6 (1.2–2.3)
Soil/field dust	96	28.1	375	24.9	1.2 (0.9–1.5)
Whey dust	7	2.1	38	2.52	0.8 (0.3–2.0)
Paper dust	31	9.1	180	11.9	1.1 (0.7–1.6)
Wood dust	81	23.7	445	29.6	0.9 (0.7–1.2)
Coke dust	20	5.9	58	3.8	1.9 (1.1–3.3)
Stone dust	28	8.2	173	11.5	0.9 (0.6–1.4)
Grain dust	89	26.0	347	23.0	0.9 (0.7–1.3)
Sand	47	13.7	303	20.1	0.8 (0.6–1.1)
Cardboard dust	20	5.9	170	11.3	0.9 (0.6–1.6)
Metal dust	76	22.2	368	24.4	1.3 (1.0–1.8)
Coal products					
Pitch	9	2.6	38	2.5	1.0 (0.5–2.2)
Asphalt	34	9.9	142	9.4	1.1 (0.7–1.7)
Crude petroleum	29	8.5	84	5.6	1.5 (0.9–2.5)
Tar/tar products	28	8.2	143	9.5	1.0 (0.7–1.7)
Printing					
Printing inks	18	5.3	134	8.9	0.8 (0.4–1.3)
Printing fluids	11	3.2	96	6.4	0.8 (0.4–1.5)
Paints					
Paints, dyes	80	23.4	442	29.4	0.9 (0.7–1.2)
Metals					
Arsenic	6	1.8	28	1.9	1.0 (0.4–2.6)
Nickel	23	6.7	85	5.6	1.4 (0.8–2.3)
Cadmium	15	4.4	55	3.6	1.3 (0.7–2.3)
Zinc	28	8.2	103	6.8	1.3 (0.8–2.0)
Mercury	11	3.2	63	4.2	0.7 (0.4–1.4)
Chromium	12	3.5	58	3.9	1.1 (0.6–2.1)
Iron	26	7.6	100	6.6	1.6 (1.0–2.6)
Lead	39	11.4	182	12.1	1.0 (0.7–1.5)
Aluminum	36	10.5	220	14.6	0.9 (0.6–1.4)
Miscellaneous					
Asbestos	52	15.2	237	15.7	1.0 (0.7–1.4)
Used motor oil	96	28.1	400	26.6	1.2 (0.9–1.6)
Diesel exhaust fumes	112	32.7	464	30.8	1.1 (0.9–1.5)
Cutting oils	47	13.7	277	18.4	0.8 (0.6–1.2)
Cleaning fluids	85	24.8	419	27.8	1.0 (0.8–1.4)
Preservatives	3	0.9	21	1.39	0.9 (0.2–3.1)
Chlorine	36	10.5	202	13.4	0.9 (0.6–1.3)
Hair permanent solutions	4	1.2	33	2.2	0.7 (0.2–2.2)
Sour gas	24	7.0	92	6.1	1.1 (0.7–1.9)
Wood smoke	80	23.4	371	24.6	0.9 (0.7–1.2)
Lubricants	113	33.0	477	31.7	1.2 (0.9–1.6)
Solvents	122	35.7	516	34.3	1.3 (1.0–1.7)
Ether	32	9.4	170	11.3	1.0 (0.7–1.6)
Mouldy grain/forage	47	13.7	176	11.7	1.2 (0.8–1.7)
Hair dye	5	1.5	33	2.2	0.7 (0.2–1.8)
Cyanide	10	2.9	36	2.4	1.1 (0.5–2.4)

(*Continues*)

TABLE 4. Odds Ratio (OR) and 95% Confidence Interval (CI) for the Relationship Between Multiple Myeloma (MM) Incidence and Different Occupational Exposures (Ever Exposed at Work), Adjusted for Age and Province of Residence (*Continued*)

	MM (N = 342)		Control (N = 1506)		
Exposure	**N**	**%**	**N**	**%**	**OR (95% CI)**
Nonionizing radiation					
Ultraviolet light	24	7.0	151	10.0	1.0 (0.6–1.7)
Horticultural grow lights	4	1.2	39	2.6	0.5 (0.2–1.3)
Unshielded microwaves	3	0.9	25	1.7	0.6 (0.2–2.2)
Ionizing radiations					
Radium	5	1.5	12	0.8	1.8 (0.6–5.3)
Uranium	9	2.6	18	1.2	2.0 (0.8–4.5)

TABLE 5. Multivariate Conditional Logistic Regression Model (Odds Ratio (OR) and 95% Confidence Interval (CI)) of the Covariates Associated Significantly with Multiple Myeloma, Adjusted for Age and Province of Residence

Variable	**OR (95% CI)**
Exposure to Coal dust	1.7 (1.2–2.4)
Long-held occupation as a Machinist	2.4 (1.0–5.8)
Long-held occupation as a Carpenter	3.2 (1.4–7.1)
Immediate family member diagnosed with leukemia or lymphoma	1.4 (1.1–1.8)

CONCLUSIONS

Overall, the results of our study are in agreement with previous studies looking into the association of multiple myeloma and various occupational exposures. Our analysis suggests that occupations as a carpenter or machinist and exposure to coal dust, were associated with increased risk of multiple myeloma.

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