Occupation, Exposure to Chemicals, Sensitizing Agents, and Risk of Multiple Myeloma in Sweden

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Abstract

Background: **This study sought to identify occupations with high incidence of multiple myeloma and to investigate possible excess risk associated with occupational exposure to chemicals and sensitizing agents in Sweden.**

Methods: **A historical cohort of 2,992,166 workers was followed up (1971-1989) through record linkage with the National Cancer and Death Registries. For each job category, age and period standardized incidence ratios and age and period adjusted relative risks of multiple myeloma were calculated using Poisson models. Exposure to chemicals and to sensitizing agents was also assessed using two job-exposure matrices. Men and women were analyzed separately.**

Results: **During follow-up, 3,127 and 1,282 myelomas were diagnosed in men and women, respectively. In men, excess risk was detected among working proprietors, agricultural, horticultural and forestry enterprisers, bakers and pastry cooks, dental technicians, stone cutters/carvers, and prison/reformatory officials. In women, this excess was observed among attendants in psychiatric care, metal workers, bakers and pastry cooks, and paper/paperboard product workers. Workers, particularly bakers and pastry cooks, exposed to high molecular weight sensitizing agents registered an excess risk of over 40% across the sexes. Occasional, although intense, exposure to pesticides was also associated with risk of myeloma in our cohort.**

Conclusions: **Our study supports a possible etiologic role for farming and use of pesticides in myeloma risk. The high incidence found in both female and male bakers and pastry cooks has not been described previously. Further research is required to assess the influence of high molecular weight sensitizing agents on risk of multiple myeloma.** (Cancer Epidemiol Biomarkers Prev 2008;17(11):3123–7)

Introduction

Multiple myeloma is a disease of malignant differentiated B lymphocytes. There are no established risk factors other than male gender, age, African American ethnicity, family history of lymphatohematopoietic cancer, and monoclonal gammopathy of undetermined significance. Chronic immune stimulation and autoimmune disorders have been less consistently related (1, 2).

Occupational studies have detected excess risk among farmers, mainly attributable to pesticide exposures (3, 4). Less consistent positive results have been observed among hairdressers, spray painters, firefighters, workers in the chemical, petroleum, timber, footwear, rubber and plastic industries, and workers exposed to ionizing radiation, asbestos, metals, engine exhausts, and specific solvents such as benzene (1, 2, 5). Due to the fact that multiple myeloma is a rare tumor, most occupational cohort studies lack statistical power, and case-control studies report a low number of exposed workers in certain occupations or chemical exposure categories (1).

This study sought to identify occupations displaying a high risk of multiple myeloma and to investigate the relationship between multiple myeloma and occupational exposure to chemicals and sensitizing agents in a cohort of almost 3 million Swedish workers followed up for 19 years, a cohort in which the relationship between occupation and various tumors had been studied previously (6, 7).

Materials and Methods

The historical cohort of all active Swedish men ages 25 to 59 years, recorded in the 1960 census, and gainfully employed and over age 24 years in the 1970 census (1,890,497 men and 1,101,669 women), was followed up from 1971 to 1989 through record linkage with the Swedish Cancer Environment Register (8, 9) and National Death Registry. This record linkage has been described in detail elsewhere (9).

The overall person-time that each person contributed to the study was allocated to the corresponding cells of the variables of stratification (occupation, industrial branch, sex, 5-year age group, calendar period, and county of residence in 1970). Whereas occupations were coded according to the Nordic Classification of Occupations at a three-digit level (9), industrial branch was

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coded on a four-digit basis in accordance with the Nordic Registry of Industries (10).

Exposure to 13 chemical agents was assessed by linking any given occupation-industry combination to a qualitative job exposure matrix developed for the Swedish workforce (11). This classified combinations as ''unexposed'' (<10% of workers exposed to levels exceeding 1/10 of the Swedish occupational exposure limit for a given substance in 1970), ''possible exposure'' (10-66% of workers exposed to such levels), and ''probable exposure'' (>66% workers exposed). It covered 73.2% of the male and 75.2% of the female cohorts used in this study, as certain combinations of job and industry were not assessed owing to the low number of subjects. The chemicals included were asbestos, chromium/nickel, lead, mercury, metals, oil mist, polycyclic aromatic hydrocarbons, pesticides/herbicides, pesticides/herbicides at peak exposure (mainly sprayers), petroleum products, quartz, solvents, and textile dust. Peak exposure to pesticides/herbicides was solely classified as ''possible exposure.'' Quartz was solely classified as ''probable exposure.''

Exposure to high molecular weight (HMW) and low molecular weight (LMW) sensitizing agents was assessed by linking the job codes to an asthma-specific job exposure matrix (12) adapted to the Nordic Classification of Occupations. HMW agents (>5 kDa) included allergenic proteins derived from animals, plants (including flour and latex), microorganisms, or biological enzymes. LMW agents included a variety of highly reactive chemicals, antigenic wood dusts, and metal antigens. For each occupation, a semiquantitative estimate was included as (*a*) unexposed, (*b*) possibly exposed, and (*c*) probably exposed to each category of sensitizing agent.

Age and period standardized incidence ratios (SIR) were calculated for each occupation using the whole

Table 1. Multiple myeloma risk among men workers by sector and occupation adjusted for age, period, and geographic area

Occupation*	Whole cohort			Subcohort 1960-1970		
	Cases	SIR†	RR‡ (95% CI)§	Cases	SIR†	RR‡ (95% CI)§
Sector 0: Professional and technical work	465	98	0.98 (0.89-1.08)	230	98	0.98 (0.86-1.12)
004 Chemical engineers and technicians	19	97	0.96 (0.61-1.51)	11	145	1.44 (0.80-2.61)
007 Surveyors, measurers, cartographers	6	195	1.95 (0.88-4.34)	5	245	2.46 (1.02-5.91)
011 Chemists	7	189	1.90 (0.91-4.00)	4	284	2.87 (1.08-7.65)
023 Agricultural horticultural researchers/advisors	6	201	2.00 (0.90-4.45)	2	125	1.26 (0.31-5.04)
052 Teachers in theoretical subjects	26	142	1.42 (0.97-2.09)	16	180	1.80 (1.10-2.94)
054 Teachers of music, arts or crafts	12	146	1.46 (0.83-2.58)	9	179	1.79 (0.93-3.44)
085 Journalists, editors	13	158	1.57 (0.91-2.71)	7	137	1.36 (0.65-2.86)
Sector 1: Administrative and managerial	106	87	0.87 (0.71-1.05)	36	76	0.75 (0.54-1.04)
Sector 2: Bookkeeping and clerical work	134	99	0.99 (0.84-1.18)	32	94	0.94 (0.66-1.33)
296 Insurance raters, claims adjusters	7	141	1.40 (0.67-2.94)	5	295	2.91 (1.21-6.99)
Sector 3: Sales work	215	99	0.98 (0.86-1.13)	86	92	0.91 (0.74-1.13)
301 Working proprietors, wholesale trade	14	142	1.41 (0.83-2.39)	4	110	1.09 (0.41-2.92)
332 Shop managers	29	118	1.18 (0.82-1.71)	12	122	1.22 (0.69-2.16)
Sector 4: Agriculture, forestry, and fishing	498	116	1.18 (1.07-1.30)	359	113	1.15 (1.03-1.28)
401 Working proprietors, agricultural, horticultural, and forestry enterprisers	317	121	1.22 (1.09-1.37)	259	115	1.16 (1.02-1.32)
412 Horticultural workers	35	131	1.32 (0.94-1.84)	13	140	1.41 (0.82-2.43)
431 Fishermen	14	151	1.50 (0.89-2.54)	13	168	1.67 (0.97-2.88)
Sector 5: Mining and quarrying	23	132	1.32 (0.88-2.00)	9	131	1.31 (0.68-2.52)
Sector 6: Transport and communications	230	96	0.96 (0.84-1.09)	147	103	1.02 (0.86-1.20)
644 Road traffic supervisors	12	148	1.49 (0.84-2.62)	3	149	1.49 (0.48-4.61)
Sector 7: Production I	861	95	0.94 (0.87-1.02)	447	94	0.93 (0.84-1.03)
735 Black smiths and forgers	14	125	1.26 (0.75-2.13)	11	159	1.61 (0.89-2.90)
738 Other metal processing work	7	129	1.39 (0.66-2.91)	3	223	2.42 (0.78-7.50)
744 Dental technicians	6	334	3.33 (1.50-7.42)	6	370	3.70 (1.66-8.24)
774 Frame, circular sawyers, and planers	19	131	1.31 (0.83-2.05)	4	130	1.32 (0.50-3.52)
782 Industrial spray painters	11	127	1.27 (0.70-2.30)	3	76	0.76 (0.24-2.35)
Sector 8: Production II	418	99	0.99 (0.89-1.10)	139	85	0.85 (0.72-1.01)
822 Baker and pastry cooks	23	154	1.53 (1.02-2.31)	16	125	1.25 (0.76-2.04)
852 Plastic products workers	11	124	1.21 (0.67-2.19)	0	0	0.00 (0.00-.)
856 Stone cutters and carvers	10	219	2.19 (1.18-4.08)	4	163	1.65 (0.62-4.40)
872 Crane and hoist operators	13	128	1.31 (0.76-2.26)	4	95	0.98 (0.37-2.61)
874 Construction machine operators	24	129	1.29 (0.86-1.93)	11	146	1.46 (0.81-2.64)
Sector 9: Services and military work	177	107	1.07 (0.92-1.25)	86	108	1.08 (0.87-1.33)
904 Prison and reformatory officials	7	215	2.16 (1.03-4.53)	5	340	3.40 (1.41-8.18)
908 Other civilian protective service work	19	123	1.24 (0.79-1.94)	3	96	0.97 (0.31-3,00)
932 Cleaners	14	122	1.22 (0.72-2.07)	2	124	1.24 (0.31-4.95)
941 Hairdressers, beauticians	12	126	1.26 (0.71-2.22)	11	121	1.21 (0.67-2.19)
981 Member of the armed forces	22	123	1.20 (0.79-1.82)	17	115	1.12 (0.70-1.81)

*Occupations with at least 5 observed cases and RR ≥ 2.00 or at least 10 observed cases and RR ≥ 1.20 in whole cohort or in subcohort.
†SIR: age and period SIR using the whole cohort as reference.
‡RR: age, period, and geographic area RR for each occupation in comparison with all others.
§95% confidence intervals for the RR.

Table 2. Multiple myeloma risk among women workers by sector and occupation adjusted for age, period, and geographic area

Occupation*	Whole cohort			Subcohort 1960-1970		
	Cases	SIR †	RR ‡ (95% CI)§	Cases	SIR †	RR ‡ (95% CI)§
Sector 0: Professional and technical work	216	100	0.99 (0.86-1.15)	92	106	1.06 (0.86-1.31)
042 Attendants in psychiatric care	12	185	1.86 (1.06-3.29)	3	101	1.01 (0.33-3.15)
053 Class teachers	20	100	1,00 (0.64-1.55)	20	129	1.29 (0.83-2.00)
Sector 1: Administrative and managerial	16	114	1.14 (0.70-1.87)	3	140	1.39 (0.45-4.31)
Sector 2: Bookkeeping and clerical work	188	97	0.96 (0.82-1.12)	48	111	1.09 (0.82-1.46)
201 Bookkeepers and office cashiers	35	101	1.01 (0.72-1.41)	18	153	1.51 (0.95-2.41)
Sector 3: Sales work	167	96	0.94 (0.80-1.11)	62	99	0.97 (0.75-1.26)
Sector 4: Agriculture, forestry, and fishing	85	101	1.01 (0.81-1.26)	10	99	0.98 (0.53-1.83)
401 Working proprietors, agricultural, horticultural, and forestry enterprisers	13	166	1.70 (0.98-2.93)	4	175	1.78 (0.67-4.75)
Sector 5: Mining and quarrying	0	0	0.00 (0.00-.)	0	0	0.00 (0.00-.)
Sector 6: Transport and communications	38	97	0.96 (0.69-1.32)	11	77	0.76 (0.42-1.38)
Sector 7: Production I	100	104	1.08 (0.88-1.33)	30	85	0.89 (0.62-1.28)
750 Toolmakers, machine-tool setters and operators	12	176	1.79 (1.01-3.15)	1	185	1.85 (0.26-13.16)
758 Other engineering and building metal work	14	174	1.73 (1.02-2.93)	2	116	1.13 (0.28-4.52)
Sector 8: Production II	96	133	1.35 (1.10-1.66)	26	152	1.53 (1.04-2.26)
822 Baker and pastry cooks	13	209	2.06 (1.20-3.57)	5	207	2.06 (0.86-4.96)
857 Paper and paperboard product worker	6	254	2.58 (1.16-5.76)	2	256	2.54 (0.63-10.16)
881 Packers	17	125	1.27 (0.78-2.04)	3	123	1.26 (0.40-3.90)
883 Store and warehouse workers	14	129	1.29 (0.76-2.18)	3	168	1.68 (0.54-5.22)
Sector 9: Services and military work	376	96	0.94 (0.84-1.06)	86	95	0.93 (0.75-1.16)
911 Catering supervisors	22	131	1.31 (0.86-1.99)	9	149	1.48 (0.77-2.85)

*Occupations with at least 5 observed cases and RR ≥ 2.00 or at least 10 observed cases and RR ≥ 1.20 in whole cohort or in subcohort.
† SIR: age and period SIR using the whole cohort as reference.
‡ RR: Age, period, and geographic area RR for each occupation in comparison with all others.
§ 95% confidence intervals for the RR.

cohort as reference. Log-linear Poisson models adjusted for geographic area were fitted to obtain relative risks (RR) for (*a*) each occupation, (*b*) possible and probable exposures to a specific chemical compared to zero exposure, and (*c*) probable exposures to HMW and LMW sensitizing agents. In these models, the number of expected cases was introduced as an offset (13). As the expected number of cases was computed by taking the age- and period-specific rates of the study cohort as reference, the RR was likewise age adjusted and period adjusted. Analyses of multiple myeloma risk by occupation were repeated for the subcohort reporting the same occupation in the 1960 and 1970 censuses. In the analysis of exposure to sensitizers, exposed occupations were deemed to be only those that had a high likelihood of exposure, and these were compared with unexposed occupations, thereby increasing the specificity of the study and reducing possible misclassification bias. Given the existence of occupations with exposure to both HMW and LMW allergens, the RRs were calculated by introducing both variables into the model. Due to differences in multiple myeloma incidence and occupational distribution between the sexes, separate analyses were done for men and women.

Results

A total of 3,127 and 1,282 cases of multiple myeloma were diagnosed in men and women, respectively. Only those occupations with at least 5 observed cases were analyzed. Tables 1 and 2 show the SIRs and RRs for all occupational sectors and for occupations with at least 5 observed cases and a RR ≥ 2.00 or with at least 10 observed cases and a RR ≥ 1.20 in the total cohort or in the subcohort.

In men (Table 1), the only occupational sector with a significant excess risk was the agriculture/forestry/fishing sector both in the general cohort [RR, 1.18; 95% confidence interval (95% CI), 1.07-1.30] and in the subcohort (RR, 1.15; 95% CI, 1.03-1.28). A significant excess risk was also detected in both analyses among working proprietors, agricultural, horticultural and forestry enterprisers, dental technicians, and prison/reformatory officials. Bakers and pastry cooks (RR, 1.53; 95% CI, 1.02-2.31) and stone cutters/carvers also displayed a clear excess risk in the cohort and a high, although nonsignificant, risk in the subcohort.

Female workers in production sector 2 (printing, ceramics, food, paper, rubber, and other chemical products) registered a significant excess risk (Table 2) both in the total cohort (RR, 1.35; 95% CI, 1.10-1.66) and in the subcohort (RR, 1.53; 95% CI, 1.04-2.26). Attendants in psychiatric care, toolmakers, machine-tool setters/operators, other engineering/building metal workers, bakers and pastry cooks, and paper/paperboard product workers registered a significant excess risk in the cohort analysis. Similar or even increased risks were detected in the subcohort, although in this case the estimators failed to attain statistical significance.

Table 3 sets out the RRs of multiple myeloma in men and women associated with occupational exposure to chemicals and sensitizing agents. Only those chemicals with at least 10 probable exposed cases are shown. Women were less exposed than men. The only significant excess risk was associated with occasional, although intense, use of pesticides/herbicides by men (RR, 1.20; 95% CI, 1.07-1.34), principally among working

proprietors and agricultural/horticultural/forestry enterprisers (data not shown). Exposure to HMW sensitizing agents registered a significant excess risk among male (RR, 1.45; 95% CI, 1.06-1.98) and female (RR, 1.59; 95% CI, 1.02-2.49) workers alike. Bakers and pastry cooks accounted for ~60% of exposed cases in both sexes (data not shown).

Discussion

This cohort study suggests the possibility of an excess risk of multiple myeloma linked to bakers and pastry cooks of both sexes as well as an elevated risk in agricultural/horticultural/forestry workers, dental technicians, stone cutters/carvers, and prison/reformatory officials among men and attendants in psychiatric care, metal workers, and paper workers among women. The results also indicate a positive association with occupational exposure to peak exposures of pesticides among men and among workers, mainly bakers and pastry cooks, exposed to HMW sensitizers.

Among our study's principal strengths are its considerable size, the stratification of the analysis into men and women, and the possibility of reassessing the results using the subcohort of persons reporting the same occupation in the 1960 and 1970 censuses. Furthermore, our analysis used two complementary approaches to the study of occupational risks associated with multiple myeloma: on the one hand, we studied the risks linked to specific occupations; on the other, we assessed the risks associated with exposure to specific agents using job exposure matrices.

Our study also displays some limitations. First, we were unable to adjust for confounding factors other than age, period, and geographic area. Second, occupation was allocated based on subjects' occupational category at the beginning of the study. Nevertheless, there are ecologic data to show that the Swedish employment market was quite stable during the study period (14). Moreover, the use of a subcohort with a more specific definition of occupation served to confirm the associations observed in the general cohort. Third, the so-called ''mass significance phenomenon'' may produce spurious significant associations due to multiple comparisons. Among occupations with at least 5 observed cases analyzed in our study, chance would account for 3 occupations with significant excess risk among men and 1 such occupation among women. These figures suggest that chance alone cannot explain all the increased risks found in our study. Finally, the use of job exposure matrices is an imperfect measure for estimating exposure

Table 3. Multiple myeloma risk associated with occupational exposure to chemicals and sensitizing agents among men and women workers adjusted for age, period, and geographic area

Occupational exposure factors	Men		Women	
	Cases	RR* (95% CI) †	Cases	RR* (95% CI) †
Chemicals ‡				
Asbestos				
No exposure	2,072	1.00	961	1.00
Possible	218	1.00 (0.87-1.15)	0	0.00 (0.00-.)
Probable	38	0.96 (0.69-1.32)	1	4.86 (0.68-34.56)
Metal compounds				
No exposure	2,250	1.00	962	1.00
Possible	27	1.15 (0.78-1.68)	0	0.00 (0.00)
Probable	51	0.87 (0.66-1.15)	0	0.00 (0.00)
Polyaromatic hydrocarbons (combustion products)				
No exposure	2,053	1.00	950	1.00
Possible	86	0.98 (0.79-1.21)	12	1.11 (0.63-1.95)
Probable	189	1.07 (0.92-1.25)	0	0.00 (0.00-.)
Pesticides/herbicides peak exposures				
No exposure	1,978	1.00	942	1.00
Possible	350	1.20 (1.07-1.34)	20	1.29 (0.83-2.00)
Solvents				
No exposure	1,922	1.00	931	1.00
Possible	293	0.97 (0.85-1.09)	23	1.20 (0.79-1.81)
Probable	113	1.11 (0.92-1.35)	8	1.60 (0.80-3.20)
Textile dust				
No exposure	2,294	1.00	926	1.00
Possible	15	0.65 (0.39-1.09)	21	0.60 (0.39-0.92)
Probable	19	1.13 (0.72-1.78)	15	0.75 (0.45-1.25)
Sensitizing agents				
LMW				
No exposure	1,209	1.00	609	1.00
Probable	524	0.99 (0.89-1.10)	46	0.98 (0.72-1.34)
HMW				
No exposure	1,693	1.00	634	1.00
Probable	40	1.45 (1.06-1.98)	21	1.59 (1.02-2.49)

*RR: age, period, and geographic area RR for each chemical factor compared to no exposure, and RR for LMW exposure adjusted for simultaneous exposure to HMW exposure and vice versa.
† 95% confidence intervals for the RR.
‡ Occupational exposure factors with at least 10 probable exposed cases among men or women workers.

and generally involves nondifferential classification bias. This misclassification, coupled with the impossibility of measuring exposure outside the job setting, would inevitably entail an underestimation of the effect. Yet we feel that, even with this limitation, job exposure matrices offer the advantage of greater statistical power resulting from pooling subjects from different occupations having a similar estimated range of exposure.

In our study, a significant excess risk was detected among male agricultural, horticultural, and forestry enterprisers. The association between multiple myeloma and farming has been extensively studied in the literature (4), but as yet the exposures responsible for this association are not sufficiently known. Among the possible etiologic agents, exposure to diesel exhausts, zoonotic virus infections, and exposure to pesticides have all been mooted (3). Indeed, the results of our study reflect an excess risk among workers exposed to pesticides that are used occasionally. Some herbicides have been shown to impair cytokine production and induce immunosuppression (3). Even so, there is no consistent evidence to date of an exposure-response gradient of or a recognized biological mechanism for the role of pesticides in multiple myeloma carcinogenesis (15).

The bakers and pastry cooks in our cohort, male as well as female, registered an elevated risk of multiple myeloma. In 1970, there were 14,924 males and 5,126 females employed as bakers/pastry cooks, accounting for 0.7% of the gainfully employed Swedish population. We found no previous study in the literature that described an association between these professions and multiple myeloma. Bakers and pastry cooks feature among the occupations exposed to those HMW sensitizing agents for which our study shows a significant association with multiple myeloma. This result highlights the fact that exposure to HMW agents commonly occurring in the bakery environment may constitute one of the causative factors underlying the excess of myelomas in this group. Among these agents are certain fungal enzymes and flour dust. As a consequence of these allergens, respiratory problems, or sensitization have been observed in this group (16, 17). Specifically, Swedish bakers, and chiefly those who worked in this profession in the 1970s and 1980s, have been reported as having an elevated risk of some immunologic responses (18, 19).

Yet, the relationship between allergic conditions and multiple myeloma is not well understood. The hypothesis that chronic immune stimulation might cause myeloma was based on the assumption that antigenic stimulation could increase the likelihood of a malignant transformation in mature B cells. More recent research has shown that malignant transformation in myeloma occurs at the level of the pre-B or stem cell, which is not stimulated by antigen. Nonetheless, chronic immune stimulation could have a promotional effect on myeloma, although there is no experimental evidence to support such a hypothesis (2). Due to the discrepancy in the results obtained in the various epidemiologic studies, it is reasonable to surmise that, if an association were to exist between chronic exposure to sensitizing agents and risk of myeloma, its biological mechanism would be complex and might be influenced by the type of allergen, individual susceptibility, simultaneous exposure to different agents, or to other as yet unknown factors.

This study indicates an elevated incidence of multiple myeloma in the agriculture/forestry/fishing sector and in bakers and pastry cooks. Workers exposed to HMW sensitizing agents, particularly bakers and pastry cooks, also registered a high risk, as did those occupations with occasional, although intense, exposures to pesticides. Some of these results should provide stimulus for further studies, particularly in the bread- and pastry-making sector where no association with this tumor has been described previously.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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