

# Multiple myeloma among Danish women: employment history and workplace exposures

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To investigate the role of employment history and workplace exposures as risk factors for multiple myeloma among women, a population-based case-control study using the Danish Cancer Registry data linkage system was conducted. All cases of myeloma diagnosed in Danish women between 1970 and 1984 (1,010 cases) and 4,040 age-matched women alive at the time of case-diagnosis were identified. Industry histories from 1%4 forward were obtained from the nationwide Pension Fund for 363 cases and 1,517 controls, and the most recent occupation on the tax record was available for 607 cases and 2,596 controls. Using industry/occupational-code combinations for the cases and controls who had industry employment, Danish industrial hygienists assessed the likelihood of exposure to 47 workplace substances. An increased myeloma risk (odds ratio [OR] = 1.2, 95 percent confidence interval [CI] = 1.0-1.5) was seen for women not in the Pension Fund but who had an occupational title coded as 'Mrs/homemaker.' Nonsignificantly elevated risks of 1.3 or greater were observed for employment in: production of agricultural products; orchards/nurseries; spinning/weaving; other textile and plastics manufacturing; hotel, entertainment and social services industries. Elevated, but nonsignificant risks were observed for possible and probable exposure to exhaust fumes, formaldehyde, wood dust, animals or animal products, and pesticides. The strongest association with myeloma was employment in the agricultural industry (OR = 1.5, CI = 0.8-2.8), however, the number of women who worked on family farms was unknown and could not be included in this risk estimate.

**Key words:** Agriculture, case-control study, Denmark, females, industry, multiple myeloma, occupation, textiles.

## Introduction

The etiology of multiple myeloma (MM) is largely unknown. A number of epidemiologic studies has shown an increased risk of myeloma among men employed in occupations or industries associated with agriculture, rubber manufacturing, and petroleum refining. Data on occupational risk factors for women with myeloma, however, have been limited. The Danish computerized-linkage system<sup>2</sup> that combines data in the national Cancer Registry with population census

data and industry histories from a national Pension Fund, afforded us the opportunity to conduct a large occupational case-control study of myeloma among women.

## Materials and study population

Women diagnosed with MM between 1970 and 1984

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( $n = 1,010$ ) were identified from the Danish Cancer Registry (DCR),<sup>1</sup> a national computerized registry of all malignancies diagnosed in Denmark. It has been estimated that 95-98 percent of all cancers diagnosed in Denmark since 1943 are included in the DCR.<sup>1</sup> Cases diagnosed with another cancer more than three months prior to the diagnosis date of myeloma or born prior to April 1897 were excluded from the study.

Four population-based controls per case ( $n = 4,940$ ) were selected from the Central Population Registry (CPR),<sup>2</sup> a computerized roster containing personal information (e.g., vital status, date of death, occupational title) on all Danish residents. The controls were matched to each case on year of birth and gender, and had to be alive in the diagnosis year of the case (index date). Potential controls were excluded if they were diagnosed with a malignancy more than three months prior to the index date.

#### *Linkage with employment information*

Industry information since 1964 was obtained by linking the civil registration number of each case and control to the Supplementary Pension Fund (SPF).<sup>3</sup> The SPF, established in 1964, is compulsory for Danish wage-earners, aged 18 to 66, who are employed at least 10 hours per week by any one employer. Employment information such as name and address of the company, type of industry, and date of employment at each company is retained in the SPF files on employed individuals (other than self-employed), pensioners, and deceased workers. Since occupation was not available from the SPF, the Central Population Registry was used to obtain the occupational title that was reported on the subjects' most recent annual income-tax form. The date associated with this tax form was not available. Occupation and industry were coded using a five-digit number based on the 1968 *International Standard Industrial Classification of All Economic Activities*.<sup>4</sup> Women who listed Mrs, Miss, or homemaker as their occupational title were considered to be unskilled workers if they had an industrial history recorded in the Pension Fund. If they were not listed in the Pension Fund, they were classified as 'Mrs/homemaker' and were excluded from the industry and exposure analyses.

#### *Exposure assessment*

For each subject in the SPF, the most recent occupational title available from the Central Population Registry was combined with each industry code. These industry/occupational-code combinations were distributed among four Danish industrial hygienists who assessed exposure to 20 broad substance categories and 27 specific substances for each combination. Like-

lihood of exposure to each substance was designated as none, possible, probable, and unknown. For most of the industry/occupation combinations, the hygienists gave primary weight to industry, and used occupation to determine whether the worker was likely to be exposed to the process of production in a 'blue-collar' job or not ('white-collar'). Women with no industry history, including those coded as 'Mrs/homemaker,' were excluded from this exposure assessment.

#### *Statistical analysis*

Maximum likelihood procedures were used to compute estimates of age-adjusted odds ratios (OR) and 95 percent confidence intervals (CI) as described by Gart.<sup>5</sup> For each occupational title, ORs were calculated by comparing each individual occupational title with all other occupational titles combined. ORs for each industry were calculated by comparing individuals employed in an industry with those never employed in that particular industry. Only women with an industry history were included in the analysis of workplace exposures. ORs were calculated for probable and possible exposure to a workplace exposure using subjects unexposed to that substance as the comparison group.

## **Results**

### *Occupation*

Sixty percent (607) of the cases and 64 percent (2,596) of the controls reported an occupational title on their tax records. Of these individuals, occupations of percent of the cases and 49 percent of the controls were coded as 'Mrs/homemaker.' An additional 19 percent of the cases and 22 percent of the controls were coded as 'unskilled' workers, not-otherwise-specified (NOS), leaving a total of 166 cases and 765 controls with a specific occupational title. Table 1 presents the age-adjusted ORs for 29 individual or grouped occupational titles. Only women with the occupational title 'Mrs/homemaker' who were not in the SPF had a statistically significant elevated risk of myeloma. Of the professional occupations, only the engineer/lawyer/accountant category was associated with myeloma risk. For the blue-collar jobs, elevated, but nonsignificant, risks were seen for: food/alcohol/tobacco workers; spinning/weaving textile workers; miscellaneous workers; cook/kitchen assistants; and household help. No elevation in risk was observed for farmers, cutter/milliner/dressmakers, or unskilled workers. No cases worked in the paper/printing occupations, or in dry-cleaning/laundry operations (occupations found to be a risk factor for men in previous studies).

### Industry

According to the SPF computer files, 61 percent of both the cases and controls were not employed in an industry since 1964. These subjects, in addition to 28 cases and 71 controls who were in the SPF but had an employer for which the industry could no longer be identified, were excluded from the analysis. The final population on which the industry analysis was based was 363 cases and 1,517 controls. The average length of employment since 1964 (the date of SPF start-up) was 5.4 years for cases and 5.8 years for controls. The mean number of industries in which cases and controls worked was 2.6.

Table 2 presents the age-adjusted ORs of MM associated with employment since 1964 in selected

industries. Although none of the risks was statistically significant, elevations in risk of 30 percent or more were observed for employment in the following industries: production of agricultural products; orchards/nurseries; spinning/weaving; other textile and plastics manufacturing; hotel, entertainment, and social services. When analysis was restricted to women born after 1913, thus aged 50 and younger in 1964—the group more likely to have been employed at the start up of the Pension Fund—the ORs increased to 1.9 for production of agricultural products, 2.0 for orchards/nurseries, and 2.5 for plastics manufacturing, and stayed about the same for spinning/weaving, other textile, hotel, entertainment, and social services industries.

Based on the occupational title from the tax record, over 80 percent of the women (both cases and controls) employed in the agricultural, spinning/weaving, and other textile industries were 'blue collar' workers.

Table 1. Age-adjusted odds ratios (OR) of multiple myeloma for most recent occupational titles among Danish women

| Occupational title                | Cases<br>(n = 607) | Controls<br>(n = 2,596) | OR  | (CI) <sup>a</sup> |
|-----------------------------------|--------------------|-------------------------|-----|-------------------|
| Farm/land owner, farmer           | 4                  | 15                      | 0.9 | (0.3-3.0)         |
| Tenant farmer/gardener            | 0                  | 7                       | 0.0 | —                 |
| Food/alcohol/tobacco<br>worker    | 4                  | 8                       | 2.2 | (0.5-7.9)         |
| Cutter/milliner/<br>dressmaker    | 11                 | 49                      | 1.0 | (0.5-1.9)         |
| Spinning/weaving/other<br>textile | 3                  | 8                       | 1.6 | (0.3-6.8)         |
| Paper/printing                    | 0                  | 4                       | 0.0 | —                 |
| Plant owner/foreman               | 1                  | 8                       | 0.5 | (0.0-4.2)         |
| Warehouse/factory<br>worker       | 7                  | 33                      | 0.9 | (0.4-2.2)         |

Table 2. Age-adjusted odds ratios (OR) of multiple myeloma associated with employment since 1964 in selected industries among Danish women

| Industry              | Employed since 1964 |                         |     |                   |
|-----------------------|---------------------|-------------------------|-----|-------------------|
|                       | Cases<br>(n = 363)  | Controls<br>(n = 1,517) | OR  | (CI) <sup>a</sup> |
| Agricultural products | 14                  | 41                      | 1.5 | (0.8-2.8)         |
| Orchards/nurseries    | 11                  | 31                      | 1.5 | (0.7-3.2)         |
| Food                  | 33                  | 117                     | 1.2 | (0.8-1.8)         |
| Alcohol               | 4                   | 17                      | 1.0 | (0.3-3.1)         |
| Tobacco               | 2                   | 12                      | 0.7 | (0.1-3.3)         |
| Spinning/weaving      | 7                   | 21                      | 1.1 | (0.4-3.2)         |

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Only one case employed in the plastics industry had an occupational title and it was coded as 'unskilled, NOS.' Of the 12 controls employed in the plastics industry, the only non-'blue collar' occupational code was for one office assistant.

#### Exposures

Table 3 presents the age-adjusted ORs associated with possible and probable exposure to 20 broad categories of workplace substances for the 1,880 subjects with industry information. ORs for the 27 specific substances are not presented in the table since exposure to only a few of these substances increased MM risk (discussed below). Among the substances within the broad categories, elevated, but nonsignificant, risks were observed for both possible and probable exposure to exhaust fumes, formaldehyde, wood dust, animals or animal products, and pesticides. Exposure to gasoline, a specific exposure (not shown), had elevated but nonsignificant risks for possible (OR = 1.8; 4 cases, 10 controls) and probable exposure (OR = 2.1; 1 case, 2 controls). Exposure to domestic animals and raw milk contributed the most to the increased risk of myeloma associated with the exposure category 'animals or animal products.' Risks of one or less were seen for probable and possible exposure to coal and oil products, organic solvents, paints, plastic materials, soldering,

metals, silica dust, other inorganic dust, and ionizing radiation.

#### Discussion

This population-based case-control study is one of the first to evaluate employment history and workplace exposures as risk factors for women with MM. Access to the Danish record-linkage system provided over 1,000 newly diagnosed cases of myeloma among women from 1970-84. Although only 36 percent of these cases and 38 percent of the controls worked in an industry since 1964, these employment figures are comparable to those in the United States based on 1970 labor statistics.<sup>4</sup> This underscores the difficulty in studying workplace exposures among women, especially for diseases that affect the elderly such as MM.

No specific industry or workplace exposure was found to be statistically associated with myeloma risk among Danish women. However, nonsignificant risks of 1.3 or greater were observed for several occupations, industries, and workplace exposures which have been suggested as risk factors in previous studies.

Employment in agricultural activities such as farming is a well-documented risk factor for myeloma among males<sup>5</sup> and has been suggested as a risk factor

Table 3. Age-adjusted odds ratios (OR) of multiple myeloma associated with possible and probable workplace exposures among Danish women\*

| Exposure                                | Possible exposure |          |     |                   | Probable exposure |          |     |                   |
|-----------------------------------------|-------------------|----------|-----|-------------------|-------------------|----------|-----|-------------------|
|                                         | Cases             | Controls | OR  | (CI) <sup>b</sup> | Cases             | Controls | OR  | (CI) <sup>b</sup> |
| Coal and oil products                   | 39                | 170      | 1.0 | (0.7-1.5)         | 2                 | 11       | 0.8 | (0.1-3.9)         |
| Exhaust gases                           | 8                 | 26       | 1.4 | (0.6-3.2)         | 4                 | 11       | 1.6 | (0.4-5.5)         |
| Organic solvents                        | 59                | 277      | 0.9 | (0.7-1.3)         | 6                 | 46       | 0.6 | (0.2-1.4)         |
| Paints and lacquers                     | 10                | 54       | 0.8 | (0.4-1.6)         | 7                 | 43       | 0.7 | (0.3-1.7)         |
| Rubber manufacturing/vulcanization      | 0                 | 2        | 0.0 | —                 | 1                 | 2        | 2.1 | (0.1-30.2)        |
| Plastic materials/adhesive <sup>c</sup> | 13                | 54       | 1.0 | (as-2.0)          | 8                 | 35       | 1.0 | (0.4-2.2)         |
| Formaldehyde                            | 56                | 233      | 1.1 | (0.8-1.6)         | 4                 | 12       | 1.6 | (0.4-5.3)         |
| Phenol                                  | 28                | 108      | 1.2 | (0.7-1.9)         | 3                 | 23       | 0.6 | (0.1-2.2)         |
| Metals and metal compounds              | 20                | 91       | 1.0 | (0.6-1.8)         | 3                 | 36       | 0.4 | (0.1-1.3)         |
| Soldering                               | 3                 | 31       | 0.4 | (0.1-1.5)         | 0                 | 1        | 0.0 | —                 |
| Wood dust                               | 5                 | 12       | 1.8 | (0.6-5.7)         | 3                 | 7        | 1.9 | (0.4-8.1)         |
| Leather dust                            | 1                 | 2        | 2.1 | (0.1-29.7)        | 1                 | 0        | ∞   | —                 |
| Other biologic organic dust             | 51                | 306      | 0.7 | (0.5-1.0)         | 51                | 198      | 1.1 | (0.7-1.6)         |
| Asbestos                                | 2                 | 8        | 1.1 | (0.2-5.4)         | 0                 | 1        | 0.0 | —                 |
| Silica dust                             | 2                 | 14       | 0.6 | (0.1-2.8)         | 0                 | 1        | 0.0 | —                 |
| Other inorganic dust                    | 44                | 229      | 0.8 | (0.6-1.2)         | 17                | 78       | 1.0 | (0.5-1.7)         |
| Animals or animal products              | 20                | 80       | 1.2 | (0.7-2.0)         | 26                | 102      | 1.2 | (0.7-1.9)         |
| Pesticides                              | 24                | 84       | 1.3 | (0.8-2.1)         | 3                 | 7        | 1.9 | (0.4-8.4)         |
| Ionizing radiation                      | 6                 | 29       | 0.9 | (0.3-2.3)         | 0                 | 6        | 0.0 | —                 |
| Nonionizing radiation                   | 6                 | 21       | 1.2 | (0.4-3.3)         | 0                 | 0        | —   | —                 |

\* Based on 363 cases and 1,517 controls who had an industry history.

<sup>b</sup> CI = 95% confidence interval.

<sup>c</sup> Does not include formaldehyde and phenol-based adhesives.

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for women in at least one study.<sup>8</sup> The specific exposures responsible for this association are not known, although suspected agents include pesticides,<sup>9,11</sup> engine exhausts,<sup>12,13</sup> grain dusts,<sup>14</sup> and domestic animals.<sup>15</sup> In this study, Danish women employed in the agricultural industry had a 2.5-fold risk of myeloma. Elevated nonsignificant risks of myeloma were observed among women with possible and probable exposure to pesticides and animals or animal products. NO risk was seen for the occupational title 'farmer' as listed on the tax record, however, the self- or family-employed women who worked on family farms but did not list their occupation as farmers were not included in this analysis. Thus, this report may not accurately reflect the agriculturally related risk of myeloma among women.

The elevated risk of myeloma among Danish women employed in the spinning/weaving and other textile industries resembles findings from a Swedish study which noted an increased risk of myeloma among female textile workers in the wool industry.<sup>16</sup> Delzell *et al.*<sup>17</sup> observed no excess of myeloma, however, in a cohort study of female textile workers.

Positive associations also were found for women employed in food, restaurant, hotel, and entertainment industries. Specific occupations such as food/alcohol/tobacco workers, and cooks/kitchen assistants had elevated risks. This is in agreement with several other studies which showed increased risks for various food/beverage-related jobs.<sup>8,18</sup> Employment as household help also was associated with myeloma in our study. Other studies have shown excess myeloma with employment as a maid or janitor.<sup>8,19</sup>

Employment in the plastics manufacturing industry was associated with myeloma risk, although based on small numbers. The plastics industry has not been singled out previously as a workplace with excess myeloma incidence; however, organic solvents and other potential carcinogens are used commonly. A few studies have suggested a link between myeloma and occupational exposure to benzene<sup>19,20</sup> but our exposure analysis revealed NO association with any organic solvents including benzene ( $OR=0.8$ , for possible or probable exposure). Excess deaths due to myeloma have been reported for women employed in an aircraft maintenance facility, who had exposures to a variety of solvents.<sup>21</sup> Although an association with organically high polymers (plastics and elastomers) has been observed in a population-based case-control study,<sup>22</sup> exposure to plastic materials or nonformaldehyde or phenol-based adhesives, in our study, did not increase the risk of myeloma. Our data do suggest that, unlike other studies,<sup>22</sup> exposure to formaldehyde may influence myeloma risk. Excesses of myeloma among

women occupationally exposed to rubber have been reported in two previous studies.<sup>23,24</sup> In our study, however, only one case was exposed to rubber manufacturing or vulcanization.

A significantly elevated myeloma risk was observed for the women who listed Mrs, Miss, or homemaker ('Mrs/homemaker') as their occupation on their tax records and who were not in the Pension Fund. Because no date was associated with an occupational title, it is unclear for how many years these women were so listed on their tax records. We only know that since 1964, they did not have an industry history. Although Danish women may become homemakers later in life, they tend to retain their past occupational titles on their tax records, especially if schooling was required to attain the position. This also suggests that these women were probably homemakers. Homemakers potentially are exposed to a number of chemicals, cooking fumes, and other indoor pollutants that could put them at increased risk of cancer. The possibility of a chance finding, however, cannot be ruled out. Women who listed the occupational title Mrs, Miss, or homemaker but who worked in an industry at least since 1964 (considered here 'unskilled workers, NOS'), did not have an increased risk of myeloma.

Two previous studies have suggested a positive association between myeloma and employment as a cosmetologist,<sup>25,26</sup> while a large cohort study of cosmetologists in Connecticut<sup>27</sup> and an Australian population-based case-control study<sup>8</sup> showed no association. Other studies have reported excesses of MM among users of hair dyes.<sup>28,29</sup> In our study, no excess risk of myeloma was observed among hairdressers (based on one case and six controls).

Several aspects of this study need to be considered when interpreting the findings. Although the percentage of Danish women employed since 1964 was similar to that of other developed countries, the number of women working in any one specific industry was fairly small. The power to detect significant findings was low for some of the narrowly defined industries, however, it was not low for some of the broader industries or for many of the exposures. Industrial employment histories since 1964 were based on records maintained in a nationwide central office and were highly accurate and complete. Industry information prior to 1964 was not available; thus, industrial workplace exposures which occurred earlier in life could not be evaluated. The occupational title, from the tax record, reflected only the most recent occupation with no year associated with it. Therefore, the occupational title was used primarily to distinguish between 'blue-collar' and 'white-collar' jobs for assessing workplace exposures. The exposure assessments provided by the industrial hy-

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gienists were based on their general knowledge of the coded industries and occupations rather than interview or monitoring data. This method of evaluation had a number of limitations: (i) exposure misclassification may have occurred if occupation and industry codes could not be linked specifically to exposures; (ii) the specific chemicals used by certain industries may not have been evident from the industry codes; and (iii) changes in exposures over time could not be addressed.

Despite these potential limitations, the Danish linkage computerized system was an excellent resource for identifying female myeloma cases and controls and for investigating employment history and workplace exposures as potential risk factors. Our findings of an increased myeloma risk among Danish women employed in agricultural and textile industries are consistent with previously suggested associations and deserve further investigation.

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