ORIGINAL ARTICLE

Asbestos exposure and differences in occurrence of peritoneal mesothelioma between men and women across countries

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Objective: In several countries the incidence of peritoneal mesotheliomas among women closely mirrors the pattern among men. The aim was to investigate the role of asbestos exposure in the aetiology of peritoneal mesotheliomas in women and men.

Methods: All cases of peritoneal mesothelioma were selected from the Swedish and Netherlands Cancer Registers for the period 1989–2003. For both countries incidence rates were calculated and stratified by sex. A linear regression analysis was used to analyse the existence of a trend over time.

Results: Among men the incidence rate of peritoneal mesothelioma in the Netherlands (0.60 per 100 000 persons) was consistently higher than in Sweden with an average ratio of 1.8 (range 1.4–2.8). In both countries no trend over time was observed. During the 15-year period in the Netherlands the incidence rate among men was about 3.3-fold higher than among women. In Sweden the incidence rate among women was slightly higher than in men up to 1999, and thereafter about threefold higher among men. This sudden shift was statistically significant and seemed mainly caused by changes in classification of peritoneal tumours.

Conclusion: The absence of a time trend in the incidence rate of peritoneal mesothelioma in the Netherlands and Sweden in the past 15 years may point to a more limited role of occupational exposure to asbestos in the aetiology of peritoneal mesothelioma than for pleural mesothelioma, especially among women. The observed drop around 2000 in annual incidence of peritoneal mesothelioma among Swedish women indicates the presence in the past of a substantial misclassification with other tumours in the peritoneum.

In many Western countries the pleural mesothelioma incidence among men has increased dramatically in the past 30 years.¹ In recent years in some countries a deceleration or leveling off of mesothelioma rates has been observed,^{2–4} whereas in other countries the mesothelioma incidence is still expected to rise until 2020.^{5–7} These trends have been attributed to occupational exposure to asbestos which has been substantial throughout the workforce from the 1930s up to the 1980s. It was estimated that among men with pleural mesothelioma the attributable risk was 88%.⁸ In some countries the pleural mesothelioma risk among women appears to be constant over time, suggesting that the incidence among women may be less dependent on occupational asbestos exposure.^{2–5,8} It has also been suggested that the constant incidence among women implies that environmental exposure to asbestos is associated with a negligible risk⁵ or that the typical levels of environmental asbestos exposure will not exceed the threshold for mesothelioma risk.²

Peritoneal mesothelioma is also linked to asbestos exposure, although with a much lower attributable risk than for pleural mesothelioma—that is, about 58% among men and less than 23% among women.⁸ Another study on elevated asbestos fibre contents in lung tissue concluded that 75% of peritoneal mesothelioma in men were most likely asbestos-related, whereas only 33% of the cases among women were attributed to asbestos exposure.⁹ It has been suggested that peritoneal mesotheliomas occur primarily among workers with higher cumulative exposures¹⁰ and that the risk increases more steeply at high exposures compared with pleural mesothelioma.^{11–12} The participation of women in the industrial workforce was low, especially in occupations with high asbestos exposure such as insulators, miners and shipyard workers. Thus, a primary hypothesis would be that the peritoneal mesothelioma rates between men and women differ at least to the same extent as those for pleural mesothelioma.

Trends in peritoneal mesothelioma among men and women are not as well described as trends for pleural mesothelioma. However, in the few countries with published data on trends, the annual incidence of peritoneal mesothelioma among women closely mirrors the pattern among men.^{6–13–14} This surprising finding raises several important questions. First, is peritoneal mesothelioma in women the same disease as peritoneal mesothelioma among men? Second, do peritoneal mesothelioma and pleural mesothelioma differ between men and women with regard to asbestos exposure as a causal factor? The aims of this paper are to analyse differences in incidence rates of peritoneal mesothelioma in two countries and to evaluate time trends in incidence of peritoneal mesothelioma among men and women.

MATERIAL AND METHODS

Data collection

All cases of malignant peritoneal mesothelioma were selected from the Swedish and Netherlands Cancer Registers. Since the Netherlands Cancer Registry has complete national coverage from 1989 onwards only, the period for both countries was limited to 1989–2003. For all cases of malignant peritoneal mesothelioma information was retrieved on year of birth, year of diagnosis, and sex. All cases were pathologically confirmed and topographical and morphological classifications were coded according to the International Classification of Diseases for Oncology (ICD-O).¹⁵ Cases were defined by the localisation “peritoneum” (C48 according to ICD-O 10; 158 according to ICD-O 7, 8 and 9) and by morphological codes for peritoneal mesothelioma (codes M9050 to M9055 in the Netherlands; code 776 in Sweden). Permission for this study was granted by

Abbreviations: ICD-O, International Classification of Diseases for Oncology

Figure 1 Incidence of peritoneal mesothelioma among women (straight line) and men (dotted line) in the Netherlands in the period 1989–2003.

the Ethics Committee of the Netherlands Cancer Registry and the regional Ethics Committee in Umeå.

Analysis

Incidence rates for peritoneal mesothelioma, stratified by sex, were calculated for three-year periods by dividing the number of peritoneal mesotheliomas by the number of person-years in each period, derived from the yearly age distributions of the Dutch and Swedish populations from 1989–2003.

The distribution of peritoneal mesothelioma by age was compared between men and women by means of the Chi-square test. As the number of cases was very low, this comparison was based on three age groups (25–50, 50–69 and ≥70 years). A linear regression analysis was used to analyse the existence of a trend over time with the annual number of peritoneal mesothelioma as dependent variable and the year of diagnosis as independent variable. The effect of a change in diagnostic procedures was investigated by introducing a period effect into the linear regression model, defining different cut-off points for distinct periods. The linear regression model with

Figure 2 Incidence of peritoneal mesothelioma among women (straight line) and men (dotted line) in Sweden in the period 1989–2003.

period effect with the best goodness-of-fit (maximum likelihood) was selected.

RESULTS

In the period 1989–2003 among women in the Netherlands the annual number of peritoneal mesothelioma varied between one and 10 cases with on average five cases per year. Among men, the annual incidence of peritoneal mesothelioma varied between 11 and 23 cases with an average of approximately 16 cases per year (fig 1). Both among men and women no clear trend over time was present.

Among Swedish women from about 1999 onwards a decrease in annual incidence of peritoneal mesothelioma was observed from 3–13 cases per year to 0–5 cases per year. However, among Swedish men this trend was not present and the annual incidence varied from 2–8 cases/year with an average of about five cases/year (fig 2).

Table 1 presents the incidence rates for peritoneal mesothelioma among men and women in both countries. Among men the incidence rates were on average 0.60 per 100 000 in the

Table 1 Distribution of peritoneal mesothelioma among men and women in The Netherlands and Sweden, stratified by three-year period

Period	The Netherlands		Sweden	
	Mesothelioma, n	Incidence rate per 100 000	Mesothelioma, n	Incidence rate per 100 000
Men				
1989–91	45	0.61	13	0.31
1992–4	55	0.73	19	0.44
1995–7	44	0.57	9	0.21
1998–2000	49	0.63	20	0.46
2001–3	50	0.63	12	0.27
Women				
1989–91	18	0.24	22	0.51
1992–4	18	0.23	26	0.59
1995–7	8	0.10	15	0.34
1998–2000	16	0.20	20	0.45
2001–3	15	0.18	4	0.09

Netherlands and 0.34 per 100 000 in Sweden. The incidence rate in men in the Netherlands was consistently higher than in Sweden with an average ratio of 1.8 (range 1.4–2.8). Dutch women with peritoneal mesothelioma were statistically significantly younger than Dutch men with peritoneal mesothelioma ($\chi^2 = 6.59$, $p = 0.04$). The age group under 50 years contributed 15% and 6% to the total number of peritoneal mesothelioma, respectively. A similar pattern was observed among Swedish women, but the numbers were small and the conventional level of statistical significance was not reached.

In Sweden the incidence rate of peritoneal mesothelioma was higher among women than men in the period 1989–2000, but thereafter about threefold higher among men. The sudden drop in incidence among Swedish women was statistically significant with the best fit distinguishing between the periods 1989–99 and 2000–3.

DISCUSSION

The core findings in this study are that among men the incidence rate of peritoneal mesothelioma in the Netherlands (0.60 per 100 000 persons) was consistently higher than in Sweden with an average ratio of 1.8 (range 1.4–2.8) and that in both countries no trend in time was observed. Whereas in the Netherlands the incidence rate among men was about 3.3-fold higher than among women during the complete 15-year period, in Sweden the incidence rate among women was slightly higher than in men up to 1999, and thereafter about threefold higher among men. This sudden shift was statistically significant and is indicative for changes in classification of peritoneal mesotheliomas.

The average ratio of incidence rates of peritoneal mesothelioma among men between the Netherlands and Sweden (1.8) is close to the reported difference in the occurrence of pleural mesothelioma in both countries of 1.5–2.0.³ In addition, in both countries among men the distribution of all peritoneal mesothelioma cases across age was very similar to the age distribution among pleural mesothelioma (data not shown). As most cases of pleural mesothelioma can be attributed to exposure to asbestos,⁸ these findings suggest that the cases of peritoneal mesothelioma among men in both countries primarily reflect the effects of historical exposure to asbestos.

In contrast, there was no evidence of a trend in peritoneal mesothelioma over time and in both countries the incidence rates among men and women were remarkably stable over the 15-year period of investigation, with the exception of a period effect among Swedish women from 2000 onwards. The absence of a time trend in the incidence rate of peritoneal mesothelioma may point to a more limited role of occupational exposure to asbestos in the aetiology of peritoneal mesothelioma than for pleural mesothelioma, especially among women, because peritoneal mesothelioma cases among them were diagnosed at a younger age than men and also at younger age than pleural mesothelioma among women (data not shown). This interpretation is supported by studies that have presented attributable fractions for asbestos and peritoneal mesothelioma of 58–75% among men and 23–33% among women.^{8,9}

The absence of a time trend may also be explained by specific characteristics of the exposure-response relation for asbestos and peritoneal mesothelioma. Peritoneal mesothelioma has occurred primarily among workers with higher cumulative exposures¹⁰ and the risk of peritoneal mesothelioma seems more dependent on cumulative exposure than age at onset of exposure, as is the case for pleural mesothelioma.^{11,12} Moreover, the occurrence of peritoneal mesothelioma has been linked primarily to specific industries with high exposures, such as insulation companies and shipyards, from the use of crocidolite and amosite. A recent review has presented some evidence that

Main messages

- The absence of a time trend in the incidence rate of peritoneal mesothelioma in the Netherlands and Sweden in the past 15 years may point to a more limited role of occupational exposure to asbestos in the aetiology of peritoneal mesothelioma than for pleural mesothelioma, especially among women.
- The significant shift around 2000 in the annual incidence of peritoneal mesothelioma among women in Sweden is an indication of changes in diagnostic procedures and a reduced misclassification of tumours in the peritoneum.

Policy implications

- The evidence for a strong diagnostic shift in Sweden around 2000 will hamper comparisons of the occurrence of peritoneal mesothelioma within and across countries.
- The consequences of asbestos exposure among women can be better observed by incidence patterns of pleural mesothelioma than of peritoneal mesothelioma.
- Recognition of peritoneal mesothelioma as a compensable occupational disease due to asbestos exposure should take into account the larger diagnostic uncertainty among women than men.

peritoneal mesothelioma cases have been found more often in occupational cohorts with mixed or amphibole exposure than in studies of cohorts of workers primarily exposed to chrysotile.¹⁶ An alternative explanation of the absence of a time trend may be that the risk of peritoneal mesothelioma in both countries is already levelling off, as the jobs with high exposure to asbestos were typically present during the 1950s and 1960s. A previous analysis on incidence rates of pleural mesothelioma in the Netherlands and Sweden also failed to demonstrate time trends among women and showed that among Swedish men, the incidence rates in younger age groups decreased after 1988.³

The linear regression analysis demonstrated a clear period effect among women in Sweden, best described by a sudden drop in incidence of peritoneal mesothelioma from 2000 onwards. This drop in annual incidence strongly suggests a change in diagnostic procedures and is also indicative for the presence of a substantial misclassification before 2000. The fact that this diagnostic shift was not observed among women in the Netherlands may be partly due to the fact that in the Netherlands there is a longstanding tradition that almost all cases of mesotheliomas are reviewed and verified by a panel of pathologists.¹⁷

The observation of a diagnostic shift in women but not in men in Sweden raises the question of whether uncertainty in the diagnosis of peritoneal mesothelioma among women is different from that among men. Several studies have shown in the past that ovarian and gastrointestinal tumours may be misdiagnosed as peritoneal mesotheliomas and vice versa.^{18–20} A small proportion of misclassification of ovarian cancer may have a profound impact on the incidence of peritoneal tumours among women. In recent years there is a shift to immunocytochemical and immunohistochemical markers in the diagnosis of mesothelioma.²¹ In microscopical investigation of biopsy material it may be difficult to differentiate between mesothelioma

and adenocarcinoma, and recent immunohistochemical markers have shown good sensitivity and specificity to distinguish peritoneal mesothelioma in women from serous papillary ovarian and peritoneal carcinoma.²² The importance of such markers for the correct diagnosis has also been shown for pleural mesothelioma diagnosis, due to the introduction of specific markers for mesothelial cells and pulmonary adenocarcinoma in recent years.²³ The observed diagnostic shift in Sweden around 2000 may have also occurred in other countries which will hamper comparisons of the occurrence of peritoneal mesothelioma within and across countries.

In conclusion, this study has demonstrated a clear diagnostic trend in peritoneal tumours among women in Sweden. The absence of a time trend in the incidence rate of peritoneal mesothelioma may point to a more limited role of occupational exposure to asbestos in the aetiology of peritoneal mesothelioma than for pleural mesothelioma, especially among women.

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