Regional differences in incidence of malignant mesothelioma in Denmark

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ABSTRACT

INTRODUCTION: The incidence of malignant mesothelioma (MM) in Denmark has been rising rapidly since the 1950s. The aim of this study was to determine temporal developments of MM incidence and survival in Denmark as a whole and in the individual regions

MATERIAL AND METHODS: Data from the Danish Cancer Registry were used. Cases of MM of the pleura, peritoneum and pericardium occurring in the 1943-2009 period were included. National and regional incidence rates were calculated, age-standardised and stratified by various variables. Survival was calculated using Kaplan Meier plot.

RESULTS: The total national incidence of MM for men has been rising throughout the period and reached its maximum of 1.76 in 2008-2009. For women, the incidence rate has remained relatively steady, with a maximum of 0.5 in 1973-1977. Since the late 1980s, the Region of Northern Jutland has had the highest male incidence rate. The difference in relative risk for men in the Region of Southern Denmark and the Region of Northern Jutland was 1.53 in 2008-2009, and the relative risk of developing MM in the Region of Northern Jutland for the entire period collectively compared with Denmark as a whole was 1.38. No notable regional difference exists for women. Survival has improved for both men and women, but remains poor with a median survival of 12.5 months for men and 13.3 months for women in 2008-2009.

CONCLUSION: The national MM incidence for men continues to increase, perhaps showing a slight tendency towards deceleration in the most recent decade. A clear long-term effect of the Danish asbestos ban has not yet occurred.

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Malignant mesothelioma (MM) is a very rare and very aggressive cancer most often localised to the pleural and peritoneal cavity, and rarely to the pericardium and tunica vaginalis testis [1]. MM has a very poor prognosis, and survival has repeatedly been reported to be about one year from diagnosis [1]. MM is associated with previous asbestos exposure, which can be identified in approximately 90% of the cases [2]. MM normally has an induction period of 30-50 years [3]. Consequently, the incidence and mortality of MM reflect the use of asbestos some 30-40 years earlier. The incidence of MM has been rising dramatically in Denmark and the rest of the Western World since around the 1950s [4-6], but in some countries, the USA and Sweden among others, incidence rates have leveled off [7, 8].

The national annual use of asbestos in Denmark was almost non-existing up to the Second World War, but in the post-war period it climbed steadily until reaching a maximum of approximately 30,000 tons in the early 1970s [4-6, 9]. Nearly 90% of the national annual asbestos import was used in the manufacturing of asbestos cement products [9]. A full ban of asbestos use was implemented in 1980 with exception of asbestos cement products and brake linings [10], and in 1986 a definitive prohibition of all asbestos covering both import and consumption was implemented [11].

The aim of this study was to determine national and regional incidence rates for MM in Denmark in the 1943-2009 period. We aimed to ascertain whether the national incidence rate has decelerated, stagnated or continues to rise, and thus to explore the accuracy of a previous estimation, in which the peak incidence of MM in Denmark is to occur around 2015 [5], and if an effect of the Danish asbestos ban and regulations has occurred at present. Additionally, we investigated the temporal development of the Danish MM incidence and compared regional incidence rates. We hypothesised that the incidence rate in the Region of Northern Jutland was higher and showed a steeper increase than that of the other regions due to the fact that asbestos cement production took place only here. Lastly, we investigated the national survival of MM patients stratified by tumour localisation.

MATERIAL END METHODS

Data from the Danish Cancer Registry were used in this study [12]. The Registry, which is the oldest nationwide cancer registry in the world, has been in operation since 1943 and is considered to have a high degree of completeness and accuracy [12]. For each cancer diagnosis, this register contains the name of the patient, date of birth, address and sex. Specific diagnosis codes for MM have existed in the registry since its inception.

All cases coded as MM localised to the pleura, peritoneum or pericardium in the 1943-2009 period were

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Chrysotile asbestos.

identified. Cases with localisation to the tunica vaginalis testis were not included, as this localisation is extremely rare and was not assigned a specific code until 1978.

The Danish Cancer Registry uses the International Classification of Diseases (ICD). Data from the 1943-1977 period are coded in a special, extended version of the ICD-7, while data from 1978-2009 are coded according to the ICD-10. The ICD-10 was implemented in 2004, and all diagnoses in the 1978-2003 period were converted into ICD-10 to enhance comparability. Furthermore, the morphology classification was changed in 2004 from the ICD-0-1 to the ICD-0-3. In connection with these changes in coding, a review of diagnostic groups led to adjustments of the inclusion and exclusion criteria causing minor changes in incidence rates in this study compared with previous publications.

Incidence rates were calculated using a Danish revision of the statistical programme PYRS [13]. National and regional incidence rates were standardised according to the World Standard Population (WSTP), expressed per 100,000 person-years, and stratified by sex, age and calendar time of diagnosis (five-year periods).

Regional incidence rates were determined based on place of residence at the time of diagnosis, a variable available from the Danish Cancer Registry. Different divisions into municipalities, counties and regions have been in place in the 1943-1967, 1968-2006 and 2007-2010 periods. The place of residence of patients diagnosed in the 1943-2006 period was recoded to fit the present Danish municipalities and regions. The incidence rates of each region were stratified by sex, age and calendar periods and compared to the total national incidence, and standardised incidence rate ratios were calculated and tested for statistical significance.

Survival for MM patients, defined as the time (in months) between diagnosis and death, was calculated using Kaplan Meier plot [14]. The time of diagnosis is a variable available from the Danish Cancer Registry, and the date of death was obtained from the Central Office of Civil Registration (CPR) which is updated on a daily basis [15]. Due to a limited number of cases in some early periods, the pericardial MMs were included only in the total survival and the time period was restricted to 1963-2009.

Trial registration: not relevant.

RESULTS

We identified a total of 3,394 cases of MM of the pleura, peritoneum and pericardium in the 1943-2009 period. Men comprised the vast majority of cases (76%), and the pleural localisation was by far the most common (87%).

Figure 1 depicts national incidence rates for men and women in total and stratified by localisation. The total national incidence of MM for men has continued to rise throughout the 67-year study period, with a maximum of 1.76 per 100,000 person-years in the most recent period 2008-2009. It is apparent that the increase in incidence is attributable to the drastic increase in pleural MM. For women, however, the incidence rate has remained more or less steady since the 1990s, peaking at 0.5 per 100,000 person-years in 1973-1977. The incidence of MM of the pericardium was very low for both sexes throughout the period.

The regional incidence of MM for men and women is presented in **Figure 2**. For men, the Region of the Capital of Denmark shows the highest incidence in earlier periods, but since the late 1980s, the highest incidence rate has been observed in the Region of Northern Jutland. In 2008-2009, the difference in relative risk for men in the Region of Southern Denmark and the Region of Northern Jutland was 1.53 (95% confidence interval: 1.37-1.70). No noteworthy regional difference in incidence rates exists for women.

Table 1 depicts the relative risk of MM of the pleura, peritoneum and pericardium for men and women in Denmark, and in the five Danish regions for the entire period collectively. Two regions, the Region of Northern Jutland (standardised incidence ratio (SIR) = 1.38) and

TABLE 1

Regionally observed numbers (OBS) and standardised incidence ratio (SIR) of malignant mesothelioma with 95% confidence intervals (CI) for men and women in the 1943-2009 period.

	Men			Women		
Region	**OBS**	**SIR**	**95% CI**	**OBS**	**SIR**	**95% CI**
Northern Jutland	399	1.38	1.013-1.875	73	0.86	0.725-1.012
Central Jutland	339	0.64	0.500-0.829	121	0.75	0.658-0.854
Southern Denmark	532	0.90	0.715-1.142	163	0.89	0.786-0.999
Capital of Denmark	1,021	1.33	1.082-1.640	342	1.24	1.122-1.373
Zealand	277	0.71	0.539-0.948	125	1.05	0.915-1.213
Denmark	2,568	1.00	–	824	1.00	–

FIGURE 1

Age-standardised (World Standard Population) total and localisation-specific national incidence rates of malignant mesothelioma for men (**A**) and women (**B**) in the 1943-2009 period.

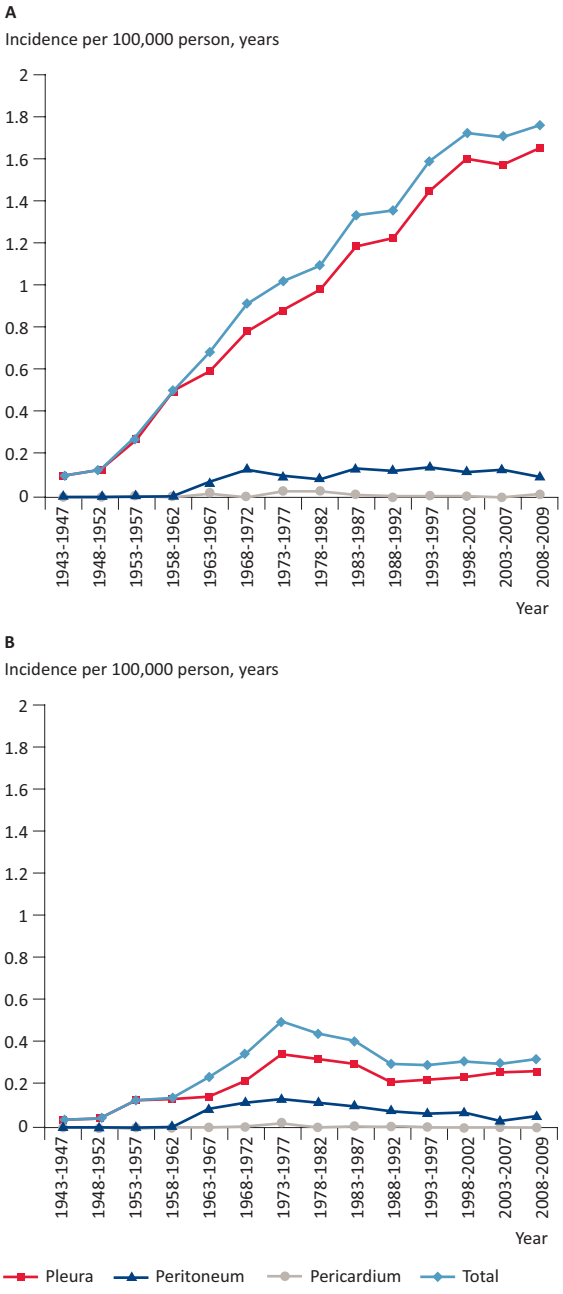
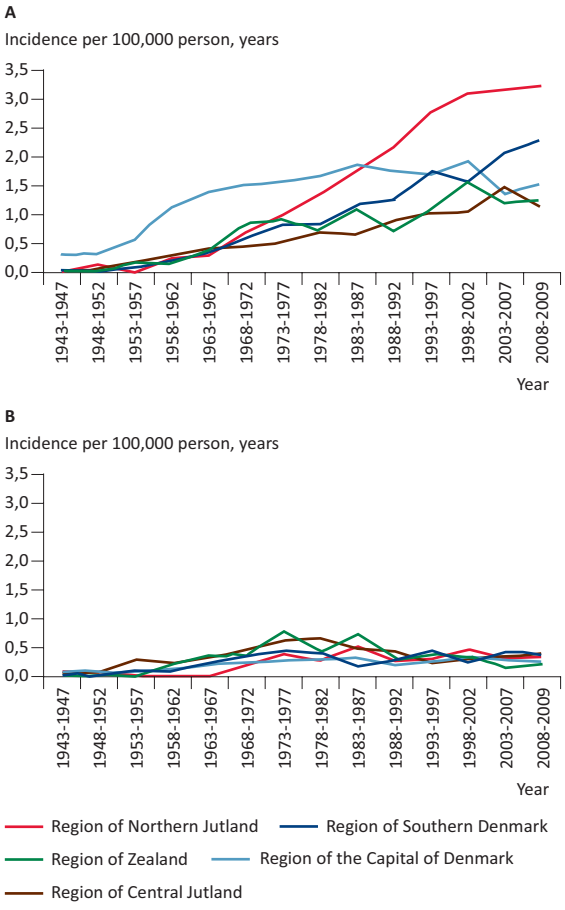


FIGURE 2

Age-standardised (World Standard Population) regional incidence rates of malignant mesothelioma for men (**A**) and women (**B**) in the 1943-2009 period.



the Region of the Capital of Denmark (SIR = 1.33), show a significantly elevated risk for men, while the Region of the Capital of Denmark alone has a significantly higher risk for women (SIR = 1.24).

Figure 3 shows the national median survival of MM for men and women in total and by localisation. When comparing the graphs, it is clear that there is no significant difference in total median survival between the sexes. The total survival has improved for both men and women, especially since the beginning of the 1990s, but remains poor with a median survival of 12.5 months for men and 13.3 for women in 2008-2009. The survival of male patients with pleural MM is considerably better than that of the male patients with MM of the peritoneum.

Moreover, the survival of the latter shows a downward tendency in the 2000s. The survival of women with peritoneal MM showed a steep increase in the late 2000s, resulting in a current, similar survival for women with pleural and peritoneal MM.

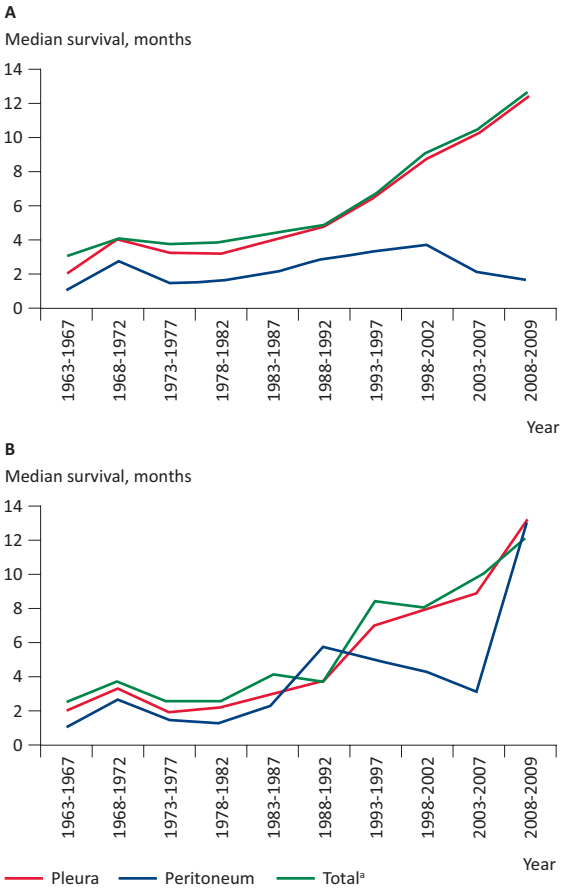
DISCUSSION

National incidence of malignant mesothelioma in Denmark

This study confirms that MM remains an uncommon disease in Denmark, especially in women. However, the total national incidence of MM for men has not declined

FIGURE 3

Age-standardised (World Standard Population) total and localisation-specific national median survival of malignant mesothelioma for men (**A**) and women (**B**) in the 1963-2009 period.



a) Pleura, peritoneum and pericardium

as per 2009, nevertheless, a tendency towards deceleration seems to have appeared during the 2000s. The graphs for total and pleural incidence for men are nearly parallel throughout the period and have risen dramatically, while the incidences for peritoneal and especially pericardial tumours have remained continuously low. This observation may be explained by the fact that the pleural cavity is the main localisation for MM and, consequently, men with pleural MM will demonstrate the largest increase in incidence. Studies have shown that peritoneal MM is associated with a higher cumulative asbestos exposure than MM of the pleura [2], and since regulations to ensure a lowering of fibre concentrations have been put in place continuously since the 1970s, this could also contribute to the difference in incidence between pleural and peritoneal tumours and possibly explain why the peritoneal incidence has not increased. The total national incidence for women shows only little increase during the period, and this is undoubtedly due to the fact that men have been more exposed to asbestos in the workplace than women [1, 2].

The most valid explanation for the continuing increase of MM-incidence in Denmark is previous national asbestos consumption, with maximum import quantities seen in the early 1970s. Improvements in diagnostic procedures and greater general awareness may contribute to this, but it is not likely that clinical improvements are responsible for an increase of this magnitude.

The highest incidence rate among men is 1.76 per 100,000 person-years in the 2008-2009 period. In comparison, the Swedish male MM incidence was 1.79 per 100,000 in 1996–2000 [16], and the corresponding US figure per 100,000 in 1999-2002 was 2.1 [17]. As previously mentioned, the incidence of MM began to decline during the 1990s in both Sweden and the US [7, 8]. The magnitude and placement in time of the peak MM incidence in a given country is associated with the total amount of asbestos imported, the proportion of different fibre types with different carcinogenic potency, and the implementation of bans and regulations regarding asbestos import and usage [8, 18]. Sweden was among the first European countries to implement asbestos bans and regulations. In 1964 the first asbestos regulation was introduced in Sweden, and a full ban including the prohibition of asbestos cement production was implemented in 1976. As a result, the Swedish national asbestos import was close to non-existing in the late 1970s [18]. Denmark introduced the first asbestos regulation in 1972 [19] and prohibited the production of asbestos cement in 1986 [11]; the total national import of asbestos in Denmark was not reduced to a negligible level until the early 1990s. This could very well be the reason why the incidence of MM in Denmark has not yet begun to decrease, while the incidence in Sweden has been decreasing for almost two decades.

Regional incidence of malignant mesothelioma in Denmark

Since the early 1990s, the incidence of MM in the Region of Northern Jutland has been consistently higher than the incidences of the other Danish regions, and the relative risk of developing MM is highest for men in this region. Furthermore, the incidence in the Region of Northern Jutland has continued to increase, while the incidence rates of the other regions seem to have stagnated. Given the well-established causal relationship between MM and asbestos exposure, it seems probable that regional differences in MM incidence are related to differences in the distribution of asbestos-consuming industries [6]. Several industries have a history of asbestos use, especially the ship building and construction industry. The asbestos cement industry in Denmark, which is represented by a single factory, Dansk Eternit-fabrik A/S,

which operated in the Region of Northern Jutland, has used the majority of the total national asbestos import [9]. Furthermore, it was the last asbestos-consuming industry subjected to prohibition. Considering these facts, it is plausible that the continuing increase in MM incidence in the Region of Northern Jutland is caused largely by the lack of timely banning of the Danish asbestos cement industry. A high relative incidence of MM was also seen in the Region of the Capital of Denmark, where the country's largest shipyards were situated.

Malignant mesothelioma survival in Denmark

The survival of MM is known to be poor [3], but according to Figure 3, there has been a definite improvement. Survival is similar between the sexes, indicating that the disease has the same natural history for men and women. The positive tendency in survival could be a result of both earlier diagnosis and more efficient treatment. For men, it is evident that survival is better for pleural than for peritoneal tumours, especially in recent years. This may, in part, be due to the fact that aggressive trimodal treatment is possible only for patients with a pleural localisation, but earlier diagnosis will most likely also have contributed.

Study limitations

This study has some limitations. The observations presented are based on data from The Danish Cancer Registry, and are generally reliable, but some degree of diagnostic misclassification and missing data is unavoidable. Also, given the rarity of MM, some groups contain very few data which increases the risk of statistical instability and random variation. Furthermore, there is a possibility of underestimation of the MM incidence due to a decline in the number of autopsies during past decades. Migration within Denmark is a potential source of error in the calculation of regional incidence, as the region of residence at the time of diagnosis is not necessarily the region in which asbestos exposure occurred. The effect of migration is reduced when dealing with a large study population, but in this study, with a rare disease and long latency, the effect of migration might be of some importance. However, a study regarding inter-regional migration in the Nordic countries showed that people with a low educational level are less disposed to migrate. As the majority of people exposed to asbestos have a low educational level, it is reasonable to assume that mobility across regions is relatively low in this group [20].

CONCLUSION

The national MM incidence for men continues to increase, perhaps showing a slight tendency of deceleration in the most recent decade. It is not possible to determine whether the estimation predicting that the peak MM incidence in Denmark will occur around 2015 is accurate [5]. It can merely be concluded that the peak MM incidence seems not to have been reached by 2009. Our results do not imply that an effect of the asbestos ban has occurred.

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