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Incidence rates of malignant mesothelioma in Denmark and predicted future number of cases among men

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Objectives This study analyzed the incidence rates of malignant mesothelioma in Denmark in order to predict the future number of cases that will occur among Danish men.

Methods The 1912 cases of malignant mesothelioma reported to the Danish Cancer registry in 1943—1993 were analyzed in order to describe current incidence rates. By a Poisson regression model the relative risks of synthetic birth cohorts were estimated and used in the prediction of the future number of cases that will occur among Danish men.

Results The incidence rate increased to 1.33 per 100 000 person-years in 1983—1987 among men and to 0.51 in 1973—1977 among women. From the Poisson regression model, the risk for birth cohorts of men, relative to the 1940—1944 cohort, peaked in the 1940—1944 cohort and decreased to 0.57 in the 1950—1954 cohort. The age-specific incidence rate peaked at 246 per 100 000 person-years in the age group 80—84 years. The future annual number of mesothelioma cases is expected to peak around 2015 with 93 cases among men born before 1955.

Conclusions The fit of the models was not ideal, but with careful interpretation of the results, it was concluded that a further increase in the number of mesothelioma cases can be expected, and the effect of regulating the environmental exposure to asbestos cannot be expected within the next 10—15 years.

Key terms age-cohort model, epidemiology.

About 65 cases of malignant mesothelioma are reported in Denmark annually (1). This rare cancer is strongly associated with exposure to asbestos (2, 3). Hence the use of asbestos in the Danish industry was banned with few exceptions in 1979 (4, 5). It is estimated that more than half the mesothelioma cases are caused by asbestos (6). Asbestos fibers are used in industry, in Denmark mostly in shipyards, for insulating materials, pipe fittings, and brake linings for trains and automobiles (3). Although the carcinogenicity of especially the amphibole asbestos fibers has been known since the 1960s, the use of asbestos in industry was continued for several years, up until the legislation prohibiting it.

The effect of banning industrial asbestos use has not yet appeared in the published incidence rates from the registry (7), perhaps due to the latency of 30 years or more from exposure to diagnosis of the disease (8, 9).

The Danish Cancer Registry was founded in 1943 and collects detailed information on diagnosed cancer cases (10).

Recent publications have predicted an alarming increase in mesothelioma deaths over the next 30 years by statistical modeling (11—13). In the present study, we aim to demonstrate an effect of the decreased exposure level through a log-linear regression analysis of the birth cohort and the period of diagnosis for Danish men, with a prediction of incidence until the year 2040. The methods of the analysis are comparable with those used in recent studies of mesothelioma trends (11—14).

Materials and methods

Data from the Danish Cancer Register were used in the study. The completeness and accuracy of the register is considered to be high (1, 10).

All cases of malignant mesothelioma diagnosed and coded as such in the period 1943—1993 were identified according to the modified ICD-7 classification (pleura,

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peritoneum and pericardium) in use prior to 1978 by the International Classification of Diseases (ICD) (1, 15) and afterwards according to the ICD-O (16) through a combination of the morphological and topographical codes. Four cases recorded as mesothelioma of the scrotum were excluded.

For each case gender, date of birth, month and year of diagnosis, and the ICD-7 or ICD-O codes were extracted and cases with ICD-O codes were converted to ICD-7 codes by a computerized conversion program into the locations pleura, peritoneum or pericardium. For calculating the incidence rates, the age distribution in the Danish population was determined through the aid of Statistics Denmark (17). Incidence rates directly standardized according to the World Standard Population (WSTP) (18) and the 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed cases (19).

The distribution of malignant mesothelioma among men by age and year of birth was analyzed by Poisson regression, as done by Peto and his co-workers (14). Birth cohorts were computed as synthetic cohorts according to age and date at diagnosis, each case being assigned to 1 birth cohort. Person-years at risk (PYR) were constructed in a similar way. Age-specific incidence rates, k_a, were estimated for the age groups 30—34 years (a=1) to 85—89 years (a=12). Birth-cohort-specific relative risks, c_b, were calculated for the cohorts born in 1875—1879 (b=1) to 1950—1954 (b=16). The relative risk for the 1940—1944 cohort, c_{14}, was set at unity.

The predicted annual age-specific incidence rates were calculated as the product of the age-specific rate and the relative risk of the birth cohort, $k_a \cdot c_b$. The fitted numbers of cases were calculated as the product of the predicted age-specific incidence rates and the person-years in the cell. Goodness-of-fit was evaluated by the Pearson's χ^2-test, and the P-values of the fit were computed (20, 21).

The predicted rates were used to estimate the number of future mesothelioma cases. The estimate was made for men born before 1955 and for all men, assuming that the relative risk for cohorts born after 1955 was 50% of the 1940—1944 cohort. This approach was used due to the very few observed cases in the younger birth cohort, since the lack of cases made the risk estimates unreliable. Population prognoses of Statistics Denmark (17) were used for calculating the estimated number of cases. The asbestos consumption in Denmark was used for estimating the exposure to asbestos (22).

For comparison a similar analysis was done using the variables period of diagnosis and age at diagnosis. The age groups were the same, and the periods, p_c, were c=1 for 1943—1947, to c=10 for the period 1988—1992. The last period (p_{11}) only contained data from 1993. The period 1988—1992 (p_{10}) was used as the basis for comparison because most of the cases were diagnosed during this period.

Results

In table 1 the total number of cases of malignant mesothelioma is shown according to their location among the men and women. The proportion of pleural mesotheliomas was greater for the men (89.5%) than the women (71.3%), and the proportion of the peritoneal tumors was greater among the women than among the men. Tumors of the pericardium comprised less than 2% of the total for both genders.

The incidence rate for the men was higher than that of the women, and it increased from 0.10 per 100 000 person-years in 1943—1947 to 1.32 (95% CI 0.47—2.17) per 100 000 person-years in 1983—1987, and then decreased to 1.31 (0.46—2.15) per 100 000 person-years in 1988—1992 (figure 1). The incidence rate for the women increased to 0.51 per 100 000 in 1973—1977, and then decreased to 0.27 in 1988—1992.

Table 2 shows the age- and birth-cohort-specific observed number (fitted number below) of cases of malignant mesothelioma among the men. Under the birth-cohort intervals the estimated birth-cohort-specific relative risks are shown, rising to a maximum (1.00) in the cohort born in 1940—1944. The estimated age-specific rates are shown under the corresponding age interval. The rate is 0.66 per 100 000 person-years in the age group 30—34 years, and it increases steadily to 246 per 100 000 person-years in the group 80—84 years. As an evaluation of the goodness-of-fit, the difference between the observed and the fitted number of cases was computed by Pearson's χ^2-test (χ^2=109, df=92, P=0.11).

Figure 2 shows the annual observed number of cases of malignant mesothelioma in quinquennia defined by midyear. Note that the period 1993—1997 only contains data of the year 1993. The estimated annual number of cases is shown for comparison, and this graph is extended into the predicted annual numbers of cases in the years

Table 1. Number of cases of malignant mesothelioma in Denmark in 1943—1993. (ICD = International Classification of Diseases)

Site of tumor	Men		Women	
	N	%	N	%
Pleura	1200	89.5	407	71.3
Peritoneum	123[a]	9.1	154	27.0
Pericardium	18	1.3	10	1.8
Total	1341	100	571	100

[a] Including one tumor coded as the ICD-7th revision code 199.3: unspecified site, abdomen.

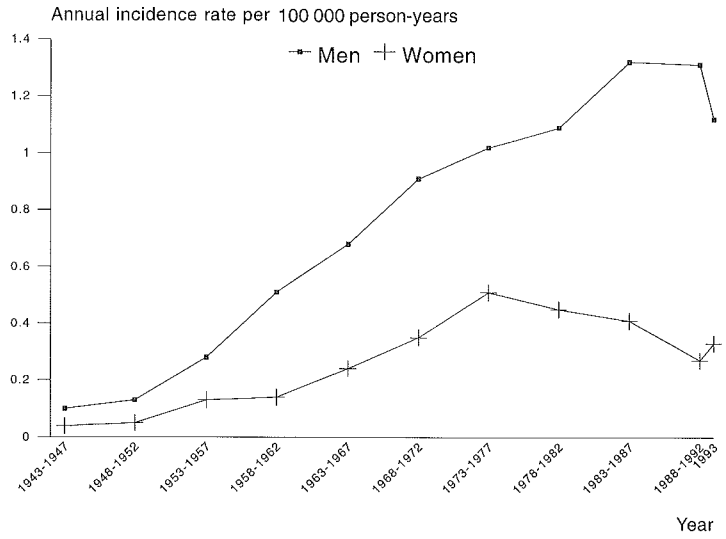

Figure 1. Age-standardized incidence rates (according to the World Standard Population) per 100 000 person-years at risk of malignant mesothelioma of the pleura, peritoneum, and pericardium among men and women in Denmark in 1943—1993.

Table 2. Cases of malignant mesothelioma among Danish men in 1943—1993 and the fitted numbers based on the birth cohort analysis. Each cell shows the observed (O) number of mesothelioma cases next to the fitted (F) number derived from the birth cohort model by multiplying the population person-years (not shown) by the product of k_a and c_b. Birth cohort, c_b, is defined by midyear.

Year of birth	Relative risk	Age group (years)[a]																					
		30—34 (0.66)		35—39 (2.22)		40—44 (4.18)		45—49 (7.76)		50—54 (19.7)		55—59 (30.8)		60—64 (57.3)		65—69 (83.6)		70—74 (130)		75—79 (185)		80—84 (246)		85—89 (220)	
		O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F
1875—1879	0.043	..		..		..		..		..		..		..		2	2.3	2	3.0	1	3.1	6	2.5	1	0.9
1880—1884	0.089	..		..		..		..		..		..		5	4.1	1	5.3	4	6.8	10	7.1	7	5.5	4	2.2
1885—1889	0.145	..		..		..		..		..		1	4.2	4	7.3	6	9.4	14	12.0	16	12.3	12	9.8	6	4.1
1890—1994	0.158	..		..		..		..		1	3.4	1	5.0	6	8.5	11	11.1	15	14.0	18	14.4	16	11.7	5	4.9
1895—1899	0.195	..		..		..		-	1.9	3	4.6	6	6.9	13	11.8	19	15.1	19	18.9	18	19.4	15	15.7	8	6.7
1900—1904	0.234	..		..		-	1.4	2	2.5	5	6.0	8	9.0	19	15.4	26	19.7	26	24.7	22	25.2	20	20.3	5	8.8
1905—1909	0.295	..		-	1.0	1	1.9	4	3.4	6	8.3	11	12.4	20	21.2	34	27.1	41	34.0	33	34.9	24	28.5	1	2.4
1910—1914	0.341	-	0.4	-	1.2	-	2.2	1	4.0	7	9.9	23	14.7	29	25.2	37	32.2	43	40.7	39	42.4	1	7.1	..	
1915—1919	0.373	-	0.4	-	1.3	4	2.3	4	4.3	13	10.5	22	15.7	23	26.8	35	34.2	36	43.4	11	9.0	..		..	
1920—1924	0.522	1	0.5	2	1.8	5	3.3	10	6.0	17	14.9	21	22.1	43	37.7	38	48.3	10	12.4	..		..		..	
1925—1929	0.574	1	0.5	4	1.8	3	3.4	8	6.2	17	15.3	20	22.6	40	38.9	6	10.3	..		..		..		..	
1930—1934	0.601	-	0.6	2	1.9	1	3.5	10	6.4	18	15.6	25	23.2	3	7.9	..		..		..		..		..	
1935—1939	0.785	2	0.8	1	2.7	5	5.0	10	9.0	24	22.2	4	6.3	..		..		..		..		..		..	
1940—1944	1.00	2	1.3	4	4.2	12	7.9	10	14.3	6	6.3	..		..		..		..		..		..		..	
1945—1949	0.617	-	0.9	5	2.8	5	5.3	1	2.0			..		..		..		..		..		..		..	
1950—1954	0.568	-	0.7	3	2.4	1	0.9	..		..		..		..		..		..		..		..		..	

[a] Incidence rate — k_a per 100 000 person-years in parentheses.

2000—2040. The predicted annual number among men born before 1955 peaks around the year 2015 by 93 cases. For all men, when a relative risk of 50% of that of the 1940—1944 cohort for men was assumed, a peak in 2020 by 110 annual cases was found. The figure levels at about 80 annual cases over the years 2030—2040.

The annual asbestos consumption in Denmark in 1910—1993 is shown in bars in figure 2. The import was greatest during 1965—1979 (approximately 30 000 tons per year) and decreased to 704 tons in 1990—1993.

Table 3 shows, like table 2, the observed number of malignant mesotheliomas above the expected number. The numbers were derived from the model of period of diagnoses and age at diagnosis. The maximum effect of period occurs for the period 1983—1988, which had a relative risk of 1.01, the goodness-of-fit having been evaluated by Pearson's χ^2-test (χ^2=80.5, df=97, P=0.89).

An analysis of the variables birth cohort, age, and period of diagnosis was also done, and it gave no better fit.

Discussion

The data of Danish cancer cases diagnosed since 1943, as registered in the Danish Cancer Register, is almost complete (10). However some misclassification of mesothelioma cases has occurred (23), and this misclassification complicates the interpretation of the results.

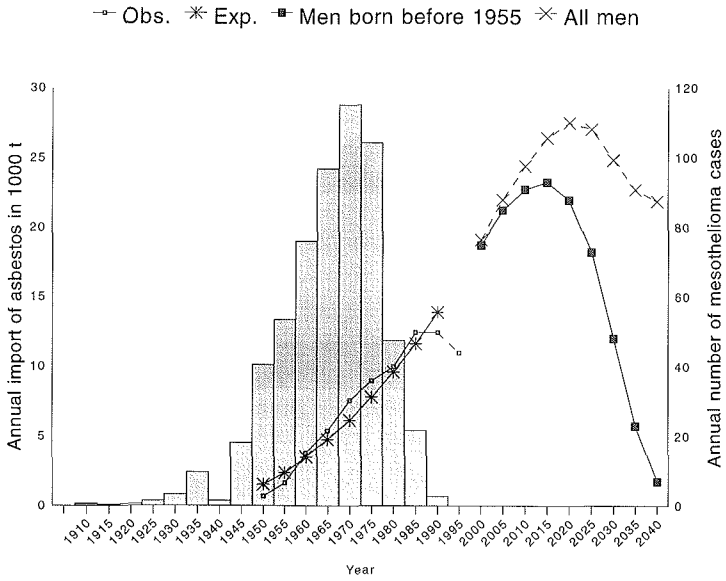

Figure 2. Observed (Obs) and expected (Exp) (fitted) number of cases of malignant mesothelioma in 1943—1993. Values of the annual number of cases for men born before 1955 and for all men predicted on the assumption of a relative risk of 50% of the 1940—1945 birth cohort. The annual asbestos consumption in Denmark in 1910—1993 is shown as the 5-year average in bars.

Table 3. Cases of malignant mesothelioma among Danish men in 1943—1993 and the fitted numbers based on a period-of-diagnosis analysis. Each cell shows the observed (O) number of mesothelioma cases next to the fitted (F) number derived from the period-of-diagnosis model by multiplying the population person-years (not shown) by the product of k_a and p_c.

Year of birth	Relative risk	Age group (years)[a]																			
		30—34 (0.66)		35—39 (2.22)		40—44 (4.18)		45—49 (7.76)		50—54 (19.7)		55—59 (30.8)		60—64 (57.3)		65—69 (83.6)		70—74 (130)		75—79 (185)		80—84 (246)		85—89 (220)	
		O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F	O	F
1943—1947	0.093	-	0.1	-	0.3	-	0.5	-	0.8	1	1.4	1	1.6	5	2.2	2	2.1	..		..		..		..	
1948—1952	0.107	-	0.1	-	0.4	1	0.6	2	1.0	3	1.8	1	2.0	4	2.7	1	2.7	2	2.6	..		..		..	
1953—1957	0.202	1	0.2	-	0.7	-	1.2	4	2.0	5	3.8	6	4.3	5	5.6	6	5.6	4	5.4	1	4.2	..		..	
1958—1962	0.4	1	0.4	2	1.3	4	2.3	1	4.1	6	8.2	8	9.3	13	12.4	11	12.0	14	11.4	10	9.1	6	5.4	..	
1963—1967	0.522	-	0.5	4	1.6	5	3.0	4	5.2	7	11.0	11	13.3	19	17.6	19	17.3	15	16.0	16	12.7	7	7.6	1	2.2
1968—1972	0.695	2	0.8	2	2.1	3	3.8	10	7.0	13	14.3	23	18.1	20	25.6	26	24.3	19	23.3	18	18.1	12	11.0	4	3.3
1973—1977	0.78	2	1.1	1	2.6	1	4.2	8	7.3	17	16.3	22	19.9	29	29.6	34	30.6	26	28.4	18	22.2	16	13.6	6	4.2
1978—1982	0.838	-	1.3	4	3.5	5	4.9	10	7.7	17	16.3	21	21.5	23	31.0	37	33.8	41	33.4	22	25.8	15	15.9	5	5.1
1983—1987	1.01	-	1.4	5	4.5	12	7.3	10	10.1	18	19.2	20	24.2	43	37.5	35	39.6	43	41.7	33	34.2	20	20.6	8	6.6
1988—1992	1	..		3	4.1	5	7.9	10	12.4	24	20.7	25	23.4	40	34.8	38	39.6	36	40.4	39	35.7	24	22.8	5	7.2
1993	0.882	..		..		1	1.3	1	2.5	6	4.0	4	4.3	3	6.0	6	6.8	10	7.3	11	6.1	1	4.3	1	1.4

[a] Incidence rate — k_a per 100 000 person-years in parentheses.

Some cases of malignant mesothelioma were diagnosed at autopsy. In a study (7) of the mesothelioma incidence rate in Denmark in 1943—1992, 25% and 29.5% of the cases among men and women, respectively, had a survival of 0 months, and most of these are likely to have been diagnosed at autopsy even though perioperative mortality might have been of some importance. During the 1970s, and particularly after the procedures changed for the autopsy requests in 1990, the rate of autopsy in Denmark declined from 45% in 1970 to 16% in 1990 (24). A Danish study concluded that a decrease in the frequency of autopsy leads to an underestimation of the incidence rate of rare cancers (25). Malignant mesothelioma is such a cancer.

The 12—13-fold increase in the male incidence rate of malignant mesothelioma since the beginning of registration until today is unlikely to be an artefact (26). Similar increases have been seen in other countries (6, 13, 14, 27).

The larger fraction of mesothelioma of the peritoneum in women may be due to a misclassification of cancers of the ovaries. In a Danish study about 30% of the peritoneal mesothelioma cases among women were found to be misclassified ovarian or gastrointestinal tumors (23).

In the Poisson regression analysis, a log-linear model with the parameters age and birth cohort was chosen because of the possibility of comparison with the results of Peto and his co-workers (14). The analysis was based only on cases among men because of the relatively low number of cases among women (table 1) and the possible misclassification of peritoneal mesotheliomas among

women (23). Because asbestos is considered to be the only important risk factor for malignant mesothelioma, other possible risk factors were omitted from the model. Smoking was also omitted because of no evidence of an effect on the risk of malignant mesothelioma in contrast to lung cancer, for which an important synergistic effect has been demonstrated (28).

The goodness-of-fit, evaluated by Pearson's χ^2-test (21), suggests that the age-birth cohort model has a poor fit, with a nearly significant P-value of 0.11 of the difference between the observed and the estimated values. This occurrence could be due to the period of diagnosis being a stronger parameter than the cohort of birth. As in the study by Peto and his co-workers (14) the number of cases and the short period at risk in the younger age groups, who have not had the same exposure level as the older groups, make the estimates for these groups uncertain. The structure of the synthetic birth cohorts makes the small changes in the data even harder to detect (21).

The results of the study by Peto and his co-workers (14) are based on mortality data, but the average survival time, being only about 7 months after the diagnosis (7), makes the mortality and the incidence rates comparable. The prediction of future incidence rates for malignant mesothelioma was done in a manner similar to that of Peto and his co-workers (14).

The prediction of the number of new cases of malignant mesotheliomas is based on the assumption that men born after 1955 have half the risk of the 1940—1944 cohort. This assumption is made under the consideration that banning the use of asbestos in the industry and improving the work environment cannot eliminate all exposure to asbestos, and similar assumptions have been made in recent studies (11, 12, 14).

The risk of mesothelioma from asbestos in the work environment was first described in 1960 (29), and the gradual improvements introduced in the work environments hereafter favors a peak in incidence rates around the year 1995. If the asbestos consumption is considered an estimate of asbestos exposure level and an average latency of 35 years is used, the maximal incidence rate cannot be expected until the year 2010.

The fit of the model using period of diagnosis being the better of the 2 models used calls for some caution in interpreting the results of the predictions made by using the birth cohort in the analysis. The period of diagnosis cannot readily be utilized in calculating the future number of cases of malignant mesothelioma because of nonexisting reliable predictions of future asbestos exposure. Prior exposure can only be quantified by the total consumption of asbestos, which is a very rough estimate of the individual exposure to asbestos. The asbestos imported after the ban has comprised chrysotile fibers, used for brakes and pipefittings, while the import of amphiboles has been completely banned (4, 5). Information on the distribution of the different fiber types, relevant to the risk of mesothelioma, is not available, not even for amphiboles and serpentine fibers.

If a prediction of the future number of mesothelioma cases were to be carried out on the basis of an analysis of the period of diagnosis and age, it would be essential to have reliable estimates of future environmental exposure levels to asbestos. These estimates cannot be made within the limits of this study.

In conclusion, with careful interpretation of the results, the annual number of malignant mesothelioma cases can be expected to increase steadily until 2010. No or little effect of banning the usage of asbestos can be expected until 2015 or later.

Acknowledgments

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