Eur J Epidemiol (2008) 23:541–546
DOI 10.1007/s10654-008-9257-z

CANCER

Prediction of mesothelioma and lung cancer in a cohort of asbestos exposed workers

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Received: 25 January 2008 / Accepted: 15 April 2008 / Published online: 26 April 2008

Abstract *Background* Several papers have reported state-wide projections of mesothelioma deaths, but few have computed these predictions in selected exposed groups. *Objective* To predict the future deaths attributable to asbestos in a cohort of railway rolling stock workers. *Methods* The future mortality of the 1,146 living workers has been computed in term of individual probability of dying for three different risks: baseline mortality, lung cancer excess, mesothelioma mortality. Lung cancer mortality attributable to asbestos was calculated assuming the excess risk as stable or with a decrease after a period of time since first exposure. Mesothelioma mortality was based on cumulative exposure and time since first exposure, with the inclusion of a term for clearance of asbestos fibres from the lung. *Results* The most likely range of the number of deaths attributable to asbestos in the period 2005–2050 was 15–30 for excess of lung cancer, and 23–35 for mesothelioma. *Conclusion* This study provides predictions of asbestos-related mortality even in a selected cohort of exposed subjects, using previous knowledge about exposure-response relationship. The inclusion of individual information in the projection model helps reduce misclassification and improves the results. The method could be extended in other selected cohorts.

Keywords Asbestos · Predictions · Mesothelioma · Lung cancer

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Introduction

Several papers have reported state-wide projections of mortality by mesothelioma during last years. These projections were published for Europe [1–4], United States [5] and, more recently, Japan [6], and were initially derived from simple models in which mesothelioma risk was independently related to age and date of birth.

These figures were verified a few years later: original predictions from United States were substantially confirmed [7], while results from many European countries turned out to be clearly over-predicted [8–10]. These findings could be associated to the lower exposure experienced by younger cohorts after some preventive measures were promoted during the 1970s. Considering the long latency from exposure to disease onset for mesothelioma [11], these measures would exert their effects 30–40 years later, and could not be detected when the original predictions were carried out. An age-cohort model is too simple to take into account these period effects, which can be seen as an interaction between birth cohort and age.

Therefore, more sophisticated methods have been proposed. Some authors proposed age-period-cohort models with strong a-priori assumptions about the period effects [8, 12], or projections based on asbestos consumptions [12]. A different method suggested that mesothelioma rate

increases according to cumulative exposure experienced by birth cohorts during specific periods, and to a power of age [13]. In all these papers, the number of mesothelioma deaths was collected from routine data, sensitive to changes in diagnostic and coding procedures. Moreover, the analyses were based on the age-cohort distribution of the general population, while cases will mainly arise from a variety of occupational populations. Projections based on individual data, with exact information about demographic characteristics, period of exposure, and cumulative exposure should reasonably be more reliable.

Surprisingly, few attempts to predict the future number of mesothelioma in selected exposed cohort have been published [14–16]. In particular, the 1991 paper [14] proposed a model based on the widely accepted quantitative relation supported by multi-stage model of carcinogenesis. It states that mesothelioma rate depends on cumulative exposure multiplied by a power of time since first exposure [17]. Furthermore, in order to explain the decline in rates after long latency periods, it has been hypothesized that the progressive elimination of fibres from the lung could reduce the associated risk. These projections were computed for period 1987–2020 in former workers of an asbestos mine at Wittenoom, Australia, in which crocidolite was used until 1966, using different assumptions about lag time and rate of fibres elimination per year. In an update of the cohort [18], the number of mesothelioma predicted for the period 1987–2000 were compared with actual deaths. The model that incorporated a gradual elimination of fibres obtained the closest prediction. A recent study has found a similar reduction in an Italian cohort of asbestos cement workers for the group with more than 50 years from first exposure [19].

This model is supported by more appropriate assumptions, and recently some papers which proposed a similar method for state-wide predictions [9, 20] have found it more adequate to explain the trend of mesothelioma deaths. In addition, this model gives the opportunity to incorporate information at individual level, such as period of exposure and dose, providing more reliable results.

The aim of this paper is to predict the future deaths attributable to asbestos in a cohort of exposed workers of a factory producing railway rolling stock in Pistoia, Italy. Predictions of deaths by mesothelioma and excess of lung cancer have been calculated for the period 2005–2050, with a method based on that previously used for the Wittenoom cohort.

Material and methods

The factory

A factory producing railway rolling stock, the Breda (Pistoia, Tuscany, Italy), used asbestos from the end of 1950s to the beginning of 1980s. The main route of exposure was the insulation of the coaches with sprayed asbestos, using crocidolite for at least 15 years followed by amosite and chrysotile in the last period. Insulation was performed in several workshops inside the factory by workers employed by small contract companies (not included in the cohort), initially without any separation and simultaneously with other activities [21]. Few ventilation and separation improvements were installed during the 1960s. Spraying activities started to be performed in a separate workshop only in 1976. Notwithstanding, sprayed asbestos was used until 1979. Other routes of exposure involving directly workers of the Breda cohort were represented by the post insulation assembling procedures, which implicated a mechanical disturb of the friable asbestos layer. Moreover, in 1974, sprayed amosite was used as roof insulation for a surface of 5,000 m^2 of the new sheds.

Environmental monitoring of asbestos airborne fibres is available only after 1990, more than 10 years after the end of the asbestos use. Airborne asbestos fibres estimated concentration was very low, with annual TWA ranging from 0.4 to $4.5 \cdot 10^{-3}$ fibres/cc [21]. A panel of hygienists estimated the intensity of exposure during the period of asbestos use, through documents, information gathered from workers, literature describing similar conditions, and dispersion models. A job-exposure matrix was then compiled, with estimated intensity of exposure that ranged from 0.01 to 3.12 fibres/cc, depending on department, task an calendar year [22].

The cohort

The cohort is composed by 2,246 male subjects working as blue collars at 1st January 1960 or hired before 31st December 1979, who worked at Breda for at least 1 month. Demographic data and work histories were collected through factory books. The beginning of exposure was considered as the hiring date or 1st January 1956 for those hired earlier, and duration of exposure corresponds to the total employment time between the beginning of exposure and 31st December 1979. Job histories were available only for a highly selected group of workers, unrepresentative of the whole cohort. Therefore, individual measures of cumulative exposure could not be assigned. For this reason, duration of exposure has been used as a proxy of cumulative dose.

The follow-up ranged from 1st January 1960 to 31st December 2004 (72,868 person-years of observation). Vital status was determined through the Official Register of the municipality of residence. For subjects residing in Tuscany, cause of death was obtained from the Tuscany Mortality Registry. Otherwise, death certificates were provided from the Official Register of the municipality of

residence and cause of death was classified by the physician responsible for coding the Tuscany Mortality Registry. Causes of death were coded according to the International Classification of Disease (9th revision). Mesothelioma cases were then confirmed by the Tuscany Registry of Malignant Mesotheliomas [23]. An analysis of mortality for the cohort was carried out to ascertain the overall mortality and the excess for lung cancer and mesothelioma. Expected deaths for these three causes were calculated using sex and calendar period specific death rates for Tuscany population, excluding the first 10 years after first exposure.

Predictions pertain to 1,146 subjects still alive at 31st December, 2004. This group has a mean age of 64.7 years (range 42.5–96.7) and a mean time from first exposure of 38.1 years (range 25.1–49.0).

Prediction methods

The future mortality of the 1,146 subjects has been computed in term of individual probability for each year in the period 2005–2050. This probability has been worked out taking into account the effect of three factors: baseline, that is the mortality the cohort would have experienced if the workers were not exposed to asbestos, excess of lung cancer and mesothelioma. Several papers reported a decline in excess risk for lung cancer after a period of time since first exposure to asbestos [19, 24, 25]. Therefore, two different situations have been considered. In a first model the excess rate for lung cancer was assumed as stable over the entire projection period, while in the other one it was supposed to decrease after a period after first exposure, according to literature and SMRs in mortality analysis. The mortality for mesothelioma has been calculated in terms of duration of exposure (as proxy of cumulative exposure) and time since first exposure, with a parameter allowing for a decline in risk due to elimination of fibres from the lung.

The probability of dying π_{ij} for the subject i in the year j after 2004 (conditional on surviving until $2004 + j - 1$) was calculated by the equation:

$$\pi_{ij} = 1 - \exp\left[-(\varphi_{a0(i)+j} + \eta_{a0(i)+j} \cdot f_{t0(i)+j} + \varepsilon_{t0(i)+j})\right]$$

where: $a0(i)$ is the age of the subject i at 31st December 2004; $t0(i)$ the time (years) after first exposure of the subject i at 31st December 2004; φ_a the baseline mortality rate at age a; η_a the excess of mortality rate for lung cancer at age a; f_t a function related to decline in the excess rate for lung cancer after a period of time since first exposure; ε_t the mortality rate for mesothelioma after t years since first exposure; φ_a and η_a have been estimated by the overall and lung cancer rates of Tuscany population for the period 2000–2004.

In particular, η_a was worked out from SMRs for lung cancer in the cohort. Fractional polynomials have been applied to smooth the 5-year age group rates at each single year. The function f_t has been chosen according to literature and results of the mortality analysis.

The mortality rate for mesothelioma ε_t depends on time t since first exposure by the equation:

$$\varepsilon_t = c \cdot (t - w)^k \cdot \exp(-\lambda t)$$

where: c is a parameter related to cumulative exposure; w the lag time (minimum latency between exposure and disease); k the parameter of the effect of time since first exposure; λ the elimination rate of fibres per year.

These parameters were estimated by a log-linear Poisson model, grouping the subjects according to 5-years categories of time since first exposure. Due to the small number of cases, the four parameters could not be estimated together. In addition, k and λ are both based on time since first exposure, with problems of collinearity and very large standard errors. Therefore, only c and k were estimated by regression models, with the other two chosen from literature. The lag time w was fixed at 5 years, according with the predictions in the Wittenoom cohort [14] and with a more recent paper [20]. The best model for the Wittenoom cohort assumed an elimination rate λ of 0.15, with an half life of about 4.2 years, while other authors proposed smaller values, close to 0.05, with an half life of 15 years [9, 20]. Different models have been fitted with both values. The effect of the cumulative exposure was estimated by duration of exposure. It was calculated by the SMR ratio between subjects exposed more or <10 years, estimated from mortality analysis.

These death rates have been applied to the population assumed to be alive on 1st January of each year. The cumulative survival probability for the subject i until the year j is the product of $1 - \pi_{ix}$ from $x = 1$ to $j - 1$ [26]. In order to calculate the probability that the subject i, still alive at 31st December 2004, will die in the year j, it is sufficient to multiply the conditional probability π_{ij} by such cumulative survival probability. Moreover, it is possible to compute the specific probability for each of the three terms alone, i.e. baseline, excess of lung cancer, and mesothelioma. The sum of individual death probabilities estimates the number of deaths in every single year for each cause of death. As expected, the sum of the deaths for the three causes is slightly higher than the total number obtained by the overall rate, due to the competing risk effect. Anyway, considering the small length of intervals, the error is negligible and less than 1% in every model considered in the analysis.

Due to the large uncertainty on the estimate of this SMR ratio, a sensitivity analysis has been carried out, restricting the predictions to subject with more than 10 years of

exposure, and considering the others as non-exposed. In addition this analysis that excludes all the subjects hired in the 1970s, allows to estimate the effect of a possible reduction of exposure in the last period, when the factory moved to the new building and more stringent safety interventions were realized.

Results

Mortality analysis

A total of 1,080 deaths have been ascertained during the follow-up (rate $14.8 \cdot 10^{-3}$ py^{-1}), with 134 cases of lung cancer (12.4% of total deaths; rate $183.9 \cdot 10^{-5}$ py^{-1}) and 16 cases of mesothelioma (1.5% of total deaths; rate $22.0 \cdot 10^{-5}$ py^{-1}). Twenty subjects were lost at follow-up (0.9%). Their person-years of observation were truncated at the date each of these workers was last observed (earlier follow-up's or date of termination). Tuscany population rates with 5-years categories for age and calendar period have been used as reference. Results are summarized in Table 1.

Excluding the first 10 years after first exposure, significant excesses have been found both for lung cancer (ICD-9 162; 132 cases; SMR 1.36, 95% CI 1.14–1.61) and for mesothelioma, coded as pleural cancer (ICD-9 163; 16 cases; SMR 8.65, 95% CI 4.94–14.05). Excluding the deaths due to excess of these two cancers, the mortality in the cohort is not different from the expected (SMR 0.98, 95% CI 0.92–1.04).

Taking into account only the period after retirement, likely more similar to the future experience of the cohort, the excess of mortality for lung cancer approaches 40% (SMR 1.39, 95% CI 1.15–1.66). Differently from mesothelioma, the analysis doesn't show any effect for duration of exposure. The stratified analysis for time since first exposure suggests a decrease after 40 years, even if the confidence intervals are quite large (SMR 1.20, 95% CI 0.75–1.84 for 40–49 category). The analysis for period of first exposure could reveal a possible decline of exposure during the last period. It doesn't suggest any decrease in risk, with the excess still high even for subject hired after 1970 (SMR 1.49, 95% CI 0.77–2.60).

The first mesothelioma death occurred in 1981, and 7 cases were ascertained in 2000–2004. There is a strong relationship both with duration of exposure and time from first exposure (Table 1). The mean time from first exposure is 34.7 years (range 21.6–44.8). The mean duration is 18.5 year for cases, compared with 11.6 in non cases, and only 2 deaths out of 16 occurred in subjects with less than 10 years of duration. The SMR ratio between subjects with more and less than 10 years is about 3.3.

Predictions

The final models for mesothelioma have been chosen on the basis of mortality analysis and previous assumptions. The rate ratio between subjects exposed more and <10 years has been fixed to 3.3, constraining the estimates of the c parameter in the two groups, while k has been estimated from the entire cohort. Two projections have been performed, with elimination rate set to 5% and 15%. For lung cancer, the excess has been set to 40% and models with and without an annually decline of 5% after 35 years since first exposure have been considered. These two models have been specified by setting the f_t parameter as 1 until 35 years after the first exposure, and $(0.95)^{t-35}$ or 1 thereafter, respectively. The number of deaths predicted for each disease, stratified by calendar period, is summarized in Table 2: the different models predict 23–35 new deaths for mesothelioma and 15–30 for excess of lung cancer

Table 1 SMRs for lung cancer and mesothelioma among 2,246 Breda workers by duration of exposure and time since first exposure[a]

	Person-years	Lung cancer			Mesothelioma		
		Obs.	Exp.[b]	SMR (95% CI)	Obs	Exp[b]	SMR (95% CI)
Duration of exposure (year)							
<1	2,925	4	2.84	1.41 (0.38–3.60)	0	0.07	–
1–10	20,199	41	27.08	1.51 (1.08–2.05)	2	0.57	3.52 (0.43–12.71)
>10	31,988	87	67.17	1.30 (1.04–1.60)	14	1.22	11.51(6.29–19.31)
Time since first exposure (year)							
10–20	21,342	21	15.69	1.34 (0.83–2.05)	0	0.22	–
20–30	18,638	40	31.75	1.26 (0.90–1.72)	3	0.53	5.71 (1.18–16.70)
30–40	10,830	50	32.18	1.55 (1.15–2.05)	7	0.63	11.14 (4.48–22.97)
>40	4,302	21	17.47	1.20 (0.74–1.84)	6	0.47	12.71 (4.66–27.67)

[a] First 10 years after first exposure has been excluded

[b] Reference: Tuscany population for 5-years categories of age and calendar period

Table 2 Predicted number of deaths due to mesothelioma (with $\lambda = 5$ and 15%) and excess of lung cancer (with and without annually decline of 5% in excess risk after 35 years), stratified for calendar period

Years	Mesothelioma		Excess of lung cancer	
	$\lambda = 5\%$	$\lambda = 15\%$	No decline	Decline of 5%
2005–2009	6.3	5.4	5.8	3.8
2010–2019	12.7	9.3	10.8	6.1
2020–2029	9.6	5.7	8.2	3.4
2030–2039	4.7	2.3	4.0	1.2
2040–2050	1.3	0.5	0.9	0.2
2005–2050	34.6	23.2	29.7	14.8

(20–40% more than those expected). The competing effects of the two diseases are negligible (the difference in the predicted numbers of lung cancer between the two mesothelioma models, and vice versa, is <1%), therefore the estimates could be interpreted as independent. The two models show that the peak of number of deaths has already been reached, but mortality related to asbestos exposure is likely to hold over a long period in the future.

Restricting the predictions to subject with more than 10 years of exposure, the two models for mesothelioma predict 18.5 and 12.1 deaths for $\lambda = 5\%$ and 15%, respectively. The effect of this restriction for excess of lung cancer is stronger, with 3.7–9.2 predicted deaths by the model with and without decline in risk.

Discussion

This study shows that in the period 2005–2050 around 23–35 new mesothelioma deaths are likely to be recorded in the Breda cohort, according to models that incorporated 15–5% of annual elimination of asbestos fibres, respectively. Moreover, 15–30 new cases of lung cancer are predicted by models with and without a 5% of decline in the excess risk after 35 years since first exposure. Deaths for mesothelioma and excess of lung cancer will occur above all in men aged 70–89 years.

These projections are based on several assumptions. Firstly, the future baseline mortality of the cohort is supposed to be the same which Tuscany population will experience. The mortality analysis seems to confirm this statement, even if the trend could diverge in the following years, far away from active working period. In addition, the future mortality has been computed according to 2000–2004 rates. It could be argued that the rates will decrease in the following years, especially in the older categories. Due to the weaker competing effect of the baseline mortality, the number of deaths for asbestos related diseases would be higher than those predicted here. A recent work [20] has found that the burden of mesothelioma deaths, computed using the current rates and compared to future projections of population mortality, provides a lower estimate of about 16%. A similar problem concerns the rates for lung cancer. It's likely that they will decrease in the future, due to a reduction in smoking habits in Italy. A recent paper showed that smoking prevalence in Italian men gradually decreased from 65% in 1957 to 38% in 1990 and 30% in 2005 [27]. Then the lung cancer rates will probably fall in future years, especially in older age categories. The excess calculated here would be therefore slightly overestimated.

There are some indications that the preventive measures undertaken in Italy during the 1970s contributed to reduce the exposure in many production settings [28] including the one described in this work. Even if an individual estimate of exposure could not be carried out, the reconstruction of the past environmental exposure [21] shows a clear decrease during the 1970s in contrast with the registered increase of asbestos consumption. Due to the long latency of mesothelioma, the effect of the reduced exposure could not have arisen yet, and consequently the estimates of the parameters would not apply in the future years. However, restricting the predictions to subject with more than 10 years of exposure, and hence considering unexposed those who worked only during the 1970s (a very unlikely assumption), the predicted deaths for mesothelioma would be in the range 12–19. The effect would be heavier for lung cancer, but the shorter latency for such disease and the fact that subjects hired after 1970 have already shown a similar excess seem to protect against a large overprediction.

The rate of elimination λ has been set to 5% and 15%, a range in agreement with previous works. A measurement study in former Wittenoom workers [29], showing an elimination rate of about 9%, seems to confirm this assumption. Experiments in rats showed higher rates of elimination of crocidolite from the lungs [30, 31], but it has been claimed that extrapolation of these results for humans is not straightforward [32].

The burden of deaths for lung cancer has been predicted with and without a decline in risk after a period after first exposure. The excess of 40% has been estimated from mortality analysis, and the 5% of decrease after 35 years, estimated from literature, is compatible with results from SMRs. The mortality analysis doesn't show an increase in SMRs with duration of exposure for lung cancer. For this reason it has been chosen to assign the same risk to each subject, even if this model could be too simple.

Strengths of this study include the completeness and the reliability of the data. All subjects working in Breda during the period of asbestos use were traced by the factory books and included in the cohort, excluding any selection bias. The follow-up was successfully completed for 99.9% of the cohort using official sources, and causes of death were

determined by the Tuscany Mortality Registry. Moreover, mesothelioma cases were confirmed by the Tuscany Registry of Malignant Mesotheliomas, excluding any effect of misdiagnosis and diagnostic changes.

In conclusion, this paper showed that is possible to compute credible predictions of asbestos-related mortality even with a small number of cases, using a simple model and previous knowledge about exposure-response relationship. Even if the computation is based on several assumptions, and a measure of uncertainty cannot be included, individual information can be incorporated in the projection model, reducing misclassification and improving results. This method could be extended in other selected cohorts with reliable information about timing and dose of exposure.

Acknowledgment This study was funded by a grant from the Fondazione Cassa di Risparmio di Pistoia e Pescia.

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