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ORIGINAL PAPER

Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973–2005

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Abstract We analyzed mesothelioma incidence in the Surveillance, Epidemiology, and End Results (SEER) database over the period 1973–2005 using extensions of the age–period–cohort (APC) models. In these analyses, the usual non-specific age effects of the conventional APC models were replaced by hazard functions derived from two multistage models of carcinogenesis, the Armitage–Doll model and the two-stage clonal expansion (TSCE) model. The extended APC models described the incidence data on pleural and peritoneal mesotheliomas well. After adjustment for temporal trends, the data suggest that the age-specific incidence rates of both pleural and peritoneal mesotheliomas are identical in men and women. Driven largely by birth cohort effects, age-adjusted rates of pleural mesothelioma among men rose from about 7.5 per million person-years in 1973 to about 20 per million person-years in the early 1990s and appear to be stable or declining thereafter. Age-adjusted rates of pleural mesothelioma among women have remained more or less constant at about 2.5 per million person-years over the period 1973–2005. Age-adjusted rates for peritoneal mesothelioma in both men (1.2 per million person-years) and women (0.8 per million person-years) exhibit no temporal trends over the period of the study. We estimate that approximately 94,000 cases of pleural and 15,000 cases of peritoneal mesothelioma will occur in the US over the period 2005–2050.

Keywords Mesothelioma · Asbestosis · Age-specific incidence · Multistage carcinogenesis

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Introduction

Mesothelioma has often been called the sentinel malignancy for asbestos exposure. Multiple epidemiological studies among cohorts of workers occupationally exposed to asbestos have reported elevated risks of mesothelioma. While there is still controversy as to whether pure chrysotile exposure, uncontaminated with amphiboles, can cause mesothelioma [1, 2], the evidence clearly shows that amphiboles are far more potent than chrysotile in causing mesothelioma [3–5]. Case–control studies [6, 7] have similarly shown that certain occupations involving exposure to asbestos are associated with an increased risk of mesothelioma. However, the fiber type, whether chrysotile, amphiboles, or a mixture of the two, is not generally reported in these studies.

Price and Ware [8] showed that the temporal trends in mesothelioma incidence among males reflect temporal trends in asbestos use in the United States with a lag of 20–40 years. They used an age–cohort model to analyze mesothelioma incidence in the Surveillance, Epidemiology, and End Results (SEER) database over the period 1973–2000. Their results suggest that age-adjusted rates among males reached a peak around the early to mid-1990s and have remained relatively constant or declined somewhat since then. They reported that the age-adjusted rates

for females are much lower and have remained more or less constant over the period of the analyses, 1973–2000. In a more recent paper, Teta et al. [9] examined the SEER data by five-year age groups over the period 1973–2002 and concluded that the temporal trends of incidence rates among men were driven largely by age groups older than 60.

The most common site for malignant mesothelioma is the pleura. However, a small but significant fraction of cases occurs in the peritoneum. In this paper, we extended the analyses of Price and Ware [8] in two ways. First, we considered pleural and peritoneal mesotheliomas separately. Second, we conducted a full age–period–cohort (APC) analysis for each of the sites. It is well known that when all three factors, age, period, and cohort, are used in analyses of registry data, there is a fundamental problem of non-identifiability [10, 11], sometimes referred to as the problem of arbitrary linear trend in the data. We finessed this problem by recognizing that age is the fundamental determinant of cancer incidence and that cohort and period effects modulate the effect of age. Specifically, we replaced the non-specific age effects of traditional APC models by parametric functions derived from multistage models of carcinogenesis. We have previously used this approach for analyses of the incidence of colon cancer [12, 13], pancreatic cancer [13], and esophageal cancer [14] in SEER.

Materials and methods

Incidence data for mesotheliomas of the pleura and peritoneum were obtained from the SEER 9 registry for the years 1973–1992 and from the SEER 13 registry for the years 1993–2005. See the SEER Cancer Statistics Review [15] for details concerning this database. For our analyses, we used the reported incidence of mesothelioma by gender, age, and calendar year in the SEER geographic areas.

The population bases were obtained from the SEER population files (based on the data from the US Census Bureau) by sex and were cross-tabulated by five-year periods over the calendar years 1973–2005 and 5-year age groups (ages from 0–85+). Model fits for each gender included all races. For all years combined, a total of 6,017 male cases (5,562 pleural, 455 peritoneal) and 1,673 female cases (1,291 pleural, 382 peritoneal) were available for the analyses.[1]

We have previously presented likelihood-based analyses of the incidence of different cancers in the SEER registry using hazard functions derived from multistage models to replace the non-specific effects of age in the traditional APC models, while secular trends, i.e., period and cohort effects, were modeled in the usual fashion (see [12–14]). Briefly, we model the age-specific incidence (age a) occurring in calendar year j as

$$h_{ij}(a) = b_i c_j h(a),$$

where $h(a)$ is the hazard function derived from a multistage model, c_j is a coefficient that adjusts for calendar year j, and the coefficient b_i adjusts for birth cohort i ($i = j - a$, stratified in 5-year groups; 1885–1889, 1890–1894,…,1955–1990, and >1960). Conforming to the SEER database format, we stratify the data in 18 age groups (0–4 years, 5–9 years,…,80–84 years, 85+ years) and into seven periods (1973–1975, 1976–1980,…,2001–2005). We then fit each of three multistage models to the number of observed mesothelioma cases stratified by age group and calendar year. We obtained parameter estimates for each model by maximizing the likelihood across all age-calendar strata assuming that the number of cases, either pleural or peritoneal, in each stratum is Poisson distributed with mean $N_{ij} * h_{ij}(a)$, where N_{ij} is the population at risk in age group i and birth cohort j, and $h_{ij}(a)$ is as defined above.

We considered three distinct multistage models for the age effects. First, we considered the Armitage–Doll [16] model of carcinogenesis. In this model, the hazard function for mesothelioma is a power of age. Peto [17] considered a similar model for mesothelioma in occupational cohorts exposed to asbestos, in which the hazard function is a power of time since first exposure. We discuss this model below. We also considered the two-stage clonal expansion (TSCE) model proposed by Moolgavkar and Venzon [18] and Moolgavkar and Knudson [19] and a three-stage extension of it as described in earlier papers [12–14].

[1] Incidence data for the same tumor can be downloaded using different coding schemes from the SEER registry. These distinct methods of downloading the data should yield identical numbers. For example, one can download mesothelioma incidence data using either ICD 10 codes (C45.0 for mesothelioma of the pleura and C45.1 for mesothelioma of the peritoneum, including omentum and mesentery), or using site & morphology = 'peritoneum, omentum and mesentery' and histology = 9,050–9,059 (mesothelial neoplasms). For peritoneum, these

Footnote 1 continued
two codings yield highly discrepant results, with the latter coding yielding approximately four times as many tumors as the former. For pleura, the appropriate equivalents to these two approaches yield identical numbers. In this manuscript, we present the results of analyses of peritoneal mesothelioma incidence based on the second approach for the following reasons. First, this is the older method of coding and, therefore, probably less susceptible to error. Second, it appears to have been the method used in the papers by Teta et al. [9] and Boffetta [31]. We have also performed the analyses using the data obtained using the first method. Our conclusions regarding trends and model fits remain unchanged. However, our estimated rates for peritoneal mesothelioma and projected number of cases are approximately a fourth of those presented here. We would be happy to share these results with any interested reader.

The Armitage–Doll model (16)

This model has the following form for the hazard (age-specific incidence) function:

$$H(t) = Ct^k,$$

where C and k are constants to be estimated and t is age.

The TSCE model (18, 19)

The two-stage model posits that cells initiated via a Poisson process undergo clonal expansion and malignant conversion via a birth–death–mutation process. The details of this model are presented in a number of publications (18–21). The hazard function for this model is considerably more complicated than that of the Armitage–Doll model. The model has four parameters, the rate of initiation, ν, the rate of division, α, and death, β, of initiated cells, and the rate of malignant conversion, μ. Not all four parameters can be estimated from incidence data alone. We estimated three identifiable parameters as described below. With constant parameters, the hazard function for this model takes the following form:

$$h(t) = \frac{\nu}{\alpha} pq \frac{e^{-qt} - e^{-pt}}{qe^{-pt} - pe^{-qt}},$$

where p and q are the roots of a quadratic equation, with $p + q = g = -(\alpha - \beta - \mu)$ and $pq = \alpha\mu$. We estimated p, q, and $r \equiv \frac{\nu}{\alpha}$, which comprise a set of identifiable parameters. Thus, the TSCE model requires the estimation of one more parameter than the Armitage–Doll model. Note that g is roughly the net rate of proliferation of initiated cells (since μ is a mutation rate and much smaller than α and β), $q \sim \mu/(1 - \beta/\alpha)$, and r is what Fisher has called the index of diversity [22]. More details are provided in the papers referenced above [12–14, 19–21].

We also fit a three-stage extension of the TSCE model to the data as described in earlier papers [12–14].

We fit models to the data by maximizing likelihoods. In the current context, models arising from the use of distinct multistage hazard functions are not hierarchical. We therefore used the Akaike Information Criterion (AIC) to judge the relative fits of the different models.

All analyses were conducted separately for pleural and peritoneal mesotheliomas. At each site, we first fit models separately to male and female data. We began by fitting the conventional APC model in which separate parameters were fit for each age group, birth cohort, and period (not shown). Although this model suffers from parameter non-identifiability problems, the expectation is well defined and the maximized likelihood is unique. As judged by the AIC, models in which non-specific age parameters were replaced by hazard functions from multistage models did better than the conventional APC model (see Table 1). Moreover, the three-stage extension of the TSCE model did no better than the TSCE model and we therefore do not consider it further. The TSCE model consistently described the data better than the Armitage–Doll model as judged by the AIC and we focus here on results of analyses based on the TSCE model. However, since the Armitage–Doll model has the virtue of transparency and simplicity and, moreover, has been in use for more than two decades we discuss the age-specific incidence estimated from that model as well.

Mesothelioma projections

We projected mesothelioma incidence to the year 2050 in the United States using methods similar to those in Price and Ware [8]. First, we projected the US year 2002 population into the future using mortality rates from the US decennial life tables for 1989–1991 [23]. New births statistics from 2002 to 2005 were obtained from the CDC

Table 1 Parameter estimates and 95% confidence intervals of the TSCE and Armitage–Doll models fits to pleural and peritoneal mesothelioma incidence in SEER 1973–2005

Model	Parameter	Pleura	Peritoneal
TSCE	r	2.80×10^{-4} $(2.30, 3.41) \times 10^{-4}$	3.17×10^{-5} $(2.41, 4.18) \times 10^{-5}$
	$-p$	0.12 (0.114, 0.127)	0.11 (0.096, 0.13)
	q	1.40×10^{-5} $(1.04, 1.90) \times 10^{-5}$	1.78×10^{-4} $(0.98, 3.24) \times 10^{-4}$
	AIC[a]	−24603	1390.6
Armitage–Doll	C	3.36×10^{-15} $(1.41, 7.99) \times 10^{-15}$	1.75×10^{-11} $(0.56, 5.50) \times 10^{-11}$
	k	5.14 (4.95, 5.34)	2.79 (2.53, 3.08)
	AIC[a]	−24532.2	1424.4

Wald confidence intervals were estimated on logit transformed parameters and then back transformed to the original scale

[a] Akaike information criterion

Age–cohort model AIC: pleural mesothelioma = −24578.24, peritoneal mesothelioma = 1429.7

Age–period–cohort model AIC: pleural mesothelioma = −24576.74, peritoneal mesothelioma = 1446.4

National Vital Statistics System (see http://www.cdc.gov/nchs/births.htm and [24]). For future years, we assumed that the number of births in each year is equal to those in 2005.

Future birth cohort and calendar year coefficients were assumed to equal the last estimated value.

Results

Table 1 shows the parameter estimates together with the AIC of the Armitage–Doll and TSCE models. We also fit the traditional age–cohort and APC models to the male and female data sets separately and computed the AICs for these models. The AICs for the conventional age–cohort and APC models are reported in the legend to Table 1. Recall that the smaller the AIC, the better the fit of the model. By this criterion, the TSCE model is the best model for both pleural and peritoneal mesotheliomas. The Armitage–Doll model fit is worse than the conventional models for pleural mesothelioma but better for peritoneal mesothelioma.

Figure 1 shows the age-adjusted (to the 2000 US population) mesothelioma incidence in SEER over the period 1973–2005 and the predictions made by our preferred models (see below).

Pleural mesothelioma

Based on the AIC, the incidence of pleural mesothelioma in SEER is described best by a model that postulates a common age-specific incidence curve for males and females, with separate birth cohort and period effects in the two sexes. Figure 1 shows the age-adjusted rates in the SEER data together with the rates predicted by the TSCE model. This figure shows that the age-adjusted incidence among males rose rapidly from 1973 to about 1990 when it reached a peak. There is a hint of a decline beginning in the early 1990s. The age-adjusted incidence among females appears to be more or less constant over the entire period of observation. Figure 2 shows the estimated age-specific incidence curves using the TSCE and Peto models. Temporal trends are dominated by strong cohort effects, especially among men (Fig. 3). The first three cohort effects estimates in females were almost equal to one another and had large confidence intervals, as did the last three. In the final models, the first three cohort effects for females were set equal to one another as were the last three, leading to a total of 12 cohort effects parameters in females and 16 in males. The cohort effects are modulated by period effects (Fig. 4) that are more or less constant for males, but decline modestly for females (Fig. 5). Figure 6 shows the lifetime probability of developing mesothelioma by birth year adjusted for survival from other causes of mortality (US decennial life tables for 1989–1991). Figure 7 shows the lifetime probability unadjusted for other

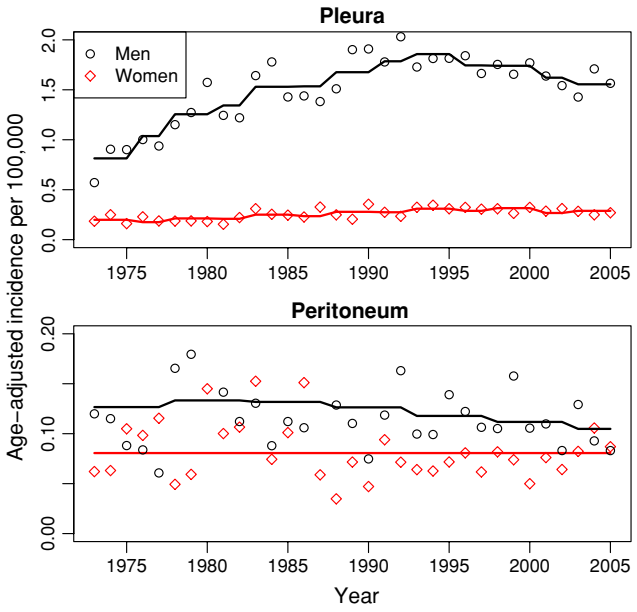

Fig. 1 Observed and expected age-adjusted incidence rates over the period 1973–2005. *Upper panel*: pleural mesothelioma; *lower panel*: peritoneal mesothelioma

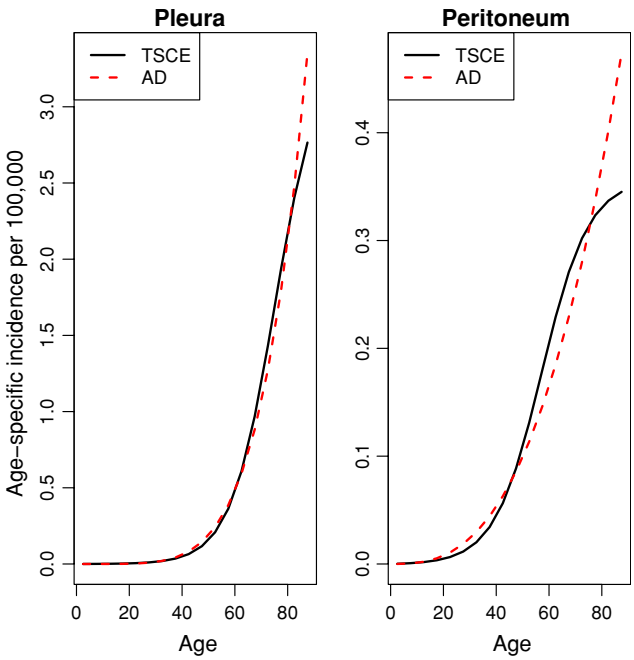

Fig. 2 Age-specific incidence curves generated by the Armitage–Doll and TSCE models. These curves represent the estimated hazard functions of these models multiplied by 100,000. *Left panel*: pleural mesothelioma. See the text for details of the constraints required for identifiability of the incidence curve for pleural mesothelioma. *Right panel*: peritoneal mesothelioma. No constraints are required for the generation of these curves since cohort effects for women are all equal to 1

cause mortality. These figures indicate that, over the period of observation, the lifetime probability of pleural mesothelioma among men showed a rapid increase by birth cohort until the cohort of the early 1920s, following which there was an equally rapid decline. These trends clearly reflect the trends in birth cohort effects shown in Fig. 3. Among females, there is a more modest increase and lifetime risks appear to have stabilized. Interestingly, male and female lifetime probabilities are virtually identical in the earliest and latest birth cohorts.

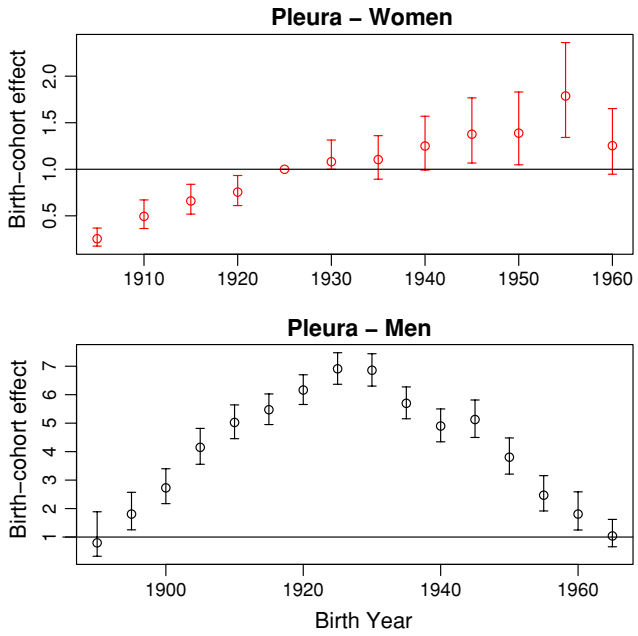

Fig. 3 Birth–cohort effects and 95% confidence intervals for pleural mesothelioma. *Upper panel*: women; *lower panel*: men

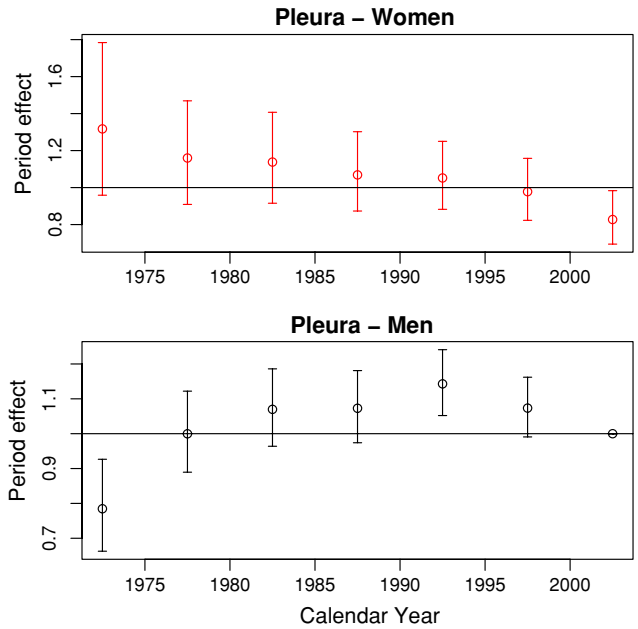

Fig. 4 Period effects and 95% confidence intervals for pleural mesothelioma. *Upper panel*: women; *lower panel*: men

Peritoneal mesothelioma

The incidence of peritoneal mesothelioma in SEER is described best by a model that postulates common

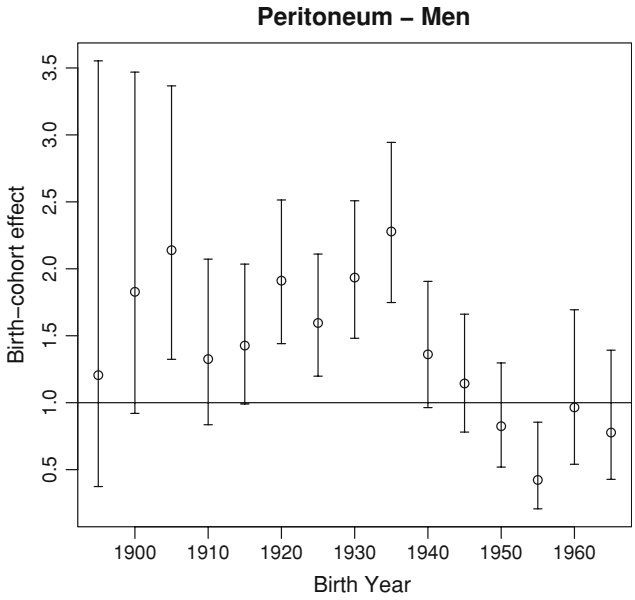

Fig. 5 Birth–cohort effects and 95% confidence intervals for peritoneal mesothelioma among men

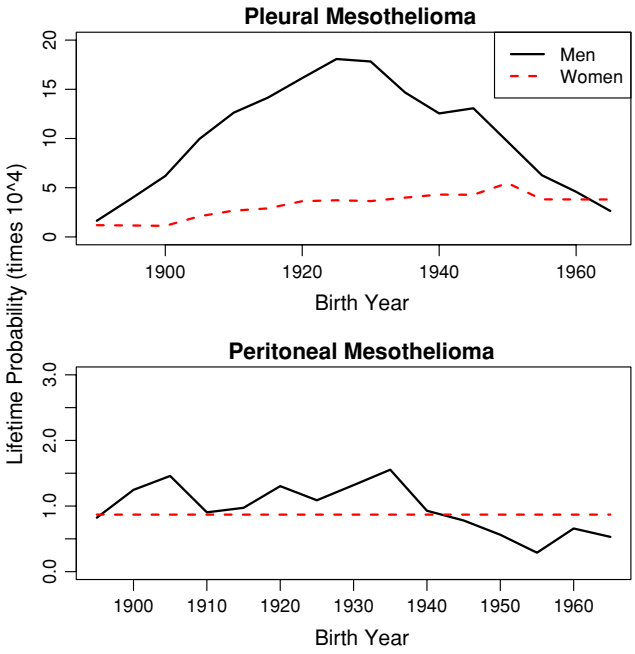

Fig. 6 Lifetime probability of mesothelioma by birth cohort after adjustment for other cause mortality. *Upper panel*: pleural mesothelioma; *lower panel*: peritoneal mesothelioma

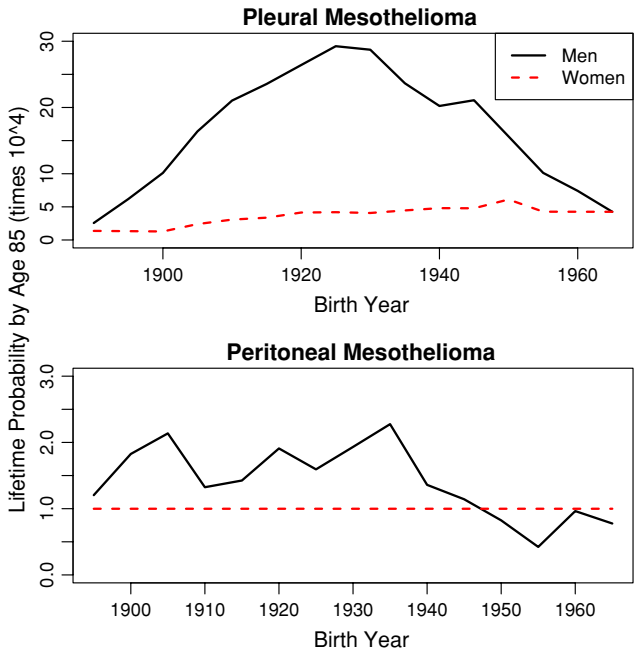

Fig. 7 Lifetime probability of mesothelioma by birth cohort without adjustment for other cause mortality. *Upper panel*: pleural mesothelioma; *lower panel*: peritoneal mesothelioma

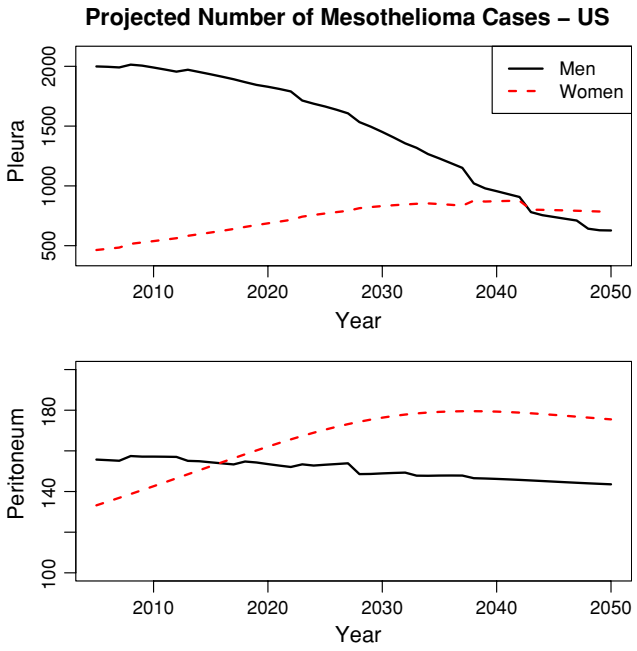

Fig. 8 Projected number of mesothelioma cases in the US to the year 2050. *Upper panel*: pleural mesothelioma; *lower panel*: peritoneal mesothelioma

age-specific incidence rates in males and females with birth cohort effects identically equal to one among females and period effects identically equal to one in both genders. The estimated cohort effects among males have wide confidence intervals, but suggest a pattern similar to the cohort effects for pleural mesothelioma among males. Thus, the data are consistent with no secular trends in peritoneal mesothelioma incidence among women and only weak trends among men over the period 1973–2005. Figure 2 shows the age-specific incidence curves for peritoneal mesothelioma generated by the Armitage–Doll and the TSCE models. Since there have been no temporal trends, the lifetime probability of peritoneal mesothelioma among women, adjusted for other cause mortality, is constant at approximately 1×10^{-4} over all the birth cohorts in the data. Among men, this probability lies between 1×10^{-4} and 1.5×10^{-4} for all birth cohorts (Fig. 6). The lifetime probability (to age 85) unadjusted for other cause mortality is about 1×10^{-4} among women and ranges between 1×10^{-4} and 2.5×10^{-4} among men (Fig. 7).

Projected incidence

The total numbers of incident cases of pleural and peritoneal mesothelioma in the US projected to the year 2050 are shown in Fig. 8.

Discussion

In this paper, we have used APC models to investigate age effects and temporal trends in mesothelioma incidence in SEER, with the non-specific age effects of traditional APC models replaced by parametric incidence curves based on the ideas of multistage carcinogenesis. Both the Armitage–Doll and TSCE models describe the data well within this analytic framework. The age effects isolated by this procedure approximate the age-specific incidence curves of pleural and peritoneal mesotheliomas after adjustment for temporal trends that are largely due to asbestos exposure, although other factors could be involved. We have also used a number of assumptions to project mesothelioma incidence in the US to the year 2050.

Age-specific incidence

As seen in Fig. 2, the incidence curves predicted by the two models are similar, with the Armitage–Doll model predicting somewhat higher incidence rates at the older ages. For pleural mesothelioma, the exponent k of the Armitage–Doll model is estimated to be ~ 5 as shown in Table 1.

Peto et al. [17] in an analysis of the insulator database found that the mortality rates among those continuously exposed was described well by a model in which duration of exposure is lagged by 10 years and raised to the power 3.2. However, in a document prepared for the U.S. EPA in 1986 [25], Nicholson pointed out that Peto et al. [16]

excluded workers who entered the workforce before 1922 and after 1946 and who were over the age of 80. For the entire cohort, Nicholson found that a model with time since first exposure raised to the power 5 described the data well.

Nicholson et al. [26] estimated the number of mesotheliomas that could be expected for different occupations from 1980 through 2030, using data from the insulator cohort to estimate the parameters of the mortality rate as function of time since first exposure, which he also assumed to be proportional to time raised to a power. He found that the risk of death increased as the fourth or fifth power of time from onset of exposure for about 40 or 50 years, without giving a precise value of the exponent. We estimate from the data presented in the Nicholson paper that the exponent is about 4.5. Thus, the value of the exponent of the Armitage–Doll model given by the modified APC approach used here is consistent with values found in the literature. It should be kept in mind, however, that in the model here it is the age that is raised to the power 5, whereas in the analyses of Peto and Nicholson it is time since first exposure.

An analogous situation obtains with lung cancer. Doll and Peto [27] have reported that lung cancer mortality rates increase with between the fourth and fifth power of age among non-smokers and with a similar power of duration of smoking among smokers. The multiplicative parameter C in the Armitage–Doll model is not uniquely identifiable in an APC model because the estimate of this parameter depends upon which of the cohort or period parameters is anchored at 1. For the same reason, although ν/α is an identifiable parameter of the TSCE model, when the TSCE model is embedded in an APC model, this parameter is identifiable only up to a multiplicative non-zero constant. In these analyses, the parameters for the birth cohort 1926–1930 for women and the period 2001–2005 for men were constrained to be 1. Then the parameters C and ν/α are identifiable. The age-specific incidence curves in Fig. 2 are based on this choice of constraints.

For peritoneal mesothelioma the exponent is close to 3 and so is smaller than the exponent for pleural mesothelioma. There are no analyses of peritoneal mesothelioma comparable to the analyses of Peto and Nicholson discussed above.

Within the framework of the Armitage–Doll model, these results suggest that approximately six and four mutations, respectively, are involved in the genesis of pleural and peritoneal mesotheliomas. Moreover, the constant C, which is the product of the number of cells at risk and the mutation rates, is considerably larger in peritoneal than in pleural mesothelioma (Table 1). This finding is to be expected since C involves the product six mutation rates, each much smaller than 1, for pleural mesothelioma, and only four mutation rates for peritoneal mesothelioma. Within the framework of the TSCE model, these results suggest that the higher age-specific incidence of pleural mesothelioma can be mainly attributed to a higher index of diversity r, due either to a higher background initiation rate, ν, or a lower rate of cell division, α, or both. The initiation rate, ν, depends both on the number of target cells and on the rate of the initiating mutation.

For peritoneal mesothelioma, the age-specific incidence curves in Fig. 2 can be interpreted to be the best estimates from the SEER data of the incidence in a population unexposed to asbestos. For pleural mesothelioma, the age-specific incidence curves represent the best estimate of the age distribution of pleural mesothelioma incidence in a population unexposed to asbestos, but the actual magnitude of the age-specific incidence rates is not identifiable.

Temporal trends

Over the period of this study, there have been no secular trends in peritoneal mesothelioma among women and only weak trends among men. This observation suggests that asbestos exposure was responsible for only a minor fraction of peritoneal mesotheliomas in SEER over the period 1973–2005. Spirtas et al. [6] reported that about 58% of peritoneal mesotheliomas among men in their study population were attributable to asbestos exposure. For females, they were unable to estimate separate attributable fractions for pleural and peritoneal mesotheliomas, but reported that the attributable fraction for both sites combined was 23%. Our results here suggest that, at least in the SEER data over the period of observation, the attributable fraction for male peritoneal mesotheliomas was lower than that reported by Spirtas.

Similar results have been reported in other registries. Hemminki and Li [28] examined trends in the incidence of peritoneal mesothelioma in Sweden over the period 1961–1998. Among men they reported that only 29% had "typical asbestos-related jobs…" Interestingly, the age-adjusted incidence rates were virtually identical in men and women. Since men are much more likely to be occupationally exposed to asbestos, this finding suggests that a large fraction of peritoneal mesotheliomas in Sweden over this period were unrelated to asbestos exposure. Moreover, the generally increasing trends in incidence over this period are probably attributable to factors other than asbestos.

Burdorf et al. [29] examined the incidence of peritoneal mesothelioma among men and women in Sweden and the Netherlands over the period 1989–2003 and reported absence of any trends. They concluded, "[t]he absence of a time trend in the incidence rate of peritoneal mesothelioma in Sweden and the Netherlands in the past 15 years may point to a more limited role of occupational exposure to asbestos in the etiology of peritoneal mesothelioma than for pleural mesothelioma, especially among women."

Seidman and Selikoff [30] reported 282 peritoneal mesotheliomas out of a total of 453 mesotheliomas in the cohort of US and Canadian insulators. One would expect to see such a large number of cases reflected in the temporal trends in peritoneal mesothelioma rates in a population-based registry. Why then do we observe only weak temporal trends in peritoneal mesothelioma incidence among men in the SEER database over the period 1973–2005? The 282 peritoneal mesotheliomas reported by Seidman and Selikoff occurred over the 20-year period 1967–1986. Some fraction of these occurred in Canada and thus would not be reflected in the US statistics. Moreover, some fraction of the US cases occurred prior to 1973 and would thus not be reflected in the SEER database starting in 1973. Finally, SEER represents only about 10% of the US population. Thus, one would expect the peritoneal mesotheliomas in the insulators' cohort to have only a small impact on temporal trends in the SEER registry over the period 1973–2005.

In a recent review of the epidemiology of peritoneal mesothelioma, Boffetta [31] reported that there was a strong correlation between the fraction of deaths from pleural and peritoneal mesothelioma in cohorts occupationally exposed to high levels of asbestos. This finding suggests that occupational exposure to asbestos can increase the risk of both pleural and peritoneal mesothelioma. In contrast, Boffetta reported low correlation between the incidence of pleural and peritoneal mesothelioma in population-based registries. This finding suggests that, in the general population, a smaller fraction of peritoneal than pleural mesothelioma is attributable to asbestos exposure.

As reported by Price and Ware [8], trends in pleural mesotheliomas among men clearly reflect temporal trends in asbestos use in the US. There has been a strong cohort-wise increase in the rates of pleural mesotheliomas among men reaching a peak with the birth cohorts of the early 1920s and declining thereafter. The birth cohort of 1965 appears to have approximately the same risk as that of 1890, so that by the cohort of 1965 the epidemic of asbestos-induced pleural mesothelioma appears to have abated. Among women, the birth cohort effects appear to have increased, albeit much slower than among the men, until about the cohort of 1925. The birth cohort effects appear to be more or less flat from 1925 to 1965. As reported earlier in 'Results', period effects are declining slightly among the women, which contributes to the generally flat age-adjusted incidence rates despite the increase in birth cohort effects. We note here that information on the earliest and latest cohorts among men are based on few observations so that conclusions about them must be made with caution.

The differences in the patterns of birth cohort and period effects between males and females suggest that factors other than asbestos exposure are responsible, in part, for the observed temporal trends.

Figures 6 and 7 show the lifetime probabilities of developing pleural and peritoneal mesothelioma by birth cohort adjusted and unadjusted for other cause mortality, respectively. It is of interest to note that the lifetime probabilities in males and females are similar in the earliest and latest birth cohorts, suggesting a beginning and an end to the epidemic of asbestos-related pleural mesotheliomas.

Background rates

There is some interest in estimating the background rates of pleural and peritoneal mesotheliomas, i.e., the rates that would be expected in the absence of any recorded exposure to asbestos. Background rates are easiest to define for peritoneal mesothelioma since there appear to have been no secular trends among women associated with the use of asbestos in the US, and only weak trends among men. Clearly, incidence rates depend upon age as shown in Fig. 2. Any summary age-adjusted rate depends on the standard population used for the adjustment. With the standard population used in this paper, the age-adjusted background peritoneal mesothelioma rate is approximately 1 per million individuals per year, as indicated in Fig. 1. The lifetime probability of developing peritoneal mesothelioma, when adjusted for other cause mortality, likewise depends on the specific life-table used for the adjustment. With the life tables used in this paper, the lifetime probability of peritoneal mesothelioma is 1 per 10,000 women and between 1 and 1.5 per 10,000 men. These probabilities can be taken to be estimates of the background risks of peritoneal mesothelioma among women and men, respectively.

For pleural mesotheliomas, background rates are more difficult to estimate because there have been secular trends among both men and women. The secular trends among men are clearly dominated by the use of asbestos in the work place, although other factors could also be at play. Among women, birth cohort effects have risen modestly while period effects have declined leading to age-adjusted incidence rates that have remained more or less constant over the period of this study at about 3 per million individuals per year. This observation suggests that, even if some fraction of female cases can be attributed to asbestos exposure, the background rates are between 2 and 3 per million individuals per year. If the pathogenesis of spontaneous pleural mesotheliomas is similar in men and women, a not unreasonable assumption, this range of estimates can be taken to represent estimates of the background rate of pleural mesothelioma in men as well. Thus, the background rates of pleural mesotheliomas appear to be approximately 2–3 times higher than the background rates

of peritoneal mesothelioma. Among men, the cohort-wise life-time probability of pleural mesothelioma, adjusted for other cause mortality, increased from about 2 per 10,000 individuals in the cohort of 1890 to approximately 18 per 10,000 in the cohort of 1925 before decreasing again to about 2 per 10,000 in the cohort of 1965. Among women, over the same period of time, the lifetime probability increased modestly from about 2 per 10,000 in the cohort of 1890 to about 4 per 10,000 in the cohort of 1925 and remained more or less constant in later cohorts. These observations suggest that the background lifetime probability of pleural mesothelioma is approximately 3 per 10,000. Thus, the lifetime probability of pleural mesothelioma is about 2–3 times larger than that of peritoneal mesothelioma. For comparison, Price and Ware [8] estimate that the background lifetime probability of pleural and peritoneal mesothelioma combined is 3.6 per 10,000 individuals.

Projections

Figure 8 shows the number of mesothelioma cases that would be expected to occur in the US under the assumptions discussed above. The top panel shows the number of pleural mesothelioma cases among men and women, whereas the bottom panel shows the number of peritoneal cases over the period 2005–2050. We estimate approximately 62,000 pleural mesotheliomas among men and approximately 32,000 pleural mesotheliomas among women over this period. The corresponding figures for peritoneal mesotheliomas are 7,600 and 6,900, respectively, among men and women. The larger number of pleural mesotheliomas among men reflects the continuing, but declining, impact of asbestos use on pleural mesothelioma. The larger projected number of peritoneal mesotheliomas among women reflects the higher life expectancy of women in the US population. Our projections of the total number of mesotheliomas are in reasonable agreement with those of Price and Ware [8].

Conclusions

Although both pleural and peritoneal mesotheliomas are known to be associated with exposure to amphibole asbestos, the trends in the incidence of peritoneal mesothelioma in both sexes in SEER have not been influenced by the trends in occupational asbestos exposure in the US. In contrast, trends of pleural mesothelioma among men have been strongly influenced by occupational exposure to asbestos. Background incidences and life-time probabilities of mesothelioma at both sites appear to be similar in men and women with these rates for pleural mesothelioma being 2–3 times higher than those for peritoneal mesothelioma. After adjustment for secular trends, the age-specific incidence of mesothelioma at both sites is well described by the TSCE and Armitage–Doll models.

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