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ORIGINAL ARTICLE

Malignant mesothelioma diagnosed at a younger age is associated with heavier asbestos exposure

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Abstract

Asbestos exposure is the main etiology of malignant mesothelioma, but there are conflicting data on whether the intensity of exposure modulates the development of this disease. This study considered 594 patients with malignant mesothelioma for whom count data on asbestos bodies and fibers (per gram of wet lung tissue) were available. The relationships between age at diagnosis (a time-to-event outcome variable) and these two measures of internal asbestos exposure, along with other possible modulating factors (sex, tumor location, histological subtype and childhood exposure), were assessed on multivariable Cox proportional hazard models, stratifying by decade of birth year. For both measures of asbestos in lung tissue, younger age at diagnosis was associated with higher internal measures of exposure to asbestos. Stratified Cox analyses showed that for each doubling in asbestos body count patients were 1.07 times more likely to be diagnosed at a younger age [hazard ratio (HR) = 1.07; 95% confidence interval (CI), 1.04–1.09; $P = 2.2 \times 10^{-7}$] and for each doubling in asbestos fiber count patients were 1.13 times more likely to be diagnosed at a younger age (HR = 1.13; 95% CI, 1.09–1.17; $P = 8.6 \times 10^{-11}$). None of the other variables considered were associated with age at diagnosis. Our finding that tumors become clinically apparent at a younger age in heavily exposed subjects suggests that asbestos is involved not only in the malignant mesothelioma tumor initiation but, somehow, also in the progression of the disease.

Introduction

Malignant mesothelioma is one of several diseases caused by exposure to asbestos, a silicate mineral that forms fibrous crystals. Exposure to asbestos is often occupational (e.g. during mining and preparation of products containing asbestos) but may also be environmental (1–4). Because asbestos fibers are easily inhaled, malignant mesothelioma often originates in the pleura, although it may also affect the peritoneum and, in rare cases, the pericardium, tunica vaginalis testis and hernia sacs.

Asbestos fibers in lung tissue can be identified and quantified by digestion of tissue fragments obtained by biopsy or autopsy, including paraffin-embedded material (5,6). These methods have revealed that most asbestos fibers have a lifetime persistence in the organism (7,8) and can be detected in the lung tissue of malignant mesothelioma patients dozens of years after their exposure to asbestos (7,9–11). For this reason, the risk of malignant mesothelioma increases with time following exposure to asbestos. For example, among 707 cases of pleural mesothelioma with a median duration of exposure of 3.75 years, including 25% of cases with an exposure <1 year, the adjusted log risk of this disease increased over time, since first exposure, for up to 45 years, and then appeared to increase at a slower rate (12). This unusual pattern of increasing cancer risk after cessation of exposure, due to the long biopersistence of asbestos, is opposite that seen, for example, in lung cancer, where risk decreases after smoking cessation (13,14).

Malignant mesothelioma has a long latency period (i.e. the period between the onset of exposure and the diagnosis of the disease believed to be caused by that exposure), with several studies reporting mean or median values of over 40 years (15–19). However, some of these studies reported a large interindividual

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Abbreviations

CI	confidence interval
HR	hazard ratio
IQR	interquartile range

variability in the latency period, from <10 to >70 years (17,20). This variability may be due to difficulties in ascertaining the precise date when asbestos exposure began or to other factors such as the intensity of exposure and individual characteristics.

A few studies examined the latency of malignant mesothelioma in association with the intensity of exposure to asbestos, reporting conflicting results. One study found no correlation between latency and the asbestos fiber count in lung tissue in 42 cases of malignant mesothelioma linked to occupational exposure in Norway (19). This finding was confirmed by a study of 614 British asbestos workers who died with malignant mesothelioma between 1978 and 2005 (21). In contrast, a study of British dockyard workers found that 41 heavily exposed workers had a shorter latency than 241 less heavily exposed workers (42.0 versus 49.5 years) (18). In these latter two studies (18,21), the intensity of asbestos exposure was estimated from occupational activity.

To clarify how malignant mesothelioma latency depends on asbestos exposure and, in turn, improve our knowledge about disease development and progression, future studies should avoid methodological bias due to inaccurate estimations of intensity and time since exposure. This can be achieved by using internal, quantitative measures of asbestos exposure such as those from asbestos fiber analysis, which uses microscopy to count asbestos fibers, both free and engulfed in iron particles ('bodies'), within lung tissue. Asbestos fiber analysis reveals a person's whole past exposure from both occupational exposure and environmental exposure and is able to detect low lung burdens of asbestos in the general population ('background asbestos levels'). Moreover, rather than latency, which is subject to recall bias, age at diagnosis is a more objective measure; indeed, age at diagnosis is the end point of the latency period, so if levels of asbestos exposure do affect mesothelioma latency, they will also affect age at diagnosis of this disease. Therefore, in the present study, we examined the association between age at diagnosis of malignant mesothelioma and the intensity of asbestos exposure, measured as the number of asbestos bodies and fibers in lung tissue, in 594 patients not selected for the type or intensity of asbestos exposure.

Methods

Population series

The case series comprised 594 patients who had been diagnosed with malignant mesothelioma at Duke University Medical Center (Durham, NC) in the period 1982–2017 and for whom count data on lung tissue asbestos bodies or fibers were available. This case series is partially overlapping with those already reported in Roggli *et al.* (22) and Kraynie *et al.* (23). The diagnosis of malignant mesothelioma in all cases had been confirmed pathologically, according to international guidelines (24,25). The institutional review board of Duke University Medical Center approved the protocols for collecting and sharing the clinical data.

For this study, we obtained clinical data regarding birth year, age at diagnosis, sex, tumor location, histological subtype and whether the patient had occupational or childhood exposure to asbestos. Occupational and childhood exposures were estimated from the patient's self-reported job type and sector of activity, and time of exposure. Data from fiber analysis of surgically resected or postmortem lung tissue included asbestos body count and fiber count. Patients were grouped into eight 10-year birth cohorts by birth year.

Asbestos fiber analysis

Asbestos fiber analysis was done on formalin-fixed, paraffin-embedded peripheral lung parenchyma (taken at surgery or postmortem); specimens included lung tissue from autopsy, extrapleural pneumonectomies and large thoracoscopic biopsies (22,23,26). Briefly, asbestos body counting was done by light microscopy, on unstained filters prepared lung tissue digests, and reported per gram of wet lung tissue, with a detection limit of 3 asbestos bodies/g for a 0.3-g sample. Asbestos fibers were counted by scanning electron microscopy; all fiber types were added together to get a total asbestos fiber count per gram of wet lung tissue, with detection limits varying by fiber type as previously reported (26). In case of a count below the detection limit, an asbestos level of half of that limit was arbitrarily attributed.

Statistical analyses

Distributions of asbestos body count and fiber count were tested using the Shapiro-Wilk normality test. Spearman's rank correlation (a non-parametric test) was used to analyze the correlation between asbestos body count and fiber count. The associations between occupational exposure and both asbestos body counts and fiber counts were tested by the non-parametric Kruskal–Wallis test. The association between age at diagnosis and 10-year birth cohort was visualized with Kaplan–Meier cumulative hazard plots.

To determine the impact of asbestos exposure on age at diagnosis (a time-to-event outcome variable), we used multivariable Cox proportional hazard regression. The two quantitative measures of exposure (asbestos body count and fiber count) were $\log_2$ transformed and analyzed separately in regression models that also took into account sex, tumor location (peritoneal or pleural), histological subtype and the possibility of childhood exposure. The Cox analyses were done first in individual 10-year birth cohorts and then for all patients, stratifying by decade of birth year. These analyses produced hazard ratio (HR) estimates whose values indicated that a given factor was independently associated with a younger (if HR > 1.0) or older (if HR < 1.0) age at diagnosis of malignant mesothelioma.

Statistical analyses were done using the EZR package in R (27). A $P < 0.05$ indicated statistical significance.

Results

This study analyzed clinical and laboratory data for 594 patients with malignant mesothelioma (Table 1). The patients had been diagnosed with malignant mesothelioma over a wide range of ages, from 25 to 94 years, with a median value of 65 years. Most patients were men (n = 509, 85.7%), and most tumors were localized in the pleura (n = 549, 92.4%). The most common histological subtype was epithelioid (46.3%), followed by biphasic (31.5%) and sarcomatoid (14.5%). Many patients had had occupational exposure to asbestos (n = 367, 61.8%), and 30 cases (5.0%) had been exposed to asbestos during childhood.

Asbestos body count, available for 587 cases, ranged from 1 to 1 600 000 g^{-1} wet tissue, with a median of 230 g^{-1} and a mean of 11 931 g^{-1} (SD = 87 287 g^{-1}). Asbestos fiber counts, available for 577 cases, ranged from 180 to 11 900 000 g^{-1}, with a median of 6840 g^{-1} and a mean of 89 219 g^{-1} (SD = 588 413 g^{-1}). Histograms of both counts showed that their distributions were heavily skewed to the right (high exposure values), and although $\log_2$ transformation of the values improved the distribution curves, they remained significantly deviated from normality ($P < 0.001$, Shapiro-Wilk normality test; Supplementary Figure S1A and B, available at *Carcinogenesis* Online). The two measures of asbestos exposure ($\log_2$ transformed) were strongly, positively correlated (rho = 0.82, $P < 2.2 \times 10^{-16}$, Spearman's rank correlation; Supplementary Figure S2, available at *Carcinogenesis* Online).

When asbestos levels in the 367 patients with occupational exposure were compared with those in the 139 patients without such exposure, we observed higher levels in the first group, as expected. Median asbestos body counts were 395 g^{-1} [interquartile range (IQR) = 34–2560 g^{-1}] and 26 g^{-1} (IQR = 5–325 g^{-1}), respectively ($P = 4.3 \times 10^{-11}$, Kruskal–Wallis test), while median

Table 1. Clinical characteristics and lung asbestos fiber burden of 594 patients with malignant mesothelioma

Characteristic	Value
Age at diagnosis, years	
Median (range)	65 (25–94)
Mean (SD)	64.0 (11.8)
Birth year	
Median (range)	1935 (1900–1977)
Mean (SD)	1936 (13)
Sex, *n* (%)	
Female	85 (14.3)
Male	509 (85.7)
Tumor location, *n* (%)	
Pleural	549 (92.4)
Peritoneal	41 (6.9)
Other[a]	4 (0.7)
Histological subtype, *n* (%)	
Biphasic	187 (31.5)
Epithelioid	275 (46.3)
Sarcomatoid	86 (14.5)
Rare[b]	27 (4.5)
Undefined	19 (3.2)
Childhood exposure, *n* (%)	
No	564 (95.0)
Yes	30 (5.0)
Occupational exposure, *n* (%)[c]	
No	139 (23.4)
Yes	367 (61.8)
Missing	88 (14.8)
Asbestos body count, g^{-1}	
Median (range)	230 (1–1 600 000)
Mean (SD)	11 931 (87 287)
Asbestos fiber count, g^{-1}	
Median (range)	6840 (180–11 900 000)
Mean (SD)	89 219 (588 413)

[a]Pericardial (*n* = 1), location not defined (*n* = 3).
[b]Desmoplastic (*n* = 23), lymphohistiocytoid (*n* = 2), osteosarcomatoid (*n* = 1) and pleomorphic (*n* = 1).
[c]Occupational exposure to asbestos estimated from the job type and sector of activity.

asbestos fiber counts were 9180 g^{-1} (IQR = 2650–31 585 g^{-1}) and 3260 g^{-1} (IQR = 930–9795 g^{-1}) ($P = 9.9 \times 10^{-9}$, Kruskal–Wallis test). The measurable asbestos counts in patients without occupational exposure are probably due to environmental exposure or unrecognized occupational exposure. Most patients who reported exposure during childhood (28 of 30; 93%) did not report occupational exposure. Consequently, patients with childhood exposure to asbestos had lower levels of asbestos bodies and fibers in lung tissue than patients without childhood exposure (not shown).

The patients' ages at diagnosis were clearly associated with their 10-year birth cohort (Figure 1). The cohort that was born in the first decade of the 20th century includes patients who had been diagnosed at a late age (>80 years), reflecting the fact that this study began to include patients only in 1982. The birth cohorts of the middle decades, instead, had a broad range of ages at diagnosis (e.g. from 28 to 65 years for those born in 1951–1960), but the hazard curves for a diagnosis at any age shifted to lower ages with each younger birth cohort. Finally, the youngest birth cohort (1971–1980) included, by definition, only patients diagnosed at a relatively young age. For this reason, analyses of association between measures of asbestos exposure and age at diagnosis were stratified by decade of birth year.

Effects of asbestos body counts on age at diagnosis of malignant mesothelioma

Median values of asbestos body count (log_2 transformed) decreased with increasing birth decade, from 11.5 g^{-1} in patients born in 1900–1910 to 2.0 g^{-1} in patients born in 1971–1980 (Table 2). This decrease probably reflects the reduction in occupational and environmental asbestos exposure that occurred especially during the last quarter of the last century; it may also be due to an enrichment of patients with a shorter duration of asbestos exposure in the younger birth cohorts compared with the older ones.

Multivariable Cox analyses revealed significant associations between asbestos body count and age at diagnosis, treated as a time-to-event outcome variable, for birth cohorts 3 (1921–1930), 4 (1931–1940) and 5 (1941–1950). These three cohorts were substantially larger than the others and, thus, had higher statistical power. In these three cohorts, higher asbestos body counts were associated with a higher risk of diagnosis of mesothelioma at a younger age (HR > 1). When all patients were analyzed together, a stratified Cox analysis showed that for each doubling in asbestos body count, patients were 1.07 times more likely to be diagnosed at a younger age (HR = 1.07; 95% CI, 1.04–1.09; $P = 2.2 \times 10^{-7}$). These analyses were all adjusted for the covariates sex, tumor location, histological subtype and possibility of childhood exposure. These covariates were not associated with age at diagnosis (Supplementary Table S1, available at *Carcinogenesis* Online).

Effects of asbestos fiber counts on age at diagnosis of malignant mesothelioma

Association analyses were repeated using asbestos fiber count instead of asbestos body count. As in the case of asbestos body count, median asbestos fiber count (log_2 transformed) decreased with increasing birth decade, from 15.6 g^{-1} in patients born in 1900–1910 to 8.5 g^{-1} in patients born in 1971–1980 (Table 3). Multivariable Cox analyses in individual birth cohorts revealed significant associations between asbestos fiber count and age at diagnosis for cohorts 3 (1921–1930), 4 (1931–1940) and 5 (1941–1950), with higher asbestos fiber counts associated with a higher risk of diagnosis of malignant mesothelioma at a younger age (HR > 1). For all patients together, stratified Cox analysis showed that, for each doubling in asbestos fiber count, patients were 1.13 times more likely to be diagnosed at a younger age (HR = 1.13; 95% CI, 1.09–1.17; $P = 8.6 \times 10^{-11}$).

No significant association was found between the patients' ages at diagnosis and sex, tumor location, histological subtype or childhood exposure (Supplementary Table S2, available at *Carcinogenesis* Online).

Discussion

In this study of 594 cases of malignant mesothelioma, age at diagnosis was younger in patients who were exposed to higher levels of asbestos. Both measures of internal exposure to asbestos, namely asbestos body count and asbestos fiber count, showed that patients with higher asbestos lung burden were significantly more likely to develop the disease at a younger age than patients with a lower asbestos lung burden. Sex, tumor location (pleural versus peritoneal) and childhood exposure to asbestos did not associate with age at diagnosis in this study.

In this series, the 10-year birth cohort was associated with age at diagnosis of malignant mesothelioma. This finding, albeit expected (younger cohorts obviously lack patients who developed the disease late in life), to our knowledge, was not kept into account in earlier studies on the latency of malignant mesothelioma. We

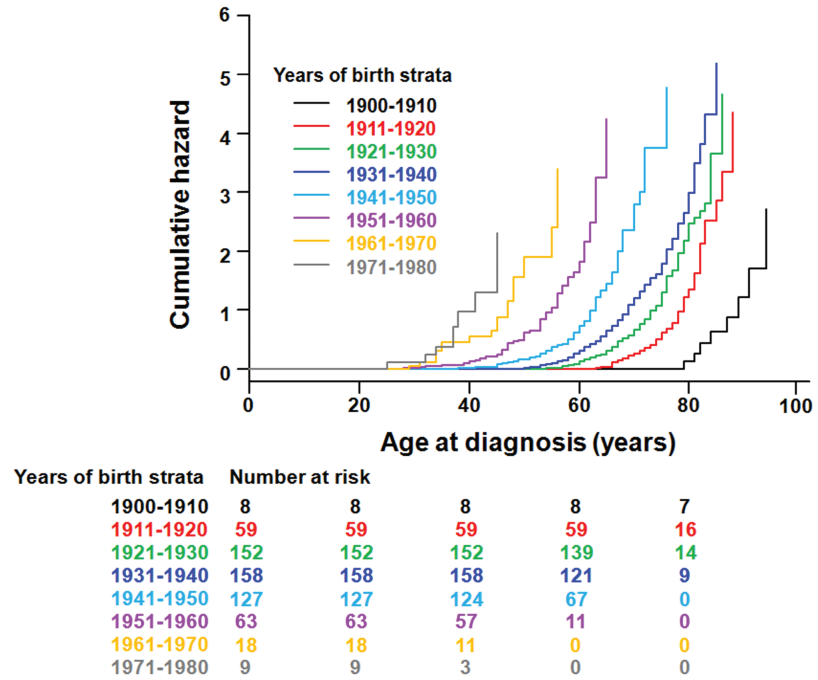

Figure 1. Kaplan–Meier cumulative hazard plots of age at diagnosis of malignant mesothelioma in 594 patients. Effects of 10-year birth cohort, adjusted by sex; first cohort started from 1900, last cohort (1971–1980), contained patients up to 1977 birth year. Below the plots are reported the number of patients at risk at the specified ages at diagnosis.

Table 2. Association between asbestos body count and age at diagnosis of malignant mesothelioma, by multivariable Cox analyses taking into account other clinical variables, for patients grouped by 10-year birth cohort and for all patients

Birth decade	Cases, *n*	Asbestos body count, median (range), g^{-1}	Asbestos body count, log_2 transformed, median (range), g^{-1}	HR (95% CI)[a]	*P*
1 (1900–1910)	7	2,920 (78–31 000)	11.5 (6.3–14.9)	0.93 (0.72–1.21)	0.598
2 (1911–1920)	59	1,970 (1–436 000)	10.9 (0–18.7)	1.05 (0.97–1.13)	0.235
3 (1921–1930)	152	490 (2–1 600 000)	8.9 (1.0–20.6)	1.06 (1.00–1.12)	0.025
4 (1931–1940)	156	255 (1–974 000)	8.0 (0–19.9)	1.09 (1.04–1.14)	4.8×10^{-4}
5 (1941–1950)	125	175 (1–69 400)	7.5 (0–16.1)	1.09 (1.03–1.15)	2.0×10^{-3}
6 (1951–1960)	62	8 (2–3050)	3.0 (1.0–11.6)	1.07 (0.98–1.17)	0.124
7 (1961–1970)	17	4 (2–1190)	2.0 (1.0–10.2)	0.71 (0.50–1.01)	0.060
8 (1971–1980)	9	4 (2–12)	2.0 (1.0–3.6)	1.48 (0.20–10.8)	0.699
All patients	**587**	**230 (1–1 600 000)**	**7.8 (0–20.6)**	**1.07 (1.04–1.09)**	$\mathbf{2.2 \times 10^{-7}}$

[a]Results of Cox's multivariable analyses, including sex, tumor location, histological subtype, childhood exposure as covariates, carried out on log_2 transformed data. Overall results for all birth cohorts are in bold type. Effects of covariates are reported in Supplementary Table S1, available at *Carcinogenesis* Online, for the overall analysis. CI, confidence interval; HR, hazard ratio.

Table 3. Association between asbestos fiber count and age at diagnosis of malignant mesothelioma, by multivariable Cox analyses taking into account other clinical variables, for patients grouped by 10-year birth cohort and for all patients

Birth decade	Cases, *n*	Asbestos fiber count, median (range), g^{-1}	Asbestos fiber count, log_2 transformed, median (range), g^{-1}	HR (95% CI)[a]	*P*
1 (1900–1910)	8	51 585 (4120–150 400)	15.6 (12.0–17.2)	0.62 (0.33–1.18)	0.145
2 (1911–1920)	58	27 305 (240–2 145 600)	14.7 (7.9–21.0)	1.07 (0.95–1.21)	0.257
3 (1921–1930)	144	10 040 (263–5 660 000)	13.3 (8.0–22.4)	1.18 (1.10–1.28)	2.2×10^{-5}
4 (1931–1940)	156	8130 (245–11 900 000)	13.0 (7.9–23.5)	1.14 (1.07–1.22)	6.8×10^{-5}
5 (1941–1950)	122	5270 (180–258 600)	12.4 (7.5–18.0)	1.16 (1.06–1.27)	1.5×10^{-3}
6 (1951–1960)	62	1385 (205–283 000)	10.4 (7.7–18.1)	1.08 (0.94–1.24)	0.303
7 (1961–1970)	18	825 (210–46 220)	9.7 (7.7–15.5)	0.89 (0.65–1.22)	0.481
8 (1971–1980)	9	360 (215–1260)	8.5 (7.7–10.3)	23.3 (0.96–566)	0.053
All patients	**577**	**6840 (180–11 900 000)**	**12.7 (7.5–23.5)**	**1.13 (1.09–1.17)**	$\mathbf{8.6 \times 10^{-11}}$

[a]Results of Cox's multivariable analyses, including sex, tumor location, histological subtype, childhood exposure as covariates, carried out on log_2 transformed data. Overall results for all birth cohorts are in bold type. Effects of covariates are reported in Supplementary Table S2, available at *Carcinogenesis* Online, for the overall analysis. CI, confidence interval; HR, hazard ratio.

made the same observation in a study on factors associated with age at diagnosis of lung adenocarcinoma (T. A. Dragani *et al.*, submitted for publication). Therefore, in the present study, we stratified the Cox regression analyses by 10-year birth cohort. We recommend that any epidemiological study of factors associated with age at disease diagnosis should take into account the birth cohort of patients to avoid biased results.

The median count of asbestos bodies in this study (230 g^{-1} wet tissue) is above the cutoff of 100 g^{-1} wet tissue established in the Helsinki criteria indicating a high probability of occupational exposure to asbestos (28). Indeed, in our series, most cases (>60%) reported occupational exposure and, as expected, patients with occupational exposure had higher levels of asbestos bodies and fibers in lung tissue than patients without occupational exposure.

This study used data from quantitative analyses of asbestos bodies and fibers in lung, considered reliable assessments of asbestos exposure (29). In fact, with these methods, it is possible to detect asbestos fibers in lung tissue both from workers who had been exposed to high levels of asbestos and from people who did not report exposure to asbestos during employment or in their daily lives. These internal measures of asbestos exposure are more reliable than questionnaires and reconstruction of occupational histories because these latter methods may generate inaccurate data due to recall bias and unrecognized past exposure to asbestos (in cases of environmental exposure). Also, external exposures may be not precisely measured or recorded and they vary with time, whereas internal measures of asbestos exposure report the cumulative lifelong exposure of a given patient to asbestos.

In a previous study (23), some of us found that 83 patients with malignant mesothelioma unrelated to asbestos [i.e. with asbestos fiber counts below reference levels for a non-exposed population (22)] were diagnosed at a younger age than 442 patients whose lung tissue had asbestos fiber counts above the reference cutoffs (mean, 55 versus 66 years, respectively), in apparent contradiction with the present study. Importantly, in the earlier study, neither the multivariable statistical analyses were done nor the effects of birth year cohort taken into consideration. Further studies are needed to better understand the etiology of mesothelioma unrelated to asbestos.

In the present study, no association was found between age at diagnosis and asbestos exposure during childhood. This negative finding may be due to the small number of cases (5% of total), as we would have expected a younger age at diagnosis associated with early exposure. Alternatively, the stratification by birth cohort and the other variables may have absorbed the possible effects of exposure during childhood on the age at diagnosis.

A possible limitation of this study is that it assessed age at diagnosis only for cases diagnosed with malignant mesothelioma, without taking into consideration other persons who were exposed to asbestos but not yet diagnosed with the disease. This criticism (30), made in regard to a cohort study of asbestos workers by Frost (21), maintains that case-only analyses are at risk of bias when time-to-event end points (e.g. survival, latency, age at diagnosis) are known only for a small fraction of the entire cohort. As Frost responded, however, the inclusion of controls (censored observations) would have confounded the calculation of survival times (31). Moreover, most clinical trials are case-only studies that have time-to-event end points. Our study did not investigate an occupational cohort but a heterogeneous collection of cases, so it would have been impossible to identify enough healthy controls who, at postmortem analysis, had high lung asbestos levels to include in the analyses. We feel that case-only analyses of time-to-event endpoints are valid and meaningful, provided that the study design is rigorous, for example, through the use of quantitative measures of asbestos lung burden and the avoidance of recall bias, as we did here. Also, statistical analyses taking into account the possible confounding factors, in particular the relationship between birth year cohort and age at diagnosis, as we did here, provide unbiased estimators of risk associated with the variables being studied.

Although malignant mesothelioma is overwhelmingly associated with asbestos exposure, Testa *et al.* found that germline mutations in *BAP1* gene predispose to this disease (32). Considering that familial cancers due to germline mutations are often characterized by an early age at onset (33), it is worth testing if *BAP1* germline mutations are an additional independent factor modulating the age at diagnosis of malignant mesothelioma.

Although the precise mechanism of asbestos carcinogenicity is not completely known, chronic inflammation elicited by asbestos fibers in the lung and mesothelium is believed to play an important role in the origin of this disease (34,35). Induction of inflammation by asbestos fibers, through the generation of iron-derived reactive oxygen species or after 'frustrated' phagocytosis, is also associated with DNA damage, genotoxicity and cell toxicity (36–39). Establishment of an inflammatory microenvironment increases the aggressiveness of cancer cells, and high levels of inflammatory players (i.e. cytokines and immunoreactive cells in the tumor microenvironment) promote the progression of neoplastic clones into advanced disease (40–43). Although there is no clear-cut evidence of a dose–response relationship for asbestos-induced inflammation in target organs, higher inflammation is often associated with higher levels of its causative agents (44–46). Accordingly, asbestosis, an inflammation-related disease (47–49), is caused by high asbestos levels but not by low levels (28,50,51). It is therefore plausible that exposure to high asbestos levels could cause severe inflammation in the mesothelium that, in turn, could somehow favor faster growth of neoplastic transformed mesothelial cells; this process could promote tumor progression, resulting in a clinically apparent malignant mesothelioma earlier than in cases exposed to low levels of asbestos.

Overall, our findings indicate that malignant mesothelioma patients heavily exposed to asbestos were diagnosed at a younger age than patients exposed to low levels. Further studies with quantitative measures of lung tissue inflammation, in patients already characterized for asbestos fiber lung burden, should clarify the relationships between asbestos levels, inflammation and age at diagnosis of malignant mesothelioma.

Supplementary material

Supplementary data is available at *Carcinogenesis* online.

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Conflict of Interest Statement: Prof. V.Roggli and Dr T.A.Dragani occasionally consult with plaintiff and defense attorneys in asbestos litigation.

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