Asbestos and Peritoneal Mesothelioma among College-educated Men

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The proportion of peritoneal mesotheliomas among all mesotheliomas has been decreasing, leading some to suggest that peritoneal mesothelioma occurs only after high levels of exposure to asbestos. To investigate the relationship between asbestos exposure and the development of peritoneal mesothelioma, a case–control study examined 40 cases of primary peritoneal mesothelioma from a single institution. This series differed from previous reports in that 75% of the cases and controls had attended college. Results show an odds ratio of 6.6 for asbestos exposure among this group of primary peritoneal mesothelioma cases with relatively slight asbestos exposures. *Key words*: asbestos; peritoneal mesothelioma; mesothelioma; case–control study.

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Peritoneal mesothelioma is a rare primary peritoneal surface malignancy. The incidence of malignant mesothelioma, pleural and peritoneal, has been rising worldwide since at least the 1970s,[1–4] with some evidence only recently of a slowing of this trend.[5] Price used data from Surveillance, Epidemiology and End Results (SEER) from 1973–1992 to describe the incidence of pleural and peritoneal mesothelioma in the United States, and to estimate the future incidence.[3] He predicted that the total number of cases per year overall would decline, with a peak incidence of 2,800 cases/year in the year 2000, but there would be a continued upward trend in older age groups that had had the highest asbestos exposures in prior decades.

Since the first report from Wagner et al. in 1960 linking asbestos exposure to malignant pleural mesothelioma,[6] many studies have reported asbestos exposure to be a significant etiologic factor in the pathogenesis of malignant mesothelioma in general, and of peritoneal mesothelioma in particular. In several countries, trends in the incidence of deaths from mesothelioma (pleural or all combined) increased in conjunction with increase in the use of asbestos, taking into account an appropriate latency period. Becklake documented a great increase in worldwide asbestos use beginning around 1940,[7] and others have described additional increases in some countries during and after World War II. In one population-based study, mortality for men in The Netherlands increased from 10.8/million for the period 1970–1978 to 20.9/million in 1979– 1987.[8] The rate for women also increased, from 2.5/million to 3.6/million. There was no change in the rates for those under 45, and the highest increase was in those over 65. In addition, the geographic distribution across the country showed a pattern of concentration of deaths among men in areas with many harbors, shipyards, and heavy industry. These patterns mirror the use of asbestos in that country in the 1950s and 1960s, with a 20–30-year latency period. Household exposure has been shown to cause pleural mesothelioma, with relative risk estimates from fourfold to 23-fold[9]; similar data for peritoneal mesotheliomas are not available.

Using population-based cancer registries in the United States, Spirtas et al. reported a significant increase in mesothelioma incidence during 1970–1980 among men over 55 at the time of diagnosis, with an annual increase in three different registries of 12–13%.[4] They specifically looked for bias related to increased recognition of the disease, and concluded this did not account for the increased incidence. Similar increases have been found in Finland,[10] as well as in other studies in the United States,[11] Australia,[12,13] and Norway.[14]

Peritoneal mesotheliomas make up 10–50% of all mesotheliomas in case series and case–control studies. Some investigators have advanced the hypothesis that for asbestos to cause peritoneal mesothelioma the exposures must be of a higher duration and/or intensity than the exposures needed to cause pleural mesothelioma.[15] To address this question, we present a case series of peritoneal mesothelioma among a referral population of men with predominately college educations, and conclude that intermittent or low exposure to asbestos is associated with mesothelioma.

METHODS

Cases and Controls

Potential cases in this study included every patient with a primary peritoneal surface malignancy treated at the

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Washington Cancer Institute (WCI) between 1989 and 2001. Peritoneal mesothelioma, primary peritoneal adenocarcinoma, desmoplastic small-round-cell tumor, and papillary serous adenocarcinoma were considered primary peritoneal surface malignancies. Cases of primary pleural mesothelioma with peritoneal involvement were excluded. The diagnosis of peritoneal mesothelioma in our 51 patients was made on the basis of a composite of clinical and pathologic features. First, the patients had clinical syndromes compatible with the disease, peritoneal mesothelioma. Second, examination of generous biopsies by light microscopy showed histologic features compatible with peritoneal mesothelioma. Third, the proper immunostains (calretinin and CK 5/6) were used to confirm the diagnosis.[16] For every potential participant, the diagnosis of cancer had been made at this institution, or pathology data were reassessed and the diagnosis was confirmed if the patient had been referred from another institution for treatment.

One control for each case was recruited from all appendiceal cancer patients treated at the Washington Cancer Institute from 1990 to 2000. Cases were matched to controls by sex and age within two years. When a matched control was unavailable for interview or lost to follow-up, a second control was matched to the initial case. For the 52 primary peritoneal mesotheliomas, 40 patients or next of kin were interviewed, for a response rate of 78%; the rest were lost to follow-up. Among these 40, 24 were men and 16 were women. All but three of the mesothelioma cases who were interviewed were contacted within two years of diagnosis; details of the clinical presentations and clinical courses are described elsewhere.[16] This analysis focuses on the male peritoneal mesothelioma cases and controls; results for female case and controls will be presented separately.

Exposure Assessment

After giving verbal consent, cases and controls underwent a detailed telephone interview using the questionnaire developed by Spirtas and colleagues[17] for a case–control study of mesotheliomas. In the event that cases or controls were not available for interview or were dead, a spouse or next of kin was interviewed. Information collected included sex, age, race, level of education, and lifetime occupational history. We asked whether the study subject, or a person living with the study subject, had ever worked in one of the nine following high-risk-for-asbestos-exposure processes: 1) tire and/or brake lining installation or repair, 2) furnace or boiler installation or repair, 3) building demolition, 4) plumbing or heating repair, 5) insulation installation or removal, 6) elevator installation or repair, 7) shipbuilding, ship demolition, or shipyard work, 8) production of textiles, and 9) production of paper products. We also asked whether the subject had ever been exposed to 22 specific substances, one of which was asbestos.

In order to evaluate intensity and probability of exposure to asbestos, two occupational medicine specialists (LSW, RKS) assigned a score for probability and intensity of exposure to each job identified in the detailed job history taken during the interview. Scores ranging from 0 to 3 were given for probability of exposure to asbestos, where 0 meant very unlikely, 1 meant some possibility, 2 meant probable, and 3 meant definite exposure. Scores of 1 to 3 were also assigned for intensity when the probability score was not zero, with 1 meaning low, 2 meaning medium, and 3 meaning high, based on both the type of work and its duration. Scores were calculated for each job by multiplying intensity and probability, and then the score for all jobs were summed when a subject had held more than one job. We classified jobs as unexposed when the total score was zero or 1. The raters were blind to case or control status.

In the analysis, asbestos exposure was classified in five ways.

1. The subject's answer of *yes* or *no* to the question: Have you ever been exposed to asbestos?
2. The score assigned by the probability-intensity expert rating
3. A categorization of "exposed" or "not exposed" based on the participant's report of exposure to asbestos in any of nine tasks or processes defined a priori to represent exposure
4. The subject's answer of yes or no as to whether a cohabitant had ever worked with asbestos while residing with the subject
5. A cohabitant's exposure to asbestos based on the nine tasks or processes mentioned in 3 above while residing with the subject

Overall exposure was defined as any exposure to asbestos in any of these five categories.

Statistical Analysis

To determine inter-rater reliability between the two occupational medicine specialists, a kappa statistic was used. The kappa was 0.6181, which is a good-to-intermediate kappa.[18] We then used the scores of one rater (LSW) to define job exposure to asbestos through expert opinion as a dichotomous variable. We also used the scores of both raters to create an average score for five groups by education level. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for a paired study design.

RESULTS

The mean age of the male peritoneal mesothelioma cases was 53 years, and that of controls was 55 years,

TABLE 1 Asbestos Exposures of Male Peritoneal Mesothelioma Subjects and Their Paired Colon Cancer Controls

	Cases (n = 24) No. (%)	Controls (n = 24) No. (%)
Ever exposed to asbestos?*	12 (50)	8 (21)
Ever performed*:		
Tire or brake lining work?	8 (33)	6 (25)
Furnace or boiler installation?	5 (21)	2 (5)
Building demolition work?	6 (25)	7 (29)
Plumbing or heating repair?	6 (25)	10 (42)
Insulation work?	10 (42)	6 (25)
Shipyard or shipbuilding work?	6 (25)	1 (2)
Elevator installation?	0 (0)	1 (2)
Production of textiles?	6 (25)	2 (5)
Production of paper products?	2 (8)	1 (2)
At least one of these nine activities?	21 (88)	14 (58)
Job exposure by expert rater	21 (88)	9 (38)
Cohabitant any of the nine activities	8 (33)	2 (8)
Overall reported exposure†		
Potential	22 (92)	15 (62.5)
No known exposure	2 (8)	9 (37.5)

*"Yes" answer to the question.
†"Yes" answer to "ever exposed to asbestos?" *or* any one of the nine tasks *or* cohabitant question or rated by expert rater.

with a range from 22 to 87. All but one of the 24 male cases and all of the controls were non-Hispanic whites. Seventy-eight percent of all male participants had completed at least some college, and there was no difference in race or education distributionsbetween male cases and controls. Interviews were held with the cases 50% of the time, and with the controls 58% of the time; the remainder were held with wives (41% and 29%, respectively) or with other household members (8% and 12%, respectively).

Table 1 shows the frequencies and percentages of exposures to asbestos for cases and their paired controls. All cases classified as exposed by the expert rater were also identified using the nine activities defined a priori to represent asbestos exposure. Five controls reported work in those activities but were not classified as exposed based on expert review of job descriptions.

Table 2 shows the educational levels and asbestos exposures of the participants, and an average probability-intensity expert rating score based on averaging scores from both readers for all cases or controls within each educational level. The average exposure to asbestos declined as the educational level increased.

Table 3 shows the odds ratios and 95% confidence intervals for exposures to asbestos among this group of male peritoneal cases and controls. The mesothelioma cases had an odds ratio of 6.6 for overall exposure to asbestos, with a confidence interval of 1.16–21.5.

DISCUSSION

Here we report a significant association between asbestos exposure and peritoneal mesothelioma in exposed men. In addition, we found a relationship between asbestos exposure and peritoneal mesothelioma in a group of men among whom 75% had attended college, and over 35% had graduated from college. Table 3 shows that the expert ratings of exposures and intensities among these cases are generally lower than what would be expected for a man who has had a career in the construction industry. For example, a man who has worked for 20 years as an insulator would have a score of at least 9. This study supports the conclusion that asbestos exposures cause peritoneal mesothelioma even at levels lower than exposures sustained by cohorts previously described.

Our study has some unique attributes. All cases were histologically confirmed; this is only the second study including peritoneal mesotheliomas to have done so. It is the largest series of peritoneal mesotheliomas for which an in-depth interview has been conducted; because peritoneal mesotheliomas represent less than 20% of all mesotheliomas in most studies, this tumor site is often not analyzed separately. Spirtas included 25 peritoneal mesotheliomas in his case–control study. Cocco and Dosemici[19] described the epidemiology of 657 deaths from peritoneal cancer, but they were not able to clearly identify the histologic types, and exposure was assigned based on occupation on the death certificate.

The limitations of this study are ones common to case–control studies. There may have been recall bias among both cases and controls, as may occur in a case–control design. Since cancer patients may have a heightened awareness of exposures to known carcinogens, including asbestos, we chose to use cancer con-

TABLE 2 Probability–Intensity Rating Scores* of Asbestos Exposures of Male Peritoneal Mesothelioma Subjects and Their Paired Colon Cancer Controls by Educational Level

	Mesothelioma		Colon Cancer	
	Individual Scores	Level Average	Individual Scores	Level Average
Level 1. < 8th grade	—		—	
Level 2. 8–11 years	—		4	4
Level 3. 12 years or HS grad	1.5, 4, 14.5, 7.5, 9	7.3	1, 10.5, 0, 4, 0,1, 0	2.5
Level 4. Technical school prior to HS completion	1	1	0.5	0.5
Level 5. Post-HS technical school	—		—	
Level 6. Some college/completed junior college	4.5, 14, 4, 6, 3.5, 4, 3.5, 4	5.4	11, 4, 1.5	5.5
Level 7. Graduated college	2.5, 7.5, 0, 2, 1.4, 1, 1	2.2	2, 0, 2, 0, 0.5, 7.5, 4, 0.5, 1.5, 3	2.1
Level 8. Postgrad education	2, 4	3	4, 1.5	2.75

*Scores ranging from 0 (very unlikely) to 3 (definite exposure) were given for probability of exposure, intensity was scored 1 (low) to 3 (high). A score for each job was calculated by multiplying intensity and probability. Scores for all jobs of an individual were summed.

trols to minimize a difference in recall between our cases and controls.

We used two different methods of assigning exposure, one based on self-report of exposure, and the second based on an expert rating of the subject's occupational history. Among our cases, these two methods were in full agreement on exposure status, while the two approaches differed somewhat for the controls. Prior studies have used similar methods, and some have included a formal job-exposure matrix created a priori. There is no clear advantage to the use of a job-exposure matrix (JEM) over the other two ways to characterize exposure. Ahrens et al.[20] assessed exposures to asbestos in a lung cancer case–control study, and specifically compared whether use of a supplementary questionnaire (SQ) completed during an interview led to a different assessment of exposure compared with two different JEMs. In this study, 24% of cases were classified as "certainly exposed" based on a JEM; using the SQ, this figure was 68%. Based on the JEM, 16% were certainly not exposed; using the SQ this proportion was 32%. Agreement between the methods was better when exposure definition was restricted to definite exposures (kappa = 0.67 for the two JEMs, and 0.44/0.39 comparing the SQ and each JEM). Both JEM- and SQ-assessed exposures showed dose–response associations with lung cancer in smoking-adjusted ORs, showing that each method correctly classified cases and controls in relationship to each other. Elsewhere,[21] the authors report that misclassification of exposures by the JEM resulted in overestimation of exposures. They conclude that neither an SQ nor a JEM is superior and both should be used for optimal epidemiologic performance. Cocco and Dosemici[19] used a JEM, and could exclude asbestos exposure for only 1.5% of the population; this also suggests that a JEM may result in overestimation of exposure. Based on these data, we did not find that the absence of a formal JEM limited our conclusions.

Our patients were not typical mesothelioma patients, since 75% of all participants had completed at least some college, and more than 35% had graduated. Most investigators do not report this information, but Agudo et al.,[22] in a study of mesotheliomas in Spain, found that 64% had not gone further than primary school. We believe the relatively high level of education among our cases is due to a referral bias, in that individuals with more education are more likely to seek out state-of-the-art care even if that treatment means traveling a distance and paying expenses not covered by medical insurance. Persons of higher socioeconomic status would be expected to have a lower probability of exposure to asbestos, and a lower intensity when exposed, since exposure to asbestos in industrial settings occurs in traditionally blue collar jobs such as shipbuilding and manufacturing.

Does asbestos exposure affect the likelihood of peritoneal mesothelioma differently from the way that it affects pleural mesothelioma? Twenty years ago, Browne and Smither put forth the hypothesis that peritoneal mesotheliomas are associated with longer and heavier asbestos exposures.[15] More recently, Hodgson and Darnton presented a quantitative risk analysis of mesothelioma related to asbestos exposure, and

TABLE 3 Odds Ratios (95% Confidence Intervals) for Asbestos Exposure among Men with Peritoneal Mesothelioma Compared with Men with Colon Cancer

Ever exposed to asbestos	2.0 (0.62–6.42)
Ever performed any of the nine activities	11.7 (2.7–50.5)
Job exposure rating by expert	6.6 (1.25–34.94)
Overall exposure to asbestos	5.0 (1.17–21.5)

reported different relationships between exposures and rates of pleural and peritoneal mesotheliomas.[23] They concluded that each additional unit of exposure would add less risk for pleural tumors and more for peritoneal tumors, with the result that highly exposed cohorts would have higher proportions of peritoneal tumors among all mesotheliomas. However, both Browne and Hodgson found some peritoneal mesotheliomas in all the asbestos-exposed cohorts reviewed, and they present no evidence for a threshold for peritoneal mesothelioma. The fact that peritoneal mesotheliomas are more common in highly exposed groups does not mean that cases of peritoneal mesothelioma cannot appear among groups with less exposure. Our case series is not a cohort, but the excess risk for asbestos exposure among these peritoneal mesothelioma cases is consistent with the hypothesis that peritoneal cancers occur in less highly exposed groups.

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