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Women and Mesothelioma

In this issue of *CHEST* (see page 2224), Metintas and coworkers compared the relative risk of women vs men for a malignant pleural mesothelioma (MPM) due to environmental amphibole asbestos exposure. The relative risk was higher for women than for men: 159.8 per 100,000 vs 114.8 per 100,000, respectively. A previous study from a different area of Turkey called Karain Village, where there had been environmental exposure to a highly carcinogenic fibrous zeolite called erionite, also demonstrated a female sex predilection for MPM with a risk ratio of 440.9 per 100,000 for women vs 298.1 per 100,000 for men.¹ North American, Australian, and European cohorts have always shown a much lower risk for women.²⁻⁴ Why the difference?

First of all, we do not know if this difference is simply due to higher exposures in women. In many of these small Turkish villages, the whitewashing of homes is done by women, which is the procedure associated with the highest levels of exposure. Women spend more time in the home than men, who may work in an area with lower exposure. The authors have evaluated their cohort and cannot find any significant difference in exposure levels between men and women! Traditional work-associated cohorts are predominately men since many trades commonly associated with asbestos exposure historically excluded women. This in turn means that men are overrepresented in mesothelioma cohorts. I am unaware of any North American, Australian, South African, or European cohort where sufficient numbers of women were equally exposed to the same asbestos fiber type at the same intensity for sufficient periods to evaluate the relative risk of MPM for women. Could there be a physiologic explanation for this difference?

Deposition patterns may vary by mouth vs nose breathing, or deeper slower respirations vs shallow respirations. Lung volume influences fiber deposition and retention, particularly at low functional residual capacity, such as pregnancy.⁵ Generally, fiber deposition by impaction, sedimentation, and interception increases in major airways based on lung size. People who are taller and have longer tracheas and larger lungs have more deposition in the ciliated airways than shorter, smaller people who tend to have greater alveolar deposition at the same

level of exposure.⁶ The role of body size needs to be further studied but could explain an increased female risk for mesothelioma. The effect of lung size on fiber retention might suggest that children would retain more asbestos fibers at the same exposure level than adults, but this is unproven and only speculative at this time.

Women seem also to be more susceptible to malignant peritoneal mesothelioma than men. In men, the risk increases up to fivefold with increasing exposure. In women, the relative risk for spontaneous malignant peritoneal mesothelioma is increased. Asbestos-related malignant peritoneal mesothelioma did not increase above moderate exposure in one study⁷ as opposed to men, where the risk increases continually with dose. Of course the reasonable question is: Is peritoneal mesothelioma misdiagnosed in women? Both ovarian cancer and malignant peritoneal mesothelioma derive from the same tissue, the coelomic epithelium from which the ovarian surface epithelium is derived.⁸ Pathologists, in the past, have had difficulty distinguishing histologically between epithelioid malignant mesothelioma of the peritoneum and serous adenocarcinoma of the ovary or extraovarian tissues.⁹ An association between perineal talc usage and MPM was made in 1982 when these women were exposed to older talc preparations containing tremolite asbestos.¹⁰ In older cohorts prior to modern tissue immunohistochemical staining and electron microscopic techniques, accurate diagnosis may have been a problem, but with current histopathologic techniques this is not a significant problem today.¹¹ The environmental pathology research group in Great Britain concluded on review of 177 cases of both pleural and peritoneal mesotheliomas in women that 98% had an elevated fiber burden to amphibole asbestos. The high percentage of women with elevated amphibole asbestos in this British cohort reflects a selection bias since the opposite has been the American experience, where only a minority of women with a mesothelioma of any type have a history of asbestos exposure.¹² The pathology of malignant mesothelioma is the same in men and women.¹³

The other important issue raised by this study of Metintas and coworkers is the relationship between asbestos dose and latency. The latency time was the same for both sexes and was 59.2 years. Early reviews of the effect of asbestos dose and latency suggested that latency was not greatly affected by the degree of exposure.¹⁴ Previous reviews have noted a decline in mesothelioma incidence rates after age 70 years, thought to be due to death from competing causes and the death of those individuals with the highest exposures.¹⁵ More recent cohorts have shown longer latency times since first exposure, frequently > 50

years since the first exposure to amphibole asbestos, suggesting that with lower exposures latency time increases.¹⁶ These data are still consistent with the hypothesis of Peto,¹⁷ relating risk to a linear effect of fiber type and dose to the risk of mesothelioma multiplied by time of first exposure to the exponent 3–4. This has obvious public health consequences, since it suggests that people who are now healthier than their predecessors and will live longer are at risk for MPM due to low-dose amphibole asbestos exposure. These mesotheliomas would not have been seen in this older population if they had a shorter life span. How much of the increased incidence of mesothelioma in Europe¹⁸ is due to the improved health of the general population and consequently a longer life expectancy is unclear. Certain viral infections, such as SV40, may play an important role in the pathogenesis of mesotheliomas in the certain Western countries but not in Turkey.¹⁹ The role of genetic factors in susceptibility to mesothelioma is an area of active research but is still unclear.²⁰

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