Mesothelioma Epidemiology, Carcinogenesis, and Pathogenesis

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Opinion statement
The incidence of mesothelioma has gone from almost none to the current 2500–3000 cases per year in the USA. This estimate is an extrapolation based on information available from the Surveillance, Epidemiology and End Results (SEER) Program that collects information on approximately 12% of the US population. Mesothelioma is a cancer that is linked to exposure to carcinogenic mineral fibers. Asbestos and erionite have a proven causative role; the possible role of other mineral fibers in causing mesothelioma is being investigated. Asbestos is considered the main cause of mesothelioma in the US and in the Western world. The capacity of asbestos to induce mesothelioma has been linked to its ability to cause the release of TNF-α (that promotes mesothelial cells survival), other cytokines and growth factors, and of mutagenic oxygen radicals from exposed mesothelial cells and nearby macrophages. Some investigators proposed that as a consequence of the regulations to prevent exposure and to forbid and/or limit the use of asbestos, the incidence of mesothelioma in the US (and in some European countries) should have started to decline before or around the year 2000, and sharply decline thereafter. Unfortunately, there are no data available yet to support this optimistic hypothesis. Simian virus 40 (SV40) infection and radiation exposure are additional causes, although their contribution to the overall incidence of mesothelioma is unknown. Recent data from several laboratories indicate that asbestos exposure and SV40 infection are co-carcinogens in causing mesothelioma in rodents and in causing malignant transformation of human mesothelial cells in tissue culture. An exciting new development comes from the discovery that genetic susceptibility to mineral fiber carcinogenesis plays a critical role in the incidence of this cancer in certain families. It is hoped that the identification of this putative mesothelioma gene will lead to novel mechanistically driven preventive and therapeutic approaches.
Introduction

Malignant mesothelioma (MM) is a rare but very aggressive tumor that arises from mesothelial cells lining the pleural, peritoneal, and pericardial cavities. Pleural mesothelioma is the most common type, accounting for about 70% of all MM cases [1]. MM is subtyped into three forms according to the histological morphology: epithelial, sarcomatoid, and biphasic. The prognosis of MM is poor, and the median survival time for these three types is 18, 8, and 11 months, respectively [2, 3].

Epidemiology

- The first case of MM was reported in 1947. In 1960, Wagner et al. reported a MM epidemic among asbestos miners and first demonstrated a relationship between asbestos exposure and MM.
- MM was extremely rare until the second half of the 20th century. The incidence of MM has increased significantly, and currently there are about 2000 to 3000 cases per year in the United States [4]. The continuing increase in MM incidence has been associated with widespread use of asbestos in the past century. Asbestos was widely used in the shipbuilding and construction industries, especially between the 1940s and 1979 in the United States and Europe, due to its fire-resistant properties [5]. The latency period between the time of initial exposure and diagnosis is about 30 years and ranges from 20 to 50 years [6]. Two-thirds of MM patients are between 50 and 70 years of age. Males are at a much higher risk for MM than females, likely due to occupational exposure. The expected peak incidence of MM varies among countries. Price et al. proposed that MM has already reached its peak incidence in the United States [7]. This hypothesis remains to be confirmed. However, about 70,000 new MM cases are expected in the United States over the course of the next 20 years. In Europe, the anticipated peak year of MM incidence is in the period of 2015–2020, with a predicted incidence of 250,000 cases over the next 40 years [8].
- The incidence of MM shows marked variations from one country to another. In some countries, MM incidence is low even though there is high asbestos [2, 9]. The reasons that account for these differences are unclear. Epidemiological studies found that about 5% of individuals with heavy prolonged asbestos exposure develop MM, although it has been proposed that approximately 80% of patients with MM in the United States have been exposed to asbestos. However, there is a significant difference in the percent of MM linked to asbestos exposure by different studies: from zero in some studies to 100% in others [10]. Geographical differences as well as different technical approaches used to attribute exposure are the likely cause of many of these very discrepant results. For example, some investigators will use lung content analysis studies (i.e., the amount of asbestos found in 1 cc or less of lung tissue). To attribute exposure, others will use patients interviews. It should not be unexpected that such different approaches will generate different results. What may appear as a surprise is that even within each of these two categories (i.e., lung content analysis and interviews), the results vary significantly. This is also caused by different approaches in each category. For example, some investigators establish a background level of asbestos in the general population and count only fibers with the length of 5 µm or longer. Others will measure if any type of asbestos fiber is present in the lung, and if it is, they will attribute MM to asbestos (i.e., in other words, in these studies, there is no threshold set for background accounts or for fiber size). Obviously, such studies will produce very different results. The