Mesothelioma Not Associated With Asbestos Exposure

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• ***Context.*—Despite asbestos being identified as the single most important cause of malignant mesothelioma, the tumor is known to occur in only 10% to 20% of heavily exposed individuals. In addition, about 20% of the patients have no history of asbestos exposure even after detailed assessment. Therefore, there has been speculation for some time that asbestos alone may not be sufficient to cause mesothelioma and that other factors may be involved either as cocarcinogens or as independent mechanisms of cancer causation.**

***Objective.*—To give a brief review of nonasbestos fiber erionite and therapeutic radiation as 2 established examples of asbestos-independent mechanisms, of the potential emerging role of man-made fibers such as carbon nanotubes, and of polyoma virus SV40 (simian virus 40) as a potential example of the cocarcinogenic mode of involvement.**

***Data Sources.*—Relevant recent literature has been surveyed to portray and provide the evidence in favor of the examples.**

***Conclusions.*—Erionite has emerged as the most important example of nonasbestos-mediated cause of mesothelioma in regions such as Turkey where exposure to this type of fiber is highly prevalent. Recently, the polyoma virus SV40 has been unexpectedly discovered as an effective cocarcinogen of asbestos in the causation of animal mesothelioma, though despite considerable research, its potential role in human mesothelioma remains unproven.**

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It should be realized that although there is a strong link between the development of malignant mesothelioma (MM) and asbestos exposure, not all cases are etiologically related to asbestos exposure. The proportion of cases attributable to asbestos exposure varies between the sexes and country, according to occupation and use of amphibole asbestos.[1,2] The annual risk for background mesotheliomas has been estimated at 1 to 2 per million population,[3] with the lifetime risk at 140 to 200 per million[4] and at 360 per million, based on data from 1980 to 2000 women in the United States.[5] A number of other agents have been implicated in the causation of MM but the best evidence appears to relate to another mineral fiber—erionite—and to irradiation (Table 1). However, there is strong experimental, but as yet unsettled, epidemiologic and molecular evidence to suggest a possible carcinogenic or cocarcinogenic role of viruses such as SV40, a monkey polyoma virus, in the induction of MM.

MINERAL FIBERS OTHER THAN ASBESTOS

Erionite

Considerable interest in the relationship between erionite, a fibrous form of the zeolite group of minerals, began with the discovery by Baris et al[6–8] of a high incidence of MM in certain villages (Karain, Tuzkoy, and Sarihidir) of Cappadocia, in Turkey. The MM could not be linked to environmental or occupational exposures to asbestos in this region, but instead it was found that the volcanic rocks present in this part of Turkey contained a fibrous zeolite, known as erionite, which contained a high percentage of inhalable fibers.[9] Erionite frequently occurs as a compact felt of fibers with a woolly appearance. It is probable that zeolite tuff was first used during Roman times to build houses, roads, and sewage systems and therefore, repeated exposures to erionite among the inhabitants of these Cappadocian villages has occurred, together with associated diseases, probably for many centuries.

Erionite fibers have been found in bronchoalveolar lavage fluids and lung tissues of individuals with MM as well as those of the animals resident in the villages in this region.[10–13] Zeolite ferruginous bodies have been identified in the sputa of inhabitants of these villages.[14] In experimental inhalation studies on rats, Wagner et al[15] were able to generate a high rate of MM with samples of erionite from Turkey and Oregon. Intrapleural and intraperitoneal injections of erionite in rats and mice have produced rates of MM in excess of 90% with amounts of 0.5 or 1 mg.[16,17] These rates are much higher than those observed with asbestos fibers. It has been postulated that the main reason for the greater potency of erionite compared to asbestos fibers is the greater intrinsic surface area of the erionite.[17,18]

Several epidemiologic studies of these Cappadocian villages have shown rates of MM of about 1000-fold the normal rate.[7,8,19–21] Therefore, from clinical, epidemiologic, pathologic, and experimental studies, it is reasonable to conclude that erionite fibers are carcinogenic and more

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Table 1. Malignant Mesothelioma: Putative Nonasbestos-Related Associations
Mineral fibers
Erionite; fluoro-edenite; organic
Carbon nanotubes
Irradiation
Diagnostic use of thorium dioxide (Thorotrast); atomic energy work exposure
Viruses
MC29 avian leukosis virus; SV40
Miscellaneous
Metals; chronic serosal inflammation

Abbreviation: SV40, simian virus 40.

potent than asbestos with respect to induction of MM. Studies of MM, conducted in the 3 aforementioned Cappadocian villages, showed higher rates of MM within certain families, suggesting a genetic predisposition despite the same type of erionite being found in Cappadocian villages with or without a mesothelioma epidemic.[22,23] However, the conclusions were challenged[24] and a further study found a strong association between MM and the presence of erionite in stones used for construction of certain houses, implying that the effect of genetic factors was likely to be coincidental.[25]

In a recent case report,[26] the presence of mesothelioma, pleural plaques, pulmonary fibrosis, and ferruginous bodies, in combination, was associated with erionite exposure in North America. Fibrous and nonfibrous zeolites, including erionite, are present in the western United States and Mexico, where the subject of the case report had resided.[27,28]

OTHER MINERAL FIBERS

A cluster of MM cases in Biancavilla, eastern Sicily, has been reported. In the quarries located near the city, a fibrous amphibole, fluoro-edenite, was identified and was suggested as the cause of the MMs.[29,30] The mineral is very similar in morphology and composition to the actinolite-tremolite series of minerals. A study of sputum samples from subjects living in the area revealed fluoro-edenite fibers in 50% of the subjects; the length of the fibers ranged from 20 to 40 μm.[31] Fluoro-edenite fibers were also found in the autopsy samples of a woman who died of mesothelioma[29] and in lung and lymph node tissues of sheep living in the local area.[32]

Organic fiber exposure has been implicated as a cause of MM in sugarcane workers who were potentially exposed to crystalline silica fibers of plant origin.[33] However, there have been no confirmatory studies published, and a case control study of workers in the Hawaii sugarcane industry found no evidence of a significant excess of MM in sugarcane workers.[34]

CARBON NANOTUBES

To date no mesotheliomas have been linked to exposure to man-made mineral fibers. However, recently, concern has been raised about the potential risk of developing malignant mesothelioma from exposure to carbon nanotubes (CNTs) and other high-aspect ratio nanoparticles made from other materials such as silica, silver, and nickel.[35] Carbon nanotubes are important products of nanotechnology, which are used in a wide range of applications including electronics and medicine. Comparisons can now be made between data obtained on the pulmonary and cellular effects of CNTs and asbestos, and in particular, the asbestos fiber characteristics that relate to toxicity.

Carbon nanotubes can occur as compact tangles of nanotubes or as longer, straighter ''fibers''; it is with the latter that there are toxicologic concerns.[36] Experimental studies of implantation of CNTs into the peritoneal cavity of mice showed that the long fibers of CNTs produced a similar or greater degree of inflammation and fibrosis than that produced by long amosite asbestos. Neither short asbestos fibers nor short, tangled CNTs produced any significant inflammation.[37] The key length for pathogenicity appeared to be between 15 and 20 μm. A similar experiment performed in the pleural cavity showed similar results.[36] Two recent studies have shown the occurrence of MM in genetically modified cancer-sensitized mice[38] and in conventional rats[39] exposed to intraperitoneal or intrascrotal administration, respectively.

Therefore, CNTs can show similar shape (elongated fiber-like particles), similar diameter, and similar cytotoxicity as asbestos; moreover, they can produce DNA damage and have similar effects in the peritoneal cavity of animals. However, to date there is no information with respect to human exposures.

THERAPEUTIC IRRADIATION

Ionizing radiation is a recognized human carcinogen and an established risk factor for several different types of cancers including hematologic malignancies and solid tumors. Cases of MM of the pleura, peritoneum, and pericardium have been reported in humans after therapeutic irradiation and thorium dioxide administration. The latency period has ranged from 7 to 50 years, with a mean of 21 years and an equal male to female ratio.[40–49] The evidence linking ionizing radiation to the development of MM can be looked at from 3 epidemiologic viewpoints: (1) patients exposed to thorium dioxide (Thorotrast), a diagnostic x-ray contrast medium; (2) patients receiving radiation therapy for cancers such as Wilms tumor, breast cancer, malignant lymphoma, and testicular malignancies; and (3) atomic energy workers chronically exposed to lower levels of radiation.[50]

Thorium dioxide is insoluble and once injected, cannot be excreted. It is therefore retained within a variety of tissues but continues to decay, emitting mostly α particles. Exposure to Thorotrast has been found to increase the risk for pleural and peritoneal MM in cohorts in Denmark, Sweden, Japan, Germany, and the United States.[51–56] The cohort studies have generally examined the risks of MM between the general population and patients undergoing the same radiographic procedure with and without Thorotrast. The results of these studies are consistent in showing an elevated risk for pleural and peritoneal MM with radiation exposure; since asbestos exposure was unlikely to have been different among the treatment groups, it is not likely to have been a confounding factor in these studies.[51]

The evidence linking therapeutic radiation to the development of MM has come from case reports[41–45,47,49,56] and several large-scale retrospective cohort studies.[55] The latter have used population-based registries, such as the Surveillance Epidemiology and End Results data, and second primary cancers in individuals with the same type of primary cancer, to examine the occurrence of MM

after exposure to therapeutic radiation for treatment of several different types of cancer.[44,57–64] De Bruin et al[64] found that among 2567 5-year survivors of Hodgkin lymphoma, the risk for malignant mesothelioma was almost 30-fold for patients treated with irradiation, as compared to the general population.

VIRUSES

The earliest experimental evidence of the ability of viruses to induce benign and malignant proliferations of the mesothelium in mice and hamsters was recorded in 1959[65] and 1960,[66] respectively. These studies were conducted to evaluate the carcinogenic potential of a monkey polyoma virus (simian virus 40 or SV40), a DNA virus, discovered as an accidental contaminant of the early polio vaccines produced in monkey kidney cells in the United States. In 1970, MC29 avian leukosis virus (an RNA virus) was found to cause mesotheliomas in 35% of chickens inoculated with the virus into the peritoneal, pericardial, and air sac cavities.[67] The issue remained dormant until a high frequency (62%) of pericardial mesotheliomas was found unexpectedly in baby Syrian Golden hamsters inoculated intracardially with wild-type SV40. Remarkably, direct intrapleural inoculation of wild-type SV40 produced 100% mesotheliomas.[68] This raised the question as to whether the accidental exposure of very large numbers of people (about 32 million) to an infectious form of SV40 that contaminated the early batches of polio vaccines (produced in the late 1950s and early 1960s[69]) might have contributed to the rising incidence of human mesotheliomas from the 1970s onward. Extensive molecular, epidemiologic, and experimental studies have been conducted to examine this possibility.

Below, the main findings of these studies are reviewed for the benefit of the new readership, to highlight the experimental work providing strong evidence in support of a putative etiopathogenic cocarcinogenic role of SV40 in MM, despite the data from molecular and epidemiologic analyses showing moderately strong but controversial association.

EXPERIMENTAL STUDIES

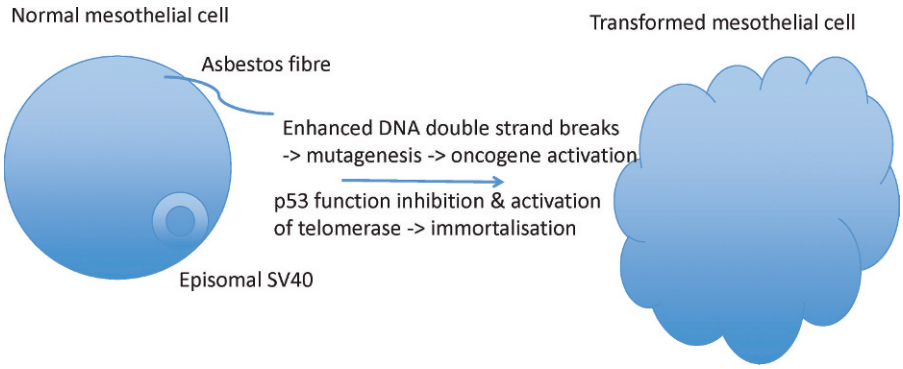
The animal model studies were repeated in mice and hamsters to evaluate the potential of the SV40 virus as a carcinogen as well as a cocarcinogen, when tested in combination with asbestos, to cause MM.[70,71] In brief, the cocarcinogenic experiments, both in mice and hamsters, showed that MM did not develop in animals exposed to subcarcinogenic doses of SV40, although a few hamsters developed lymphomas and sarcomas after a prolonged latency period. Coexposure to SV40 and asbestos caused a significantly higher incidence of MM with a significantly shorter tumor latency. The low amounts of asbestos tested (eg, 0.4 mg) were insufficient to cause MM. No tumors developed in the control group. Macroscopically, most MMs surrounded the lungs and/or the pericardium or spread along the peritoneum, and MM nodules studded both the pleural and the peritoneal cavities. The histologic appearance of these MMs was identical to that of human MMs. Most MMs in the coexposed group showed a sarcomatoid or biphasic morphology. Malignant mesotheliomas in hamsters exposed to a carcinogenic dose of crocidolite were mostly of the ''epithelial type,'' and the tumors showed a more bland, well-differentiated, tubular-papillary morphology. All tumors and derived cell lines from SV40 alone, as well as the coexposed group, contained SV40-specific DNA and tumor antigens.

The basis of the cocarcinogenic interaction of SV40 with asbestos has been studied further in an in vitro cell culture system using primary human mesothelial cell lines.[72] In these experiments, SV40 was discovered to have a unique ability to replicate in a semipermissive mode in human mesothelial cells, thus leading to subcytolytic generation of the virus in a very high proportion (80%) of the virally infected cells; in contrast, human fibroblasts all underwent cell lysis and death due to unlimited SV40 virion production. Furthermore, SV40 was found to protect mesothelial cells against the cytotoxic effects of asbestos fibers added to the cell culture system. Finally, SV40 and asbestos caused higher frequency of cell transformation with subtransforming units of the virus. To achieve these effects, SV40 relies on 2 oncogenic proteins: the large T and small t antigens. The large T antigen (Tag) is capable of inducing structural and numerical chromosomal alterations. Tag also induces insulin-like growth factor expression, inhibits p53 and the pRb family of proteins, and induces c-met activity to stimulate cell proliferation. The small t antigen (tag) inhibits cellular phosphatase 2A, stimulates MAP kinase and AP-1 activity, and works with Tag to bind and inhibit p53 and pRb.

From the above studies it is hypothesized that the combined activity of Tag and tag antigens induce Notch-1 and telomerase activity, when acting in concert with the potential mutagenic effects of asbestos fibers closely apposed to or impacted into the mesothelial cells, which leads to the malignant transformation of the mesothelial cells, as observed in the in vitro and in vivo models of SV40-asbestos cocarcinogenesis.[73,74] The fundamentals of this process are schematically represented in the Figure, designed to depict potential ''hit-and-run'' cocarcinogenic association of SV40 with asbestos in mesothelial cell transformation.

MOLECULAR STUDIES

With the polymerase chain reaction technique, SV40 DNA segments encoding for its principal oncogenic protein Tag have been detected in formalin-fixed, paraffin-embedded archival tissue samples in a high proportion (40%–70%) of malignant pleural mesotheliomas (MPMs).[75,76] Further evidence has been accumulated to suggest that the presence of SV40 DNA segments is selectively associated with MPM cells.[77] Several subsequent studies[78–80] have challenged the validity of these early molecular data, in particular to indicate that the detection of SV40 DNA in MPM is most probably an artifact of the polymerase chain reaction method, due to reagent contamination with widely used SV40 DNA–based gene constructs.[81] The latter view, however, is at variance with the data of an independent study conducted under the stringent scrutiny of the US Food and Drug Administration and the National Cancer Institute.[82] In this study, the International SV40 Working Group, comprising 9 of the original laboratories that had detected the presence of SV40 Tag sequences in mesothelial samples, showed that its methods performed well on 25 duplicate samples of human mesotheliomas, on a single set of 25 normal lung tissue samples, and on positive and negative control samples selected by an independent agency. All the samples had been blinded and each laboratory used its particular assay for detecting SV40;



Potential "hit-and-run" cocarcinogenic association of simian virus 40 (SV40) with asbestos in mesothelial cell transformation.

many of these assays had been used previously to detect the virus in mesothelioma tissue.

A question has also been raised about the low copy numbers (<1 copy/10–100 cells) of oncogenic SV40 DNA associated with the human MPM samples.[78,83] Data from the animal model of SV40-induced cancers suggest that Tag is required to induce and maintain SV40-mediated transformation and should therefore be present in all tumor cells in which SV40 is contributing to tumorigenesis. However, it has been suggested that SV40 may transform cells through a hit-and-run mechanism in which Tag would be required to induce, but not maintain, the transformed phenotype; therefore, it may not be detectable in all tumor cells. This concept is supported by the results obtained with tumors generated by SV40 Tag conditionally expressed in the salivary glands of mice (see Carbone et al[84] for review). Transformation was induced in cells expressing Tag. When Tag expression was experimentally reduced in these cells after 7 months of continuous exposure, the transformed phenotype persisted even in the absence of Tag expression. In this experiment, it is likely that these cells acquired additional genetic mutations, allowing the maintenance of the transformed phenotype in the absence of Tag expression. Acquisition of this state over a long period of time could account for the long latent period (20–50 years) associated with human MPM.

In addition, unlike the animal model, the integrated state of the SV40 genome may not be necessary for the causation of human MPM, as suggested by in vitro cell culture work with human pleural mesothelial cells, which showed that the episomal state of the virus was sufficient to cause cell transformation when added in combination with asbestos fibers.[73] Thus, it is possible that SV40 may be required only in the early stages as a cocarcinogen, to protect mesothelial cells against the initial cytotoxic effects of asbestos fiber exposure and for their neoplastic transformation, thereafter being gradually lost owing to its episomal state. In fact, when cells lose the SV40 DNA, they may be promoted to grow more aggressively owing to the inability of the immune system to react with such virus-negative tumor cells (cf, Salewski et al[85]).

EPIDEMIOLOGIC STUDIES

An estimated 62% of 92 million US residents received the potentially SV40-contaminated Salk polio vaccine for the 8 years it was used (1955–1963); of these, at least one-fifth may have received live, infectious SV40-containing vaccine. In addition, although efforts were made to exclude SV40 from polio vaccines, the testing done was not rigorous enough to totally ensure that all cohorts born after 1963 were given SV40-free polio vaccines. For example, a major eastern European manufacturer used a procedure that did not fully inactivate SV40 in oral poliovirus vaccine; these SV40-contaminated vaccines were produced from the early 1960s to about 1978 and were used throughout the world. This remains a highly controversial aspect of MPM etiology and pathogenesis. Nevertheless, it is noteworthy that SV40 has been found to be absent in mesotheliomas from patients vaccinated with an SV40-free vaccine.[86]

In relation to the possible cocarcinogenic association between SV40 and asbestos, it is noteworthy that the peak exposure of the population in the Western world to asbestos appeared to have sharply coincided with the peak exposure to SV40 as a contaminant of polio vaccines.[87] However, no reliable epidemiologic data are available to verify whether SV40 causes human mesothelioma, because it has been difficult to clearly identify SV40-affected from nonaffected cohorts (see Carbone et al[84] and Lowe et al[88] for review).

Serologic studies of SV40 infection in humans have also been complicated by the discovery of the 2 human polyomaviruses, JC virus (JCV) and BK virus (BKV), in 1971. These 2 viruses are highly homologous to SV40 and are prevalent among the human population. The large T antigens of JCV and BKV share many functional domains with, and have high homology to, SV40 Tag. In addition, the viral capsid proteins, including VP1 of JCV, BKV, and SV40, are highly homologous. Because polyomaviruses tend to be highly species-specific, the finding of these 2 human polyomaviruses was significant in addressing the specificity of human serum antibodies against SV40. It is possible that the early reports of SV40 antibody detection in human sera represented some degree of cross-reactivity with antibodies against the highly related BK and JC viruses.

Recently, the ability to determine human serum antibodies specific for SV40, JCV, or BKV has been greatly facilitated by the development of recombinant virus-like particle (VLP)–based assays. The VLP assays detect antibodies that are specific to the major capsid protein VP1 of SV40, BKV, and JCV. The development of virus-specific assays allows for the detection of antibodies specific to SV40, BKV, and JCV in human sera, as well as the ability to determine the degree of serologic cross-reactivity by competitive absorption studies. Using these methods, recent reports have confirmed high levels of cross-reactivity of human sera between SV40 and JCV or BKV. SV40-reactive antibodies found in human sera are typically present only simultaneously with antibodies to JCV or BKV (cf, Engels et al[87]).

Table 2. Association of Simian Virus 40 (SV40) With Animal and Human Malignant Mesothelioma	
Evidence	**Strength of Evidence**
Experimental	Strong
Molecular	Moderate but controversial
Epidemiologic	Moderate but controversial

With the activity needed for SV40 to induce a malignant phenotype, it is generally acknowledged that the human response to such an infectious and actively replicating virus would prompt an antibody response to viral products, with the consequent ability to isolate high copy numbers of DNA from tissue samples, as is observed in HPV infections (cf, Engels et al[87]). However, it cannot be ruled out that SV40 may not follow the mechanism described above to cause human mesothelioma and other tumors.[89]

In summary, despite a variety of methodologic concerns, there is moderate to strong evidence to suggest that SV40 is a potential human cocarcinogen (see Table 2). In particular, in vitro analysis has detailed the mechanisms surrounding transformation of animal and human mesothelial cell lines, while in vivo animal models have clearly shown tumor formation upon inoculation of SV40 alone or in combination with asbestos fibers. It is probably also no coincidence that the same malignancies observed in neonatal hamsters, associated with different routes of SV40 administration, correspond to cancer types seen in humans. There is therefore a continuing need to evaluate the potential carcinogenic link between SV40 and human mesothelioma and other cancers, as indicated by the 2002 report of the Institute of Medicine.[90]

MISCELLANEOUS

Exposure to a number of minerals other than asbestos has been implicated in the induction of malignant mesothelioma.[91] These have included nickel,[92] silica,[93] and beryllium.[94,95] However, these observations have either been based on intraserosal implantation experiments in animals, which are highly artificial and sometimes very misleading, or on rare case reports with poorly documented histopathology. At present, the weight of evidence does not support that these minerals are causes of malignant mesothelioma in humans.

Recurrent serosal inflammation and severe scarring have rarely been associated with the development of MM. Malignant mesothelioma has followed 20 years after plombage therapy with lucite spheres for tuberculosis.[96] Additional cases have been associated with chronic empyema, chronic peritonitis, induced pneumothroax for tuberculosis, and familial Mediterranean fever.[97–99]

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