RESEARCH ARTICLE

Asbestos in Talc and Mesothelioma: Review of the Causality Using Epidemiology

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Abstract

Talcum powder has long been contaminated with asbestos fibers depending on the source of the talc. Pleural and peritoneal mesothelioma are scientifically established as caused by asbestos exposures. However, when investigating causality of mesothelioma from asbestos fibers in talcum powder, epidemiology is complicated by various methodological issues and inadequacies in existing studies. The occupational and case studies are explored in an effort to bring clarity to the issue of talcum powder usage and mesothelioma. Talc is randomly and sporadically contaminated with asbestos fibers including chrysotile, tremolite and anthophyllite. Case studies of mesothelioma victims whose only asbestos exposure was to talc, found anthophyllite, tremolite and chrysotile asbestos fibers in their tissues. Exposure to all three types of asbestos fibers increases the risk of mesothelioma. The Hill criteria of causality, which considers all aspects of toxicology, biology and epidemiology, are applied to the issue. This analysis results in compelling evidence that asbestos in talcum powder is causative for mesothelioma. Thus, precaution would dictate the avoidance of the use of talcum powders.

Keywords: talc, asbestos, mesothelioma, tremolite, anthophyllite, pleural, peritoneal, epidemiology

1. Introduction

Talc is used for various industrial and cosmetic purposes and has long been known to be contaminated with asbestos [1-4], even though there are persisting legal based arguments about detection of asbestos fibers in talc [3,5,6]. The causal chain between asbestos and mesothelioma has been established in detail for over 50 years [7], and the epidemiology studies concerning perineal talc exposure and ovarian cancer incidence show a consistent association [7,8]. However, when investigating causality of mesothelioma from asbestos fibers in talcum powder, epidemiology is complicated by various methodological issues and inadequacies in existing studies. We aim here to explore the issues in using epidemiology to establish potential causality of talc exposures and mesothelioma.

Mesothelioma

The seminal publication associating mesothelioma of the pleura and peritoneum with exposure to asbestos was by Wagner et al in 1960. [9] Almost sixty years later, there is overwhelming evidence that asbestos is responsible for this fatal cancer. Mesothelioma from asbestos is the most definitive example of an environmental cause-effect cancer, involving a quickly fatal disease that has a long latent period. Due to the extensive occupational, community and para-occupational exposures to asbestos, a worldwide epidemic of mesothelioma has been reported.[10,11]

There are numerous epidemiological studies that have clearly linked all types of asbestos, including the amphiboles crocidolite, amosite, anthophyllite, tremolite and the serpentine chrysotile, to pleural and peritoneal mesothelioma. [7,12,13] The global magnitude of mesothelioma is estimated to be 38,900 in a group of 33 countries that report the disease. The actual number of cases is undoubtedly much greater as one mesothelioma is missed in every four or five reported cases because of the difficulty in establishing a pathologic diagnosis. [10]

There is a long history of asbestos fibers being found in mesothelioma tissue. [14-16] It is the consensus of the medical and scientific communities that there is no known threshold of exposure below which mesothelioma will not occur.[17,18,19] Multiple studies have shown that all levels of exposure to asbestos increase the risk of mesothelioma. [7,20,21] Brief or low exposures to asbestos are capable of causing mesothelioma. [22,23]. In fact, Lacourt et al.[24] found a four-fold increased risk of mesothelioma at cumulative exposure levels less than 0.1 f/cc, the U.S. occupational standard. Mesothelioma incidence is proportional to cumulative asbestos exposure. [25,26,27] Intensity and duration of asbestos exposure are determinant of mesothelioma risk. [26] The mainstream scientific community has concluded that there is no "safe" level of exposure to asbestos of any type and that "…an occupational history of brief or low-level exposure should be considered sufficient for mesothelioma to be designated occupationally related" to asbestos exposure. [28,29]

What is Talc

Talc is a hydrous silicate with a general composition of $Mg_3Si_4O_{10}(OH)_2$, but can contain major amounts of Fe, minor amounts of Al and F, and trace amounts of Mn, Ti, Cr, Ni, Ca, Na, and K. [30] There are two common names for commercial talc: industrial talc and cosmetic talc, even though the terms appear to be commercially and not scientifically derived. Industrial talc varies in composition and is a mixture of mineral particles. Industrial talc is used in the production of ceramics, paint, paper, plastics, roofing, rubber, flooring, caulking, and agricultural applications.[31] Cosmetic talc consists of pure "platiform" talc, meaning the "plates" of microscopic talc can easily slide past one another, which makes cosmetic talc feel smooth to the touch. Cosmetic talc is used in many personal care products like baby powder, adult body and face powder, as well as other make-up products.[32] Talc used for cosmetic purposes has been taken from mines with higher purity (>95-99 percent) platy talc, free of other minerals, whereas industrial-grade talcs usually contain 75-95% or lower of the talc mineral with other non-platy components. [33]

Talc is found in geologic fault lines and is often contaminated with the amphibole asbestos types tremolite, anthophyllite and the serpentine asbestos type chrysotile. [4,7] The asbestos fibers are more often found in the talc mines used for industrial talc as compared to the cosmetic talc mines. [33]

Van Gosen et al [30] of the U.S. Geologic Survey found that many American talc deposits, including

Gouverneur, New York, Vermont, and others, contain amphibole asbestos such as tremolite and anthophyllite. In the laboratory, talc has been shown to be contaminated with chrysotile, tremolite, and anthophyllite fibers.[34-37] Chrysotile, tremolite and anthophyllite asbestos have been shown to cause mesothelioma. [7]

3.1 Fibers, EMP's and other terminology

There is no universal method to look for asbestos fibers or particles in talc, and the terminology of the contaminating fibers or particles of asbestos, asbestiform and elongate mineral particle (EMP), is controversial and unresolved. [38]

"The term "mineral fiber" has been frequently used by nonmineralogists to encompass thoracic-size elongate mineral particles (EMPs) occurring either in an asbestiform habit (e.g., asbestos fibers) or in a nonasbestiform habit (e.g., as needle-like [acicular] or prismatic crystals), as well as EMPs that result from the crushing or fracturing of nonfibrous minerals (e.g., cleavage fragments)." Imprecise terminology and mineralogical complexity have affected progress in research." [38] (Exec Summary p. V-VI)

Egilman et al [39] systematically reviewed EMPs, cleavage fragments, short fibers, thin fibers, erionite and fibrous talc according to their potential to cause adverse human health effects. Using the Hill [40] criteria for potential to be causal in health effects, Egilman et al [39] concludes that all fiber types should be counted in laboratory mineral sample detection methodology.

Finkelstein [41] examined two samples of Mouldene industrial talc. The samples were prepared and analyzed for asbestos by polarized light microscopy (PLM), scanning electron microscopy (SEM), analytical electron microscopy (AEM), and X-ray diffraction (XRD). X-ray diffraction analysis showed that the New York industrial talc was composed of talc, tremolite and anthophyllite as major phases (each in the range of approximately 20–30% by weight). Microscopy analysis showed that the talc was composed primarily of fibrous talc, tremolite, anthophyllite and lizardite (serpentine). Some of the tremolite was not of a length and diameter to be of a respirable range.[41]

Several studies of talc workers have shown pleural thickening [4,42] and several have shown pneumoconiosis in workers exposed to talc contaminated with asbestos. [4,43,44]

3.2 Case Studies of Mesothelioma victims

Moline et al. [45] described the exposures to talcum powder leading to mesothelioma among 33 individuals referred for medico-legal evaluation. Tissue digestion was done for six cases according to standard methodology. Asbestos of the types found in talcum powder was found in all six cases evaluated. Two cases had anthophyllite fibers; one case had anthophyllite and tremolite fibers; one case had anthophyllite, tremolite and actinolite; one case had chrysotile fibers; and one case had tremolite fibers. Talcum powder usage was the only source of asbestos for all 33 cases.

Emory et al [46] described a case series of 75 malignant mesothelioma cases (gathered from medico-legal consultation) whose only exposure to asbestos was to cosmetic talcum powders. Nine of the cases were examined for asbestiform fibers by analytic electron microscopy and microprobe analysis. For the nine cases all had anthophyllite; of those, six also had tremolite fibers, and one had amosite and chrysotile fibers, in addition.

3.3 Epidemiology Studies of Miners and Millers and Mesothelioma

There have been several epidemiology studies of talc-exposed miners, millers and others that were considered negative for mesothelioma detection including the studies in Table 1.

Table 1: Studies of Talc Miners and Millers Negative for Mesothelioma Detection

Selevan et al 1979 Vermont [44]
Wild et al 2002 France [47]
Wild et al 2002 Austria [47]
Pira et al 2017 Italy [48]
Wergeland et al 2017 [49]

However, there have been mesotheliomas, or probable or possible mesotheliomas, found in other studies in talc-exposed miners, millers and others (Table 2):

Table 2: Mesotheliomas in Talc-Exposed Miners and Millers

Kleinfeld et al 1967 New York 1 fibrosarcoma of the pleura and 1 peritoneal mesothelioma [43]
Vianna 1981 New York 6 mesotheliomas (miners) [50]
Enterline et al 1987 New York 11 mesotheliomas [51]
Coggiola et al 2003 Italy 2 peritoneal cancers [52]
Hull et al 2002 New York 5 mesotheliomas (miners) [53]
Honda et al 2002 New York 2 mesotheliomas [54]
Gamble et al 2008 New York 2 mesotheliomas [55]
Finkelstein 2012 New York 5 mesotheliomas [56]
Sanyal et al 2017 New York 11 mesotheliomas [57]
Mirabelli 2018 Italy 1 pleural mesothelioma (talc mill) [58]

Issues in the Epidemiology study of Talc and Mesothelioma

The epidemiology of talc exposures and mesothelioma is not extensive and there are many problems with the existing studies.

Mesothelioma is a long-latency disease (the time between exposure and disease is 15-50 years). There is no definitive biological or environmental measurement of exposure from the distant past and thus exposure histories have to be reconstructed from indirect sources, such as job categories and years working in a certain setting. Industry records, even of these, are not adequate for estimates of exposure. Individual records often rely on memory and are not adequate. The individual is not aware of exposures to invisible-to-the-eye fibers. Sorting out multiple individual jobs and exposures is rife with difficulty.

Mesothelioma is difficult to diagnose. There was not an ICD (International Classification of Disease) code until 1999 (10th Revision).[59] Before 1999 mesotheliomas were often called lung cancer or cancer of another body site. Even in worker populations with high exposures to asbestos (spray insulators, Selikoff et al [60,61,85]) only 10% developed mesothelioma. Thus, when researching a rare disease, even in highly exposed populations, large populations are needed for study.

Epidemiology is an observational science. People cannot be manipulated as in an animal laboratory study or human clinical trial. Thus, epidemiology studies are susceptible to bias. Bias in epidemiology studies means the study variables are not reflective of the true population situation. Epidemiology studies are of convenience samples, meaning what group of people is possible to study, not what group is ideal. There can be bias in the selection of study subjects and controls, in the assessment of exposure and the ascertainment and recording of outcome. Often a specific bias occurs when there is loss of follow-up of workers who are the most affected by the illness or those who have left the job and thus are not included in the study. This is called the "healthy worker effect". The ideal epidemiology study design is often not possible or was not done in the past and we are stuck with trying to draw conclusions from the studies that were not designed for our current purpose or were inadequate for it. As emphasized by IARC[4] "The weakest aspect of epidemiological studies is the qualitative and quantitative assessment of exposure. Deficiencies in environmental data of 20-50 years cannot be rectified." [4] (p. 358) Because of these problems, it is not surprising that there are some epidemiology studies that have not detected mesotheliomas in talc workers.

Studies of Italian Talc Miners

There have been several publications of studies of Italian talc miners (Table 3):

Table 3: Studies of Italian Talc Miners

Rubino et al 1976 [62]
Rubino et al 1979 [63]
Coggiola et al 2003 [52]
Pira et al 2017 [48]
Finkelstein 2017 [64]
Pira et al 2018 [65]

Some of the studies have not detected mesotheliomas. There are multiple possible difficulties with these studies. The small size of the cohorts studied is of primary importance. Finkelstein[64] pointed out that in order to conclude that there is no risk associated with the exposure, there would need to be a much larger cohort studied for more years. The Pira et al study[48] was between 1946 and 1995, so there was no ICD classification for mesothelioma until 1999. That means that there is a high probability that there were missed cases of mesothelioma in the study. This is important for the Coggiola et al [52] study as well. The Coggiola et al [52] study looked at workers from 1946-1995, before the ICD mesothelioma code was developed. Another critique of the Coggiola et al [52] study is that even though it looked at talc workers, some of them had only been exposed to talc for as little as one year. As calculated by Finkelstein [64], the sample sizes of these studies are extremely small as compared to the potential risk that was being examined.

Some mesotheliomas or possible mesotheliomas have been detected in Italian talc workers. Coggiola[52] in Italy found two peritoneal cancers and Mirabelli, [58] also in Italy, found one pleural mesothelioma in a talc mill. Davis et al 1991 [66] conducted rat interperitoneal injection studies using differing tremolite samples including Italian tremolite (Ala di Stura). 24 of 36 animals developed mesothelioma. The results suggest that a wide-ranging group of tremolite samples all possessed some potential to produce mesotheliomas following injection into the rat peritoneal cavity. The Italian tremolite sample produced tumors in nearly 70% of rats. [66]

3.4 New York State Talc Miner Studies

The major epidemiology studies of New York state talc miners are listed in Table 1.

Hull [53] summarizes issues relating to New York state talc asbestos disease:

"Asbestos-related disease among talc miners and millers in a group of mines in two counties of northern New York State has been noted and disputed since the 1930s. One of the two counties was identified as among the 10 in the USA with the highest mesothelioma mortality up to 1981 for both men and women. Eight talc miners had been identified in previous studies as having mesothelioma. In the current study we: report five new cases of mesothelioma among talc workers; (abstract)….we found a continued trend of increased mesothelioma mortality at 5–10 times the background rate in Jefferson County from 1982 to 1997, with five new male cases (two expected) and three new female cases (0.5 expected)" (p. 134).

In the Hull[53] study, fibers of anthophyllite, tremolite/actinotlite, chrysotile and talc were observed in lung tissue. Some of the fibers were quite long and thus not cleavage fragments.

Taconite Elongate Mineral Particles (EMPs)

Taconite (iron ore) in Minnesota is contaminated with fragments called elongate mineral particles (EMPs) which are amphibole cummingtonite–grunerite short fiber (non-commercial) asbestos. These EMP's amphibole-like fibers were found in the Duluth, MN drinking water supply from Lake Superior from taconite mine tailings included in the Reserve Mining law case in the 1970's. It is well documented that short fibers are potentially toxic and small fibers can cause mesothelioma. [67-71]

There have been numerous mesotheliomas attributed to the taconite EMPs. Allen et al [72] found 30 mesotheliomas attributed to taconite, and Allen et al [73] found 51 mesotheliomas attributed to taconite mining. Lillienfeld [74] points out that this is probably an

underestimate of the mesotheliomas in this area, as before 1999 mesotheliomas were likely missed and real mesotheliomas were often called lung cancer or something else due to ICD-9 not yet having a code for mesothelioma. The Minnesota taconite exposures are relevant to the potential toxicity of talc because it shows that if one breathes in short asbestos fibers or EMPs, whatever terminology you choose, it increases the risk of mesothelioma. Mazurek et al [75] of the U.S. Centers for Disease Control (CDC) have attributed mesotheliomas in the United States to EMPs in addition to asbestos fiber exposures. "Malignant mesothelioma is a neoplasm associated with occupational and environmental inhalation exposure to asbestos fibers and other elongate mineral particles (EMPs)."[75] (p. 214)

Talc, Tremolite and Mesothelioma

In chrysotile asbestos epidemiology studies, a group of scientists claimed for decades it was the amphibole tremolite contaminant of chrysotile that caused mesotheliomas, not the chrysotile from Canada and elsewhere.[76,77] This was known as the "amphibole hypothesis", that only amphiboles could cause mesothelioma, and the serpentine chrysotile could not. The "amphibole hypothesis" specifically stated that tremolite was the actual causal agent of mesothelioma, not chrysotile. There is tremolite in talc, and these scientists have argued for years that tremolite causes mesothelioma. Roggli et al [78] *ex*amined the lungs of 312 mesothelioma cases and found tremolite in 53% of the cases and chrysotile in 10%, attributing a large proportion (40%) of the tremolite to talc exposures.

Nephrite and Mesothelioma

Nephrite or Jade is a non-asbestosiform asbestos mineral composed of microcrystalline tremolite. It is used for ornamental stones and jewelry in Taiwan. Studies of workers have shown pulmonary fibrosis and lung cancer. [79-81]

"In this study, we did not identify any deaths from cancer of the pleura. We tentatively conclude that the sample size may not have been large enough to detect such an effect in this study. However, this result may also be due to the misclassification of mesothelioma as lung cancer, as the mortality registry in Taiwan continues to use the ICD-9 system which does not contain a diagnostic category for mesothelioma. Thus, mesothelioma may have been misclassified as lung cancer, which would result in an underestimate of the SMR of mesothelioma." [81] (p. 531)

Application of Hill Criteria

A widely accepted method for determining causation in epidemiology are the guidelines that were originally suggested by Hill [40] for evaluating the studies on cigarette smoking and lung cancer and other diseases. These guidelines are not limited to just formal epidemiological studies, but rather, incorporate and evaluate the totality of the science on a given issue including cell biology, animal studies, and mechanistic studies. As Hill stated, "[n]one of [his] nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine quo non*."

The most utilized modern list of viewpoints derived from Hill's work used by epidemiologists is contained in the textbook, Epidemiology, by Leon Gordis.[82] They are:

a. Temporal relationship
b. Strength of the association
c. Dose-response relationship
d. Replication of the findings
e. Biologic plausibility
f. Consideration of alternate explanations
g. Cessation of exposure
h. Consistency with other knowledge
i. Specificity of the association

The application of the Hill Criteria to the issue of talc exposures and risk of mesothelioma:

a. **Temporal Relationship**: This requires that the cause come before the effect. This criterion is easily satisfied in the current context as the exposure to miners and millers occurs years before the outcome of mesothelioma. The exposure to asbestos occurs in the studies of these occupational exposures 15-50 years before the mesothelioma clinical diagnosis.

b. **Strength of the Association**: In epidemiology, strength of association is most often measured by comparing the incidence of disease in the exposed divided by the non-exposed in a cohort study. In the case of talc occupational exposures even a single or a few mesotheliomas would be an indication of a strong association as even in a group of 10,000, less than one mesothelioma would be expected.

c. **Dose-Response Relationship**: There is clear evidence of asbestos dose-response in mesothelioma causation. Iwatsubo et al [83] did a rigorous assessment of occupational exposure to asbestos in 405 mesothelioma cases and 387 controls. The authors found "a clear dose-response relation between cumulative asbestos exposure and pleural mesothelioma …" Examining data from the French mesothelioma registry, Lacourt et al [24]also found a clear dose-response relationship between asbestos exposure and pleural mesothelioma. In fact, there are many studies cited by IARC [7] that show that every additional exposure to asbestos leads to a greater risk of mesothelioma.

d. **Replication of Findings**: The peer-reviewed published literature contains hundreds of mesothelioma cases that have occurred in workers from exposure to asbestos-containing products encountered in many occupations. The talc worker mesotheliomas reveal another occupation where there is apparent asbestos exposure and the occurrence of mesotheliomas.

e. **Biologic Plausibility**: While the exact biologic mechanism explaining how mesothelioma develops has not been definitively identified, there is abundant literature that conclusively establishes that the exposure to any form of asbestos can result in the formation of mesothelioma. [7] There is also literature that confirms that there can be substantial amounts of asbestos fibers in the talc worker environment. Accordingly, it is biologically plausible that such exposure can cause mesothelioma.

f. **Consideration of Alternate Explanations**: There are very few documented causes of mesothelioma other than exposure to asbestos. The scientific literature contains a handful of mesothelioma cases that were purportedly caused by the administration of therapeutic radiation. In addition, exposure to erionite, an asbestos-like mineral found in Turkey, has been linked with the development of mesothelioma. Neither of these would apply as an alternative explanation for mesothelioma in talc workers. While there have been reports of "idiopathic" or "spontaneous" mesotheliomas, this term has been reserved for those instances where there is no discernable history of exposure to asbestos. Given the strong relationship between mesothelioma and asbestos, it is likely that a significant portion of those cases that have been labeled "idiopathic" are not cases where the asbestos exposure has not occurred, but rather simply could not be adequately documented. It is highly unlikely that the number of reported mesothelioma cases that have occurred in talc workers from exposure to asbestos is due to chance alone.

g. **Cessation of Exposure**: Now that the talc market is potentially shrinking because of issues of mesothelioma and ovarian cancer, it is hoped that the incidence of malignant mesothelioma will decline. However, because of the long latent period, we cannot assess this for another 10-20 or more years.

h. **Consistency with Other Knowledge**: The published literature is replete with data demonstrating that workers exposed to chrysotile, tremolite and anthophyllite asbestos from talc products are at risk for developing mesothelioma. Moreover, there are studies of talc workers that document asbestosis and/or pleural plaques that are also consistent with significant exposures to asbestos.

i. **Specificity of the Association**: This is the one criteria derived from Hill that is not useful in environmental/occupational epidemiology. For instance, cigarette smoke causes multiple diseases including lung cancer, emphysema, bladder cancer, heart disease and many other diseases. Likewise, asbestos causes malignant

mesothelioma, lung cancer, other cancers, asbestosis and pleural plaques.

Discussion

The epidemiology studies to date of miners, millers and other talc-exposed workers have inherent deficiencies. Lack of an ICD code for mesothelioma until 1999 and lack of adequate exposure data are paramount. Despite these deficiencies, a number of mesotheliomas have been detected in various studies of talc workers in Italy and in New York in the U.S. Given the whole history of mesothelioma causation by asbestos, it is impossible to dismiss those mesotheliomas as unimportant. The asbestos contamination of talc may be random or sporadic, thus accounting for the occurrence of mesotheliomas, but in small numbers. In addition, many mesotheliomas have been detected in the taconite mining areas of Minnesota in the U.S., apparently from small non-commercial EMPs which are essentially small, non-commercial asbestos fibers. Since it appears that talc can be randomly contaminated with fibrous asbestos fibers, it is risky to sell talc as a cosmetic drying agent. Even a small amount of contamination in cosmetic talc can lead to inhalation in babies or their caretakers that can eventually migrate to the pleura or peritoneum and thus cause mesothelioma.

Conclusion

Talc is randomly and sporadically contaminated with asbestos fibers including chrysotile, tremolite and anthophyllite. Exposure to all three types of asbestos fibers increases the risk of mesothelioma.[7,84,85]. Case studies of mesothelioma victims, whose only asbestos exposure was to talc, found anthophyllite, tremolite and chrysotile asbestos fibers in their tissues. [45,46] There have been mesotheliomas documented in talc workers in New York State and Italy. EMPs contaminate taconite and have caused mesotheliomas in workers in Minnesota. Small fibers and EMPs can cause mesothelioma. Exposure to talc can lead to breathing asbestos fibers or EMPs and thus can increase the risk of mesothelioma. Both pleural and peritoneal mesotheliomas have been documented from talc exposures. The International Agency on Research on Cancer [7] concluded "There is sufficient evidence in humans for the carcinogenicity of talc containing asbestiform fibres. Talc containing asbestiform fibres causes cancer of the lung and mesothelioma." (p. 294)

Even though the epidemiology studies to date of talc miners have deficiencies, the evidence of causation using the Hill criteria from all the toxicological, biological and human studies is compelling. Use of talc as a cosmetic agent on adults or babies is elevating the risk of mesothelioma.

Disclosure

Professor Kanarek has served as consultant to government and international agencies on asbestos health effects, and has been a consultant and witness on plaintiff's litigation concerning asbestos and disease.

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