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The Voice of the Defense Bar

Toxic Torts

The Newsletter of the Toxic Tort and Environmental Law Committee

8/23/2016 Volume 19 Issue 2

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Toward a Defense of Mesothelioma Cases on Causation: Low Doses and Genetics

by Mark Zellmer

Introduction

Today's defendants in asbestos litigation often face plaintiffs' claims that they have contracted mesothelioma from exposure to low or even doubtful doses of asbestos. If the mesothelioma looks to be spontaneous (idiopathic) or the result of an exposure so low that it will not cause the disease or the mesothelioma, genetics may provide the alternate explanation to satisfy the jury about why plaintiff or decedent has mesothelioma.

Genetic Predisposition: Inherited Cancer Syndromes as a Cause of Mesothelioma Independent of Asbestos

Looking to Restatement (Second) of Torts, Section 432(2) (1965), causation is not proven and in fact rebutted "if the harm would have been sustained even if the actor had not been negligent." Five to ten percent of tumors occur as a result of monogenic predispositions while another 30-50% occurs due to polygenic predispositions. Lubinski J. et al. "Molecular Basis of Inherited Predisposition for Tumors." *Acta Biochimica Polonica*. Vol. 49(3) (2001) at 571. Mesothelioma, caused by one of a number of genetic predispositions, is not any different.

TP53/Li-Fraumeni

In 1969, Frederick Li and Joseph Fraumeni first described the most clearly established, hereditary, tumor predisposition. It is an autosomal dominant pattern of various tumors including soft tissue sarcoma, breast cancer, brain tumors, adrenocortical carcinoma, leukemia, lymphoma, and melanoma as well as lung, prostate, pancreatic, and ovarian, kidney, testicular, laryngeal, head and neck cancers. Li F. et al. "A Cancer Family Syndrome in Twenty-four Kindred." *Cancer Research*. Vol. 48 (1988) at 5358. The Li-Fraumeni Syndrome, as it is now known, is a germline mutation in the TP53 gene which controls cell growth and division and "encodes" or produces the tumor suppressor protein p53. Fifty percent of individuals with the TP53 mutation developed some sort of cancer by age 30. The risk over a lifetime in men is 70% while almost 100% in women. Li-Fraumeni Syndrome is now accepted as leading to malignant mesothelioma, particularly peritoneal mesothelioma. Celeen W. "Malignant Peritoneal Mesothelioma in a Patient with Li-Fraumeni Syndrome." *Journal of Clinical Oncology*. Vol. 29(17) (2011) at 503

BAP1

In 2010 Carbone et al identified BAP1 as a germline mutation creating an autosomal dominant cancer syndrome. Carbone M. et al. "BAP1 Cancer Syndrome: Malignant Mesothelioma, Uveal and Cutaneous Melanoma and MBAITs." *Journal of Transitional Medicine*. Vol. 10 (2010) at 10.1186/1479-5876-10-179. BRCA1 the associated protein 1 (BAP1) constitutes a tumor suppressor gene located on chromosome 3p21. Its mutation was found to be associated with increased risk of malignant mesothelioma and other neoplasms. The prevalence of cancer among a BAP1-mutated cohort is seven times greater than among the non-mutated cohort, 63% compared to 9% respectively. Other cancers in this syndrome include melanoma (uveal and cutaneous), lung, breast, renal and MBAIT.

The question arises whether BAP1 is an independent factor in the cause of mesothelioma or whether asbestos is a necessary addition to cause the disease. Science has directed efforts to answer such questions. A group reviewed

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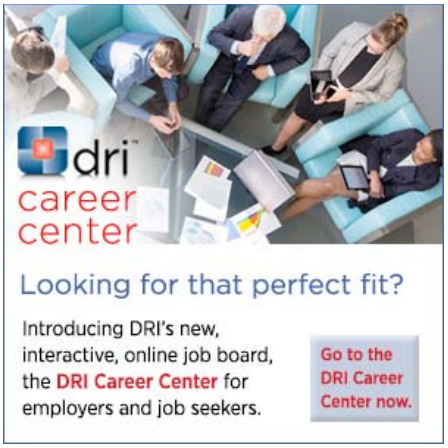


pathology from 52 mesothelioma patients exhibiting the BAP1 mutation and compared it to indicia of exposure to asbestos. They found no statistically significant association between the BAP1 mutation and asbestos exposure. Azrt L. et al. "BAP1 Protein is a Progression Factor in Malignant Pleural Mesothelioma." *Pathology and Oncology Research*. Vol. 20 (2014) at 145, 148, 149. In addition Carbone found that twenty-one percent of persons with the BAP1 mutation contracted mesothelioma while no one in the non-mutated group had contracted the disease.

More than one researcher has found the BAP1 mutations in persons with mesothelioma, but without asbestos exposure. Wiesner T. "Toward an Improved Definition of the Tumor Spectrum Associated with BAP1 Germline Mutations." *Journal of Clinical Oncology*. ico.ascopubs.org/content/30/32/e337.full; Taylor S. "Malignant Peritoneal Mesothelioma in an Adolescent Male with BAP1 Deletion." *Journal of Pediatric Hematology and Oncology*. Vol 37 (5) (2015) at 323.

NF2/Neurofibromatosis Type 2

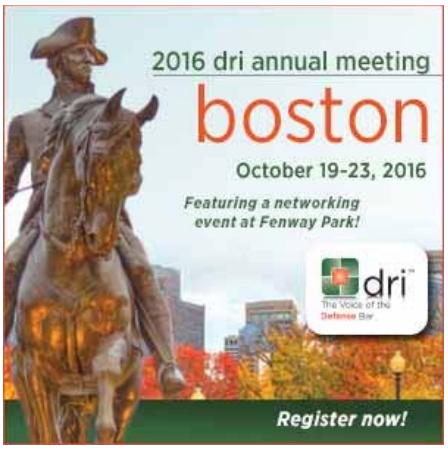
Neurofibromatosis Type 2 is a dominantly inherited tumor predisposition syndrome. NF2 refers to the tumor suppressor gene on chromosome 22q12. It provides the capability to produce an amino acid protein "595" also known as "Merlin. Yokoyama, T. et al. "YAP1 Is Involved in Mesothelioma Development and Negatively Regulated by Merlin Through Phosphorylation." *Carcinogenesis*. Vol. 59(11) (2008) at 2139. Significantly, this gene has suffered mutation in approximately 40-50% of mesotheliomas and is important to its tumorigenesis. Monteiro de Assis, L.V. at al. "The Role of Key Genes and Pathways Involved in the Tumorigenesis of Malignant Mesothelioma." *Biochimica et Biophysica Acta*. Vol. 1845 (2014) at 232, 236-237. Bianchi et al opined that "[o]ur findings clearly implicate NF2 in malignant mesothelioma tumorigenesis. . ." Bianchi A. et al. "High Frequency of Inactivating Mutations in the Neurofibromatosis Type 2 Gene (NF2) in Primary Malignant Mesothelioma." *Proceedings of the National Academy of Sciences USA*. Vol. 92 (1995) at 10856.

The NF2 mutation predisposes to a number of tumor types including bilateral vestibular Schwannomas of the eighth cranial nerve and other brain tumors (meningiomas and ependymomas) as well as melanoma and carcinoma of the breast and colon. No literature links these tumors with asbestos exposure except for possibly colon cancer for which such evidence is vanishingly close to non-existent. As a result it is easily conceivable that the pathways to induct these other tumors not related to asbestos exposure should be similar to the pathways that would induct mesothelioma without any substantial asbestos exposure.

Genetic Susceptibility—A Red Herring

Plaintiffs attempt to perpetrate a myth that mesothelioma is somehow unique among tumors. When presenting a low dose case and confronting defendant's argument of a lack of causation, plaintiff's counsel seeks refuge in a simple, but specious argument: plaintiff or decedent contracted mesothelioma because he was especially susceptible to contracting the disease from small doses of inhaled asbestos. This argument appeals to the time honored tort principle of the plaintiff with the "egg shell" skull, meaning that a defendant takes his plaintiff as he finds him. *Colonial Inn Motor Lodge, Inc. v. Gay*, 288 Ill.App.3d 32, 45, 680 N.E.2d 407, 416 (1997); *Heppner v. Atchison, Topeka, and Santa Fe Ry. Co.*, 297 S.W.2d 497, 504 (Mo. 1956). The real issue is not just susceptibility, but susceptibility to what dose. Plaintiff should prove that (1) some genetic abnormality causes susceptibility to mesothelioma from a low dose, not just any dose of asbestos exposure and (2) plaintiff or decedent in fact has this genetic characteristic. *In re Hanford Nuclear Reservation Litigation*, No. CY-91-3015-AAM, 1998 WL 775340, at 64-65.

Science supports this view that genetic make-up will cause some people to contract mesothelioma without asbestos exposure or independent of low dose exposure to asbestos while genetic susceptibility explains why some people but not others with significant occupational exposure to asbestos contract mesothelioma. Matullo G. et al. "Genetic Variants Associated with Increased Risk of Malignant Pleural Mesothelioma: A Genome-Wide Association Study." *PlosOne*. http://dx.doi.org/10.1371 /journal.pone.00861253 (April 13, 2013). They discovered that genetic alterations made "an independent contribution" to the causation of malignant pleural mesothelioma, in some instances, more than doubling the risk of the disease. They also found that it was only occupational exposure in association with these genetic alterations that substantially increased the risk of mesothelioma. The authors concluded "genetic risk factors" should be taken into account in the "risk profile of people with a high exposure to asbestos."



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Most of the talk about a special susceptibility to mesothelioma from low dose exposure comes from experiments on mice with the dominant BAP1 mutation. Of course what is found in animals may not apply to humans, particularly when the mice are exposed through direct injection into the peritoneum while human exposure almost invariably comes from inhalation. Most tellingly, finding an increased number of cases of peritoneal mesothelioma in mice from low doses is inconsistent with human experience. Prolonged and heavy exposure, not a low dose exposure, is necessary to cause peritoneal mesothelioma in humans.

Bringing It Altogether: Industrial Hygiene, Family History and Genetic/Molecular Testing

Methods of genetic testing include biochemical testing, molecular or direct and cytogenic testing. Obtaining the necessary blood or tissue for genetic testing will require a court order. Although drawing blood is of course minimally invasive, plaintiff may argue otherwise. A trial court confronted this issue in California faced with a young man claimed to be deathly afraid of needles. The court allowed the testing, including drawing blood, reasoning that the defendant had a right to present a defense. *San Francisco Examiner*, June 7, 1994 at www.nwitimes.com.

There are a number of steps in preparation of the defense.

- An industrial hygienist must calculate the dose.
- A medical expert should testify that the dose calculated by the hygienist is not sufficient to increase materially the risk of mesothelioma and in fact did not cause the mesothelioma.
- Experts must establish any family history of cancer among blood relatives as well as any prior or concurrent cancer suffered by plaintiff.
- Defendant should perform genetic testing on plaintiff's tissues.
- Defendant must be prepared to present a genetics expert to opine that a genetic predisposition is the cause of plaintiff's mesothelioma.

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