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Charleston, SC | September 16-17, 2025

The Role of Medicine and Science in Asbestos Litigation

John Hurst, Esq.
Motley Rice LLC

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ToxicoGenomica

Genetically Related Mesotheliomas ≠ Asbestos-Related Mesotheliomas

Clinical, morphologic, epidemiologic, and biologic distinctions

Len van Zyl, Ph.D.

17 September 2025

ARRAYXPRESS
Your Contract Research Partner for Next Generation Genomics

Overall Conclusions #1

- Large scale (i.e, 1000s of individuals) genetic/genomic studies using matched tumor and normal tissues show that Pathogenic Germline Mutations in Highly Penetrant Genes CAUSE Cancer and can do so independent of any other factors (*i.e.*, exogenous exposures to toxicants).

- The initiation and progression of cancers caused by pathogenic germline mutations in these highly penetrant genes are due to
  - ***endogenous genetic mechanisms*** [*i.e.*, inactivating acquired somatic mutations and/or Loss of Heterozygosity (LOF; *i.e.*, mitotic recombination, gene conversions, and interstitial deletions)], or
  - ***due to endogenous metabolic processes and the accumulation of endogenous metabolites*** (*i.e.*, formaldehyde, acetaldehyde and methylglyoxal, *etc.*).

Overall Conclusions #2

- In the context of Malignant Mesothelioma (MM), my group and I recently published a study in Nature Scientific Reports (Nielsen *et al*., 2025) confirming that highly penetrant pathogenic germline mutations in the *BAP1* Gene in mice can and do cause mesothelioma independently of asbestos exposure.

- ***"It is very important that those caring for these patients understand that genetically linked mesotheliomas, especially when detected at an early stage, have a much less aggressive clinical course compared to patients with asbestos-induced mesotheliomas: These are different diseases. The former is minimally invasive, patients survive for several years and respond to therapy. Some patients have been cured,.."*** Novelli *et al*., 2024

MM Developing in BAP$^{+/-}$ Carriers are a Different Disease, Biologically, Histologically, and Clinically

IASLC

ORIGINAL ARTICLE

Prospective Analysis of Mesotheliomas in Subjects With BAP1 Cancer Syndrome: Clinical Characteristics and Epigenetic Correlates of Disease

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ABSTRACT

Introduction: Although mesotheliomas are the most common malignancies identified in BAP1 cancer syndrome (BCS), the prevalence and natural history of the neoplasms have not been elucidated. Protocol NCT04431024 was initiated to prospectively evaluate whether high-resolution computed tomography (CT) imaging and minimally invasive surgical evaluation could facilitate detection and surveillance of mesotheliomas in subjects with germline *BAP1* mutations.

Methods: Subjects above or equal to 33 years of age with or without prior malignancies underwent CT imaging followed by bilateral thoracoscopies and laparoscopies. CT imaging and intraoperative findings were objectively scored; surgical biopsies were interpreted by two expert pathologists. Skin, peripheral blood mononuclear cells, plasma, serum, and tumor biopsies were collected for correlative research studies.

Results: A total of 50 subjects with 32 germline *BAP1* mutations were enrolled between March 2021 and July 2024. Median follow-up was 21.8 months (range: 1.7–41.1 mo). Furthermore, 16 sites of prior mesothelioma in 15 patients were excluded from the analysis. Surgical

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Journal Pre-proof

Clinical and Pathologic Phenotyping of mesothelioma developing in carriers of Germline *BAP1* Mutations

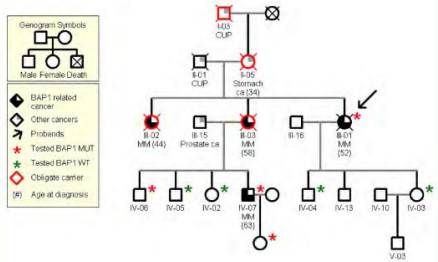
Journal of Thoracic Oncology

Introduction - The *BAP1* Cancer Syndrome and Mesothelioma (MM)

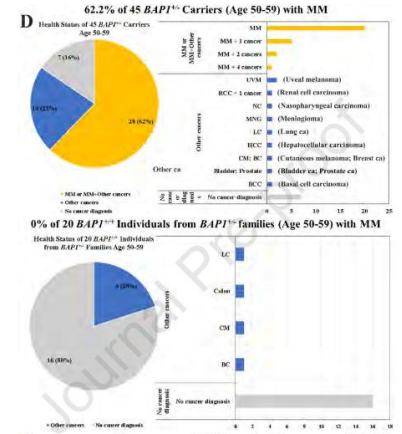
We discovered that familial MM was transmitted in a Mendelian fashion[1]; that germline *BAP1* mutations caused MM[2] and other cancers[3]; and we elucidated mechanisms of BAP1 activity.[4-6]

Here we present our findings studying from 1999-2024, 47 families carrying heterozygous germline *BAP1* mutations (*BAP1*$^{+/-}$), including 238 *BAP1*$^{+/-}$ carriers and 123 *BAP1*$^{+/+}$ relatives.

Representative Family Tree

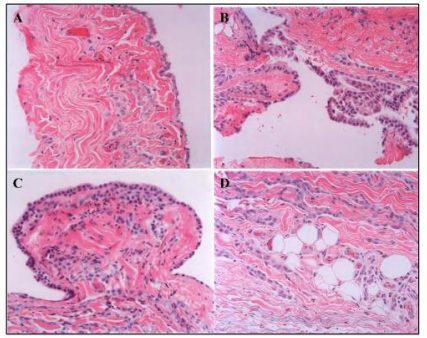


Results



There were 84 cases of MM and 22 cases of UVM among the 238 *BAP1*$^{+/-}$ carriers, 8 of them developed both malignancies. None of the 123 first and second-degree relatives with WT *BAP1*$^{+/+}$ were diagnosed with MM [$\chi^2(1) = 56.6$, $p < 0.0001$], or with UVM [$\chi^2(1) = 92.1$, $p < 0.0001$].

MM in *BAP1* mutant carriers is a different disease compared to asbestos induced MM



Characteristic Histology (A-C), most patients have three-cavitary diffuse mesothelial hyperplasia and (D), focal areas of low-grade germline-mutant-*BAP1*-associated mesothelioma (L-BAM). L-BAM are superficially invasive mesothelial neoplasms that show BAP1 loss. Most microscopic L-BAMs do not progress, if they become visible on imaging these neoplasms should be removed. This patient was treated with extrapleural pneumonectomy at age 43 and died 19.5 years later of a stroke. MM never recurred.

CONCLUSION: Compared to sporadic MM, MM developing in *BAP1*$^{+/-}$ carriers are a different disease, biologically, histologically and clinically: these patients require a tailored clinical approach. Because these patients are at high risk of developing multiple cancers, they benefit from annual screening for early cancer detection that can be life-saving.

IASLC

Carbone M, Minaai M, et al. *J Thorac Onc* (2025)

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3. Carbone M, et al. Cancer discovery 2020;10:1103-1120.
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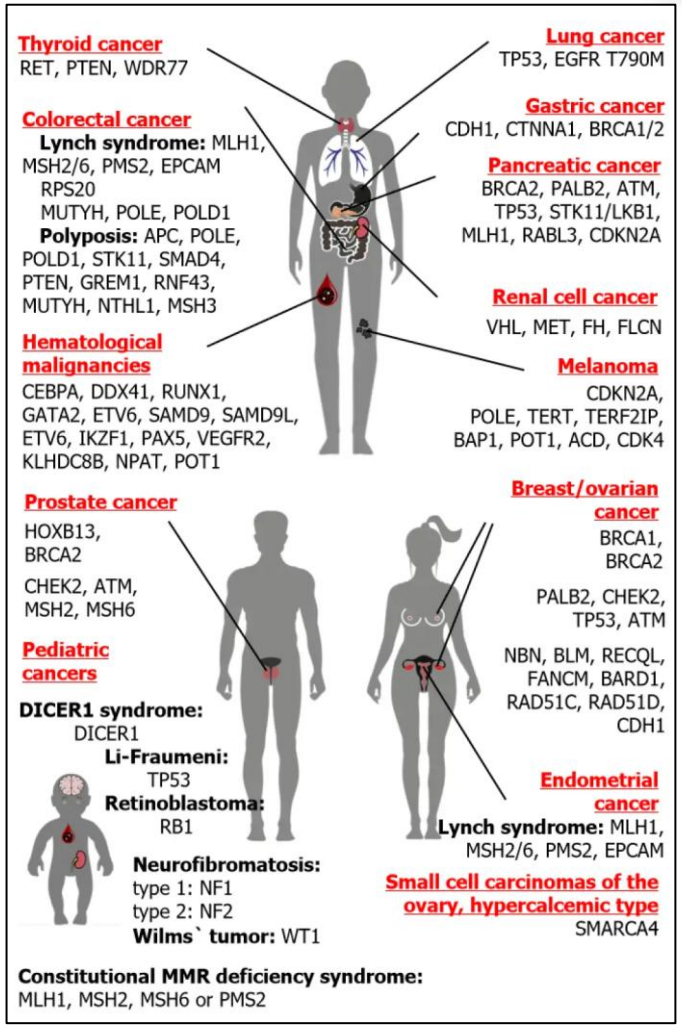
6. Bononi A, et al. PNAS 2023;120:e2217840120.

Two Independent Studies Uncover a Novel, Less Aggressive Variant of Mesothelioma Linked to Germline BAP1 Mutations (Wu 2025-National Cancer Institute NCI; Carbone 2025; University of Hawaii Cancer Center— illuminate a previously unrecognized subset of mesothelioma patients whose tumors exhibit markedly less aggressive clinical behavior and respond favorably to therapeutic interventions.

At Least 10-20% of All Cancers are Caused by Highly Penetrant Germline (Inherited) Pathogenic Mutations

- **Cancers caused by an Inherited Mutation are called Hereditary Cancers.** The remaining cancers - those not caused by an inherited mutation - are called sporadic cancers.
- **Most cancers are sporadic, but overall, about 10-20% of ALL CANCERS are caused by an inherited mutation (Facing Our Risk of Cancer Empowered (FORCE): https://www.facingourrisk.org/)**
- These Hereditary Cancer Predisposition Syndromes are caused by mutations (changes) in certain genes that are passed down from parents to children.

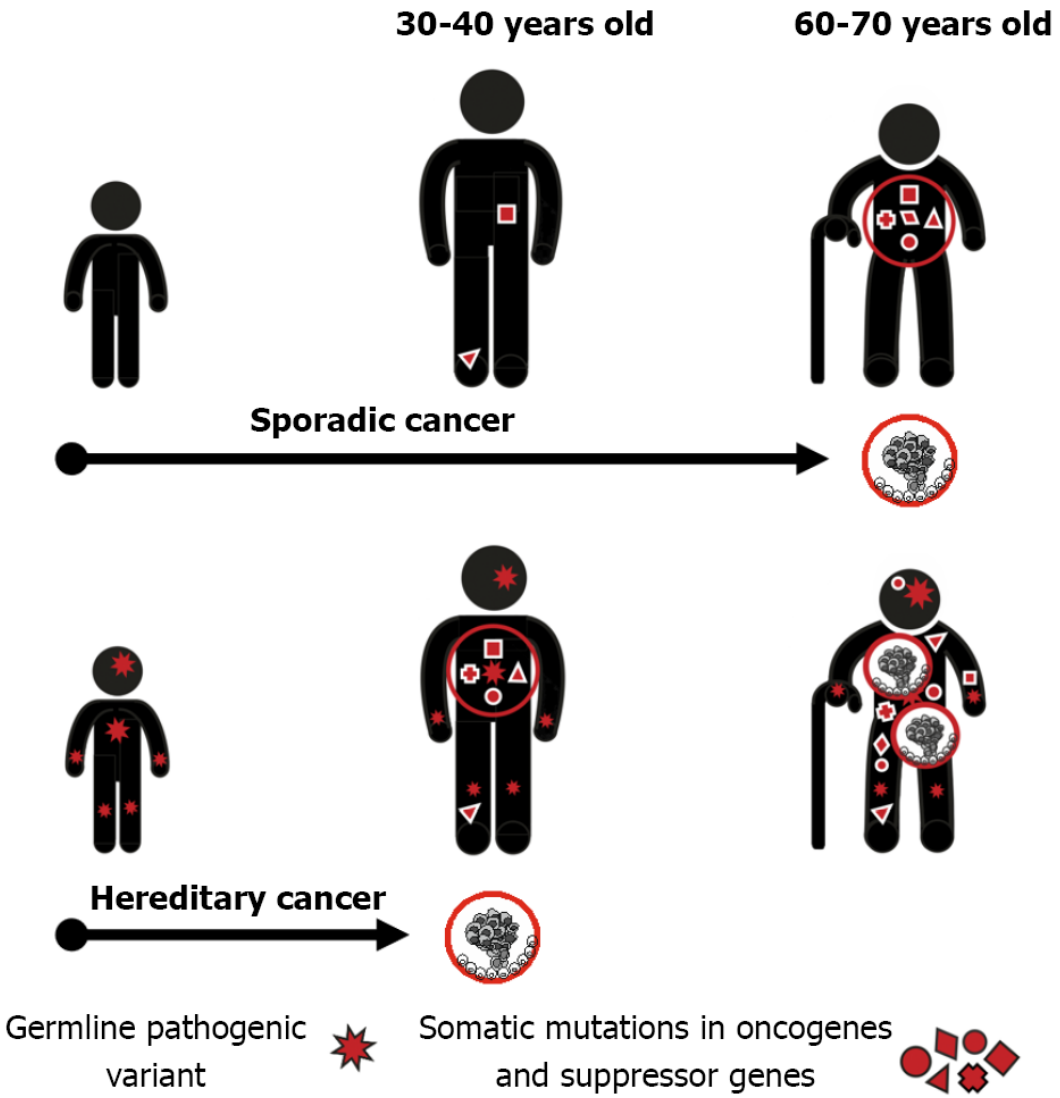


Adapted from Imyanitov *et al.*, 2023

FORCE

Facing Hereditary Cancer EMPOWERED

Hereditary Cancers Tend to Present Earlier in Life



"…since every cell in the target organ already contains one alteration in a cancer gene, the probability of accumulation of a critical mass of additional oncogenic mutations in any given cell clone is high, and cancer manifestation often occurs at a relatively young age."

Imyanitov *et al*., 2023

Adapted from Imyanitov *et al*., 2023

Highly Penetrant Pathogenic Germline Variants in Essential Genes Drive Tumorigenesis Without Other Factors

Memorial Sloan Kettering Cancer Center

GERMLINE MUTATIONS

How the germline informs the somatic landscape

How somatic and germline mutations interact in cancer remains largely unexplored. A study of 17,152 patients with cancer suggests that the relative contribution of pathogenic germline mutations is governed by lineage and penetrance.

Stephen J. Chanock

NATURE GENETICS | VOL 53 | NOVEMBER 2021 | 1522–1526 | www.nature.com/naturegenetics

SignalDB

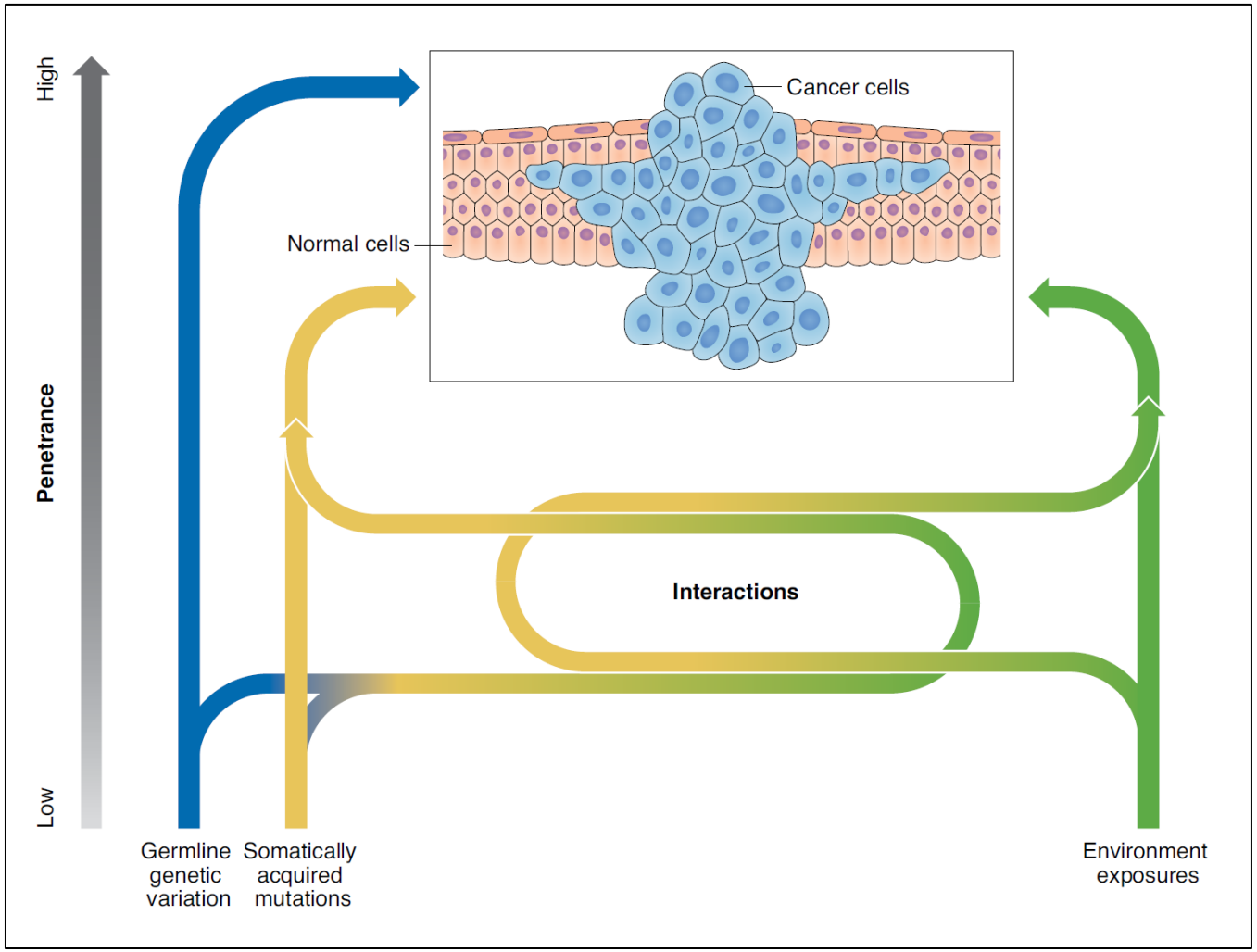
Somatic Integration of Germline Alterations in Cancer

17,152 patients and 45 cancer types

High Penetrance	Moderate Penetrance	Low Penetrance	Uncertain Penetrance
37 Genes	8 Genes	2 Genes	128 Genes

https://www.signaldb.org/

Highly Penetrant Pathogenic Germline Variants in Essential Genes Drive Tumorigenesis Without Other Factors



Dynamic Model of Carcinogenesis:

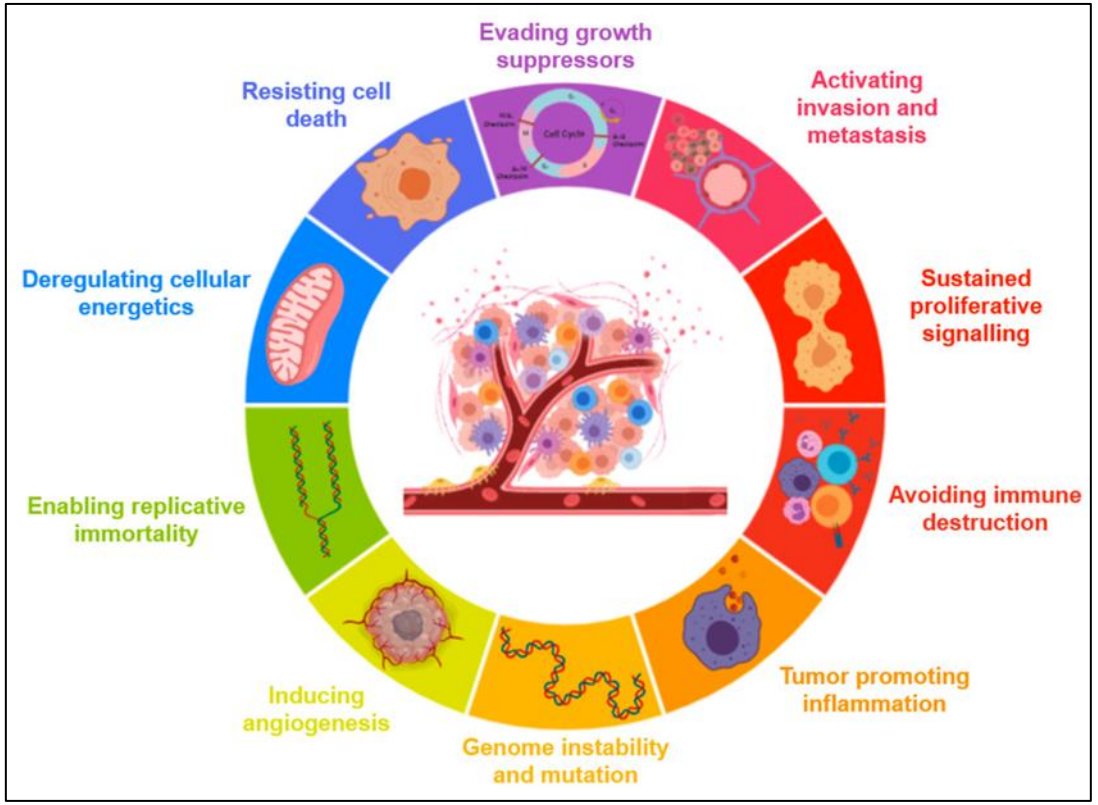
"Tumor development depends on complex interactions between germline variants (dark blue), somatically acquired variants (yellow) and environmental exposures (green). ***Penetrance also has a modifying role in which highly penetrant (germline) variants are more likely to drive tumorigenesis without the influence of other factors."***

Chanock, 2021; Nature Genetics

Adapted from Chanock, 2021; based on data generated from a massive genomics study published by Srinivasan *et al*., 2021; Nature Genetics

Highly Penetrant Pathogenic Mutations in *BAP1, TP53, BRCA1/2, BARD1, etc.* Allow Cells to Endogenously Acquire up to All 10 Hallmarks of Cancer

- Douglas Hanahan and Robert A. Weinberg published the landmark article **"The Hallmarks of Cancer"** in the journal Cell in 2000; updated in 2011, and Hanahan, 2022.
- **Hanahan and Weinberg <u>described ten principal cellular traits shared by virtually all forms of human cancers</u>.** Collectively, these essential alterations in cell physiology dictate tumor initiation, development, growth and metastases.
- Each of these 10 acquired capabilities – evasion of apoptosis, self-sufficiency in growth signals, insensitivity to growth inhibition signals, limitless replicative potential, sustained angiogenesis, and tissue invasion/metastasis, *etc.* – ***represents the successful circumvention of inherent anticancer defense mechanisms of cells and tissues.***



Adapted from Acebes-Fernandez *et al.*, 2020

Krevanko (September 7, 2025) – Genetic Predisposition is an Independent Risk Factor for Mesothelioma

"Our findings suggest that a genetic predisposition for malignancy contributes to U.S. mesothelioma rates and is a distinct risk factor independent of asbestos exposure." Krevanko *et al.*, 2025

Journal of Public Health | pp. 1–6 | https://doi.org/10.1093/pubmed/fdaf110

Potential influence of cancer history on mesothelioma incidence: an ecologic analysis in the U.S. population

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ABSTRACT

Background: There is a demand for population level research on the potential genetic-basis of mesothelioma (e.g. BRCA1-associated protein-1 [BAP1]) independent of other risk factors, such as amphibole asbestos exposure. By surrogate, another primary cancer history can be used to explore this issue, including in the USA, where the incidence rates (IRs) in men, but not women, are temporally aligned with historical asbestos consumption.

Methods: We computed age-adjusted IRs of mesothelioma in females and males stratified by other primary cancer history using publicly available U.S. cancer data from 1975 to 2021. To facilitate comparison with other cancers associated with BAP1, we calculated age-adjusted IRs for female breast cancer and melanoma.

Results: Similar to breast cancer and melanoma, ~25% of females with mesothelioma had a history of at least one other primary cancer. While IRs of mesothelioma in males without a history of other primary cancers were temporally aligned with historical asbestos consumption trends in the USA, IRs of mesothelioma among males with other primary cancer histories showed no relationship with asbestos consumption trends.

Conclusions: Our findings suggest that a genetic predisposition for malignancy contributes to U.S. mesothelioma rates and is a distinct risk factor independent of asbestos exposure.

Keywords: mesothelioma; multiple primary neoplasms; risk factors; SEER program

Introduction

In the USA, mesothelioma is a rather uncommon cancer, with an annual age-adjusted incidence rate (IR) of < 1 per 100 000 persons at risk.[1] Prior to the initial impacts of the coronavirus disease from the SARS-CoV-2 virus in 2020, mesothelioma accounted for ~0.10% of all mortality in the USA per year.[2] Mesothelioma bears a unique characteristic: incident cases in the USA occur in a relatively high percentage of individuals with a history of prior cancer of a different type.[3,4] For example, an analysis of data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program revealed that among incident mesotheliomas in 2009–2013, 10.9% of those aged 20–64 years and 23.5% of those aged ≥ 65 years had been previously diagnosed with cancer at another site.[3] For context, compared to 29 other incident cancers, the rank-order of these two percentages was one of 29 and two (tied) of 29, respectively. A more recent SEER analysis revealed that 18% of incident mesotheliomas in 2019 among those aged ≥ 18 years were among persons with a previous cancer at another site, corresponding to a rank-order of two of 29.[4]

Patients with a history of multiple primary cancers are more likely to have a hereditary predisposition to malignancy due to their increased probability of carrying germline mutations in cancer-related genes.[5,6] Accordingly, the International

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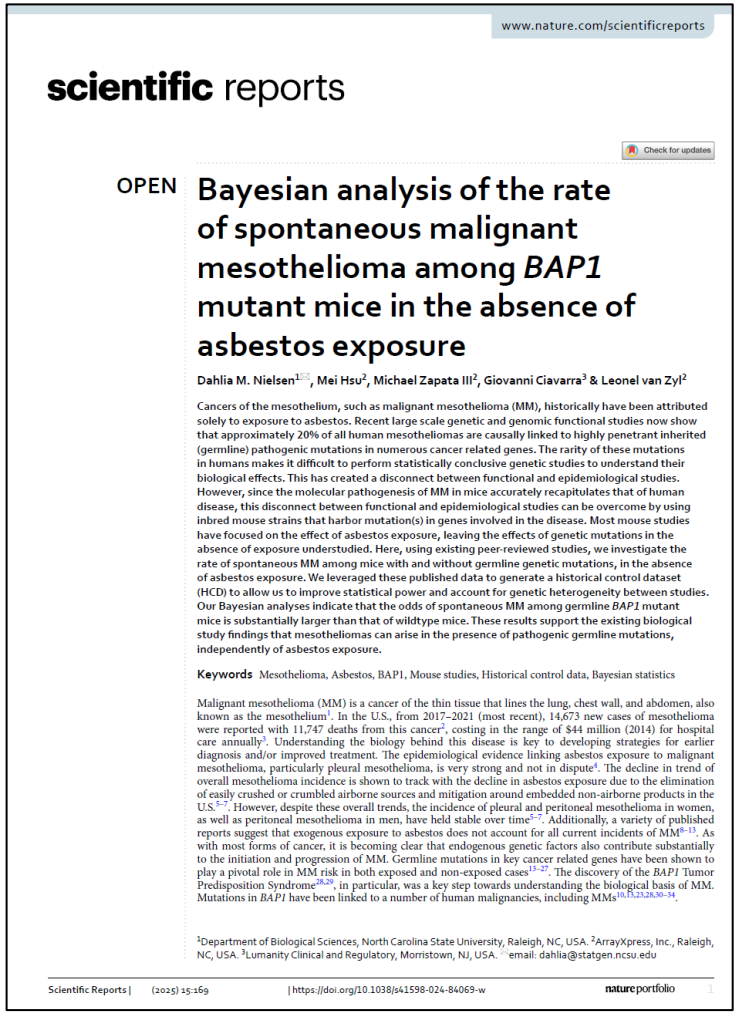
Highly Penetrant Pathogenic Mutations in the *BAP1* Gene Cause Spontaneous Mesothelioma and other Cancers Independent of Asbestos Exposure

"Pathogenic mutations in BAP1 have been shown not only to initiate tumors, but to also drive the subsequent acquisition of endogenous mutations and epigenetic changes[85–90]. Much like TP53, studies have demonstrated that BAP1 functions within the parameters of all three classes of tumor suppressor genes: as gatekeeper (directly regulating cell cycle control and cell proliferation); as caretaker (regulating genomic stability); and as landscaper (regulating chromatin modification)[30,32,91,92]. By fulfilling the function of all three classes of tumor suppressors, is it not surprising that pathogenic heterozygous germline BAP1 null mutations can behave in a haploinsufficient manner, via either dominant-negative interactions or gain-of-neomorphic function(s) effects, ultimately causing cancer in nearly all germline carriers[28,31,32,93–96]." Nielsen *et al*., 2025



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Bayesian analysis of the rate of spontaneous malignant mesothelioma among *BAP1* mutant mice in the absence of asbestos exposure

Dahlia M. Nielsen[1✉], Mei Hsu[2], Michael Zapata III[2], Giovanni Ciavarra[3] & Leonel van Zyl[2]

Cancers of the mesothelium, such as malignant mesothelioma (MM), historically have been attributed solely to exposure to asbestos. Recent large scale genetic and genomic functional studies now show that approximately 20% of all human mesotheliomas are causally linked to highly penetrant inherited (germline) pathogenic mutations in numerous cancer related genes. The rarity of these mutations in humans makes it difficult to perform statistically conclusive genetic studies to understand their biological effects. This has created a disconnect between functional and epidemiological studies. However, since the molecular pathogenesis of MM in mice accurately recapitulates that of human disease, this disconnect between functional and epidemiological studies can be overcome by using inbred mouse strains that harbor mutation(s) in genes involved in the disease. Most mouse studies have focused on the effect of asbestos exposure, leaving the effects of genetic mutations in the absence of exposure understudied. Here, using existing peer-reviewed studies, we investigate the rate of spontaneous MM among mice with and without germline genetic mutations, in the absence of asbestos exposure. We leveraged these published data to generate a historical control dataset (HCD) to allow us to improve statistical power and account for genetic heterogeneity between studies. Our Bayesian analyses indicate that the odds of spontaneous MM among germline *BAP1* mutant mice is substantially larger than that of wildtype mice. These results support the existing biological study findings that mesotheliomas can arise in the presence of pathogenic germline mutations, independently of asbestos exposure.

Keywords Mesothelioma, Asbestos, BAP1, Mouse studies, Historical control data, Bayesian statistics

Malignant mesothelioma (MM) is a cancer of the thin tissue that lines the lung, chest wall, and abdomen, also known as the mesothelium[1]. In the U.S., from 2017–2021 (most recent), 14,673 new cases of mesothelioma were reported with 11,747 deaths from this cancer[2], costing in the range of $44 million (2014) for hospital care annually[3]. Understanding the biology behind this disease is key to developing strategies for earlier diagnosis and/or improved treatment. The epidemiological evidence linking asbestos exposure to malignant mesothelioma, particularly pleural mesothelioma, is very strong and not in dispute[4]. The decline in trend of overall mesothelioma incidence is shown to track with the decline in asbestos exposure due to the elimination of easily crushed or crumbled airborne sources and mitigation around embedded non-airborne products in the U.S.[5–7]. However, despite these overall trends, the incidence of pleural and peritoneal mesothelioma in women, as well as peritoneal mesothelioma in men, have held stable over time[5–7]. Additionally, a variety of published reports suggest that exogenous exposure to asbestos does not account for all current incidents of MM[8–13]. As with most forms of cancer, it is becoming clear that endogenous genetic factors also contribute substantially to the initiation and progression of MM. Germline mutations in key cancer related genes have been shown to play a pivotal role in MM risk in both exposed and non-exposed cases[13–27]. The discovery of the *BAP1* Tumor Predisposition Syndrome[28,29], in particular, was a key step towards understanding the biological basis of MM. Mutations in *BAP1* have been linked to a number of human malignancies, including MMs[10,15,23,28,30–34].

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Nielsen 2025 v. Kadariya 2025
Evidence from Animal Models

- Bayesian analysis shows significantly higher spontaneous mesothelioma rates in *BAP1*-mutant mice vs wildtype, in asbestos-free settings (Nielsen 2025)
- Our Neilsen study involved thousand of mice as reported from Kadariya 2016; Cheung and Testa, 2017, plus data from several mouse studies
- **Nielsen approach**:
  - High statistical power because of many mice; moderate bias risk
- **Nielsen study supports a genetic causation etiology independent of asbestos exposure.**

- New Kadariya 2025 study involved 329 mice and is inconclusive
  - **Severely underpowered**: For events (MMs) occurring at ~0.6% frequency in mutant animals, detecting a statistically significant difference **requires thousands, not hundreds (329) of animals (between 2634-3088 mice per arm)**,

Similar Data for Other Highly Penetrant Genes

Novelli *et al.*, 2024

PNAS RESEARCH ARTICLE | GENETICS

Germline *BARD1* variants predispose to mesothelioma by impairing DNA repair and calcium signaling

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Affiliations are included on p. 11.

Edited by Peter Vogt, Scripps Research Institute Department of Molecular Medicine, La Jolla, CA; received March 13, 2024; accepted June 12, 2024

We report that ~1.8% of all mesothelioma patients and 4.9% of those younger than 55, carry rare germline variants of the BRCA1 associated RING domain 1 (*BARD1*) gene that were predicted to be damaging by computational analyses. We conducted functional assays, essential for accurate interpretation of missense variants, in primary fibroblasts that we established in tissue culture from a patient carrying the heterozygous *BARD1*^{V523A} mutation. We found that these cells had genomic instability, reduced DNA repair, and impaired apoptosis. Investigating the underlying signaling pathways, we found that BARD1 forms a trimeric protein complex with p53 and SERCA2 that regulates calcium signaling and apoptosis. We validated these findings in *BARD1*-silenced primary human mesothelial cells exposed to asbestos. Our study elucidated mechanisms of *BARD1* activity and revealed that heterozygous germline *BARD1* mutations favor the development of mesothelioma and increase the susceptibility to asbestos carcinogenesis. These mesotheliomas are significantly less aggressive compared to mesotheliomas in asbestos workers.

genetics | carcinogenesis | mesothelioma | gene × environment | cancer prevention

Significance

There has been an unexplained increase of mesothelioma in younger patients who have not worked in the asbestos industry. We report that inherited germline mutations of *BARD1* cause some mesotheliomas in young patients. They experience significantly prolonged survival up to 20+ y and they require tailored screening and therapeutic approaches.

Cancer for the most part is a disease of old age, however, in recent years there has been an unexplained increase of cancer diagnoses among young patients. Various hypotheses, including exposure to increasing amounts of environmental carcinogens, have been proposed, yet there are no firm data to support these hypotheses (1). Mesothelioma, one of the best examples of a cancer caused by environmental carcinogens, is one of the malignancies that we see with increasing frequency in younger patients (2). This is very difficult to explain because asbestos causes cancer about 30 to 60+ y after initial exposure, thus most asbestos workers developed mesothelioma when they are old (2). Because, asbestos use was banned in the 80 s (2), former asbestos workers are now in their 70 s to 90 s, thus we should see mesothelioma in older not younger patients! (3)

In previous studies, we found that heterozygous germline mutations in the *BAP1* gene cause the BAP1 Cancer Syndrome, characterized by a high incidence of mesothelioma (4–9). We found that *BAP1*-linked mesotheliomas had a distinct clinical presentation: These patients very rarely had evidence of asbestos exposure, the median age of onset was 54 y old, several of them were in their 20 s and 30 s, the male to female and the pleural to peritoneal mesothelioma ratios were 1:1, compared to about 7:1 in mesotheliomas developing in asbestos workers (8, 10–12). Intriguingly, mesotheliomas developing in carriers of germline *BAP1* mutations had a median survival of 5 ~ 7 y and some were apparently cured as they survived mesothelioma for >20 y (8, 10–16). In contrast, mesotheliomas developing in asbestos workers have a median survival of ~1 y, are resistant to therapy, and are uniformly fatal (14). These differences point to different mechanisms underlying the pathogenesis of these malignancies. In additional targeted next-generation sequence studies we, and others, found that ~8 to 16% of mesotheliomas developed in carriers of germline *BAP1* mutations—the most frequent mutations—and, occasionally, in the contest of other tumor predisposition syndromes (8, 10–16). We also found some mesotheliomas developing in younger patients and associated with prolonged survival that did not contain mutations of any of the genes tested, which included those known to predispose to cancer (11). We suspected that additional genes, not included in our testing panel (11) might cause or predispose to less aggressive mesotheliomas in younger patients. It is important to identify carriers of germline mutations that predispose to cancer because screening of these individuals and of their affected family members for early cancer detection can be life-saving. Also, when diagnosed with cancer, these patients

Author contributions: F.N., V.A.M.V., L.M., J.-H.K., F.K., J.S.S., G.G., C.G., P.P., H.Y., and M.C. designed research; F.N., Y.Y., V.A.M.V., L.M., J.-H.K., F.K., A.B., J.S.S., C.F., A.A.Z., L.A., J.S., S.S., and H.A. performed research; Y.Y., M.M., S.P., M.E., F.K., F.B., J.N.O., M.T., R.X., Y.T., Z.W., G.S., J.G., F.G., D.S.S., H.I.P., L.A., J.S., S.S., K.Y.S., H.A., L.H., Q.P.-H., C.G., and P.P. contributed new reagents/analytic tools; F.N., Y.Y., V.A.M.V., L.M., M.M., S.P., M.E., J.-H.K., F.K., A.B., M.T., C.F., A.A.Z., Y.T., J.G., L.A., J.S., S.S., H.A., L.H., Q.P.-H., C.G., P.P., H.Y., and M.C. analyzed data; M.C. supervision; and F.N. and M.C. wrote the paper.

Competing interest statement: M.C. has a patent issued for "Methods for Diagnosing a Predisposition to Develop Cancer." M.C. and H.Y. have a patent issued for "Using Anti-HMGB1 Monoclonal Antibody or other HMGB1 Antibodies as a Novel Mesothelioma Therapeutic Strategy", and a patent issued for "HMGB1 As a Biomarker for Asbestos Exposure and Mesothelioma Early Detection." M.C. is a board-certified pathologist who provides consultation for pleural pathology, including medical-legal.

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Cancer Medicine

WILEY

Cancer Medicine Open Access

RESEARCH ARTICLE OPEN ACCESS

Estimating Cancer Penetrance in Carriers of *BRCA2* Pathogenic Variants Using Cancer-Specific Polygenic Scores

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Received: 8 April 2025 | **Revised:** 14 May 2025 | **Accepted:** 21 May 2025

Keywords: *BRCA2* | breast cancer (female and male) | hereditary breast and ovarian cancer syndrome (HBOC) | liver cancer | lung cancer | oral cancer | ovarian cancer | pancreatic cancer | polygenic score | prostate cancer

ABSTRACT

Introduction: *BRCA2* is a causal gene for hereditary breast and ovarian cancer (HBOC) syndrome. However, its association with other cancers and interplay with polygenic scores (PGS) remains unclear.

Methods: An observational cohort study for the diagnosis of various cancers in the UK Biobank (UKB, $N = 453{,}541$) were recruited at ages of 40–69 years Association of germline pathogenic variants (PVs) in *BRCA2* and published cancer-specific PGS with cancer risk was tested using Cox proportional hazards model.

Results: The median age and interquartile range (IQR) of participants at the analysis was 58.34 (50.60–63.74) years. Carriers of *BRCA2* PVs ($N = 1629$) had a significantly increased risk for four core HBOC-associated cancers (breast, ovarian, pancreatic, and prostate) and six additional types of cancer (lung, oral, small intestine, larynx, liver, and mesothelioma), hazard ratio (HR) > 2.37, all $ps < 0.001$. For eight cancers where cancer-specific PGS is available, each PGS was significantly associated with its respective cancer risk and independent of *BRCA2*, HR > 1.25 for 1 unit increase in standard deviation, all $ps < 0.001$. For female breast and prostate cancer, a significant interaction between *BRCA2* and PGS was found (HR < 0.83, $p < 0.05$); the effect of PGS on cancer risk was weaker in carriers than noncarriers. The probability of cancer by age 75 years (P_{75}) for these 10 cancers increased with higher PGS deciles in both carriers and noncarriers. For several cancers, the P_{75} in carriers with the lowest PGS decile was lower than that of noncarriers with the highest PGS decile.

Conclusions: *BRCA2* PVs increase risk beyond core HBOC cancers and their risks are modified by cancer-specific PGS. These results suggest that genetic counseling of *BRCA2* PV carriers may extend to cancers beyond core HBOC syndrome and incorporate cancer-specific PGS in estimating their penetrance.

Brendan Prassas and Zhuqing Shi contributed equally to this study.

A Substantial Subset of Mesotheliomas are Genetically Driven

- A substantial subset (~20%) of mesotheliomas are genetically driven (e.g., *BAP1*, *BARD1*, *BRCA1/2*, *TP53*, *NF2*, *etc*.) and constitute a distinct disease entity.
- **These tumors differ from asbestos-induced mesotheliomas across epidemiology, age at diagnosis, morphology, biology, prognosis, and management**.
- Key sources: Congedo 2024; Novelli 2024; Carbone 2025; Nielsen 2025, Wu 2025, Prassas 2025, Calderon 2025, Krevanko 2025.

BAP1 Morphology & Pathology

- **Unique histologic patterns reported in *BAP1* carriers (multicompartment, less aggressive features).** (Carbone 2025; Wu 2025)
- Differential immunophenotype and molecular signatures compared to asbestos-related disease. (Carbone 2025; Wu 2025)
- **Implications for pathology workflows: integrate germline context when interpreting biopsies.**

Diagnostic & Management Implications

- Screen for germline predisposition (*BAP1*, *BARD1*, *BRCA1/2*; *TP53*, and others) in young/low-exposure patients.
- Adjust surveillance: periodic imaging and multi-tissue assessment in *BAP1* carriers. (Carbone 2025; Wu 2025)
- Therapeutic angles: DNA repair vulnerabilities; epigenetic therapies; personalized trial enrollment. (Congedo 2024; Carbone 2025; Wu 2025)

Take-Home Conclusions

- Large amounts of recent data allow experts in genetics to objectively and reproducibly distinguish between genetically caused mesotheliomas and asbestos-induced mesotheliomas.

- Lawyers and experts need to truly understand the meaning of the recent data
  - articles by experts in genetics seldom use words to state conclusions that are obvious to other scientists; they instead provide and show the data, often in figures and tables

- Data shows that genetically caused mesotheliomas differ from asbestos-induced mesotheliomas with respect to epidemiology, histopathology, molecular mechanisms, prognosis, and clinical management.

- Recognizing this distinction changes screening, counseling, and treatment.

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The Role of Medicine and Science in Asbestos Litigation: Genetics

Perrin's National Asbestos Litigation Conference
The Charleston Place Hotel
September 17, 2025
2:15-2:50PM

John Hurst, Motley Rice LLC

Susceptibility

Napolitano … (2016)

Minimal asbestos exposure in germline BAP1 heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma

Napolitano, L Pellegrini, Dey, Larson, Tanji, Flores, Kendrick, Lapid, Powers, Kanodia, Pastorino, Pass, Dixit, Yang, Carbone

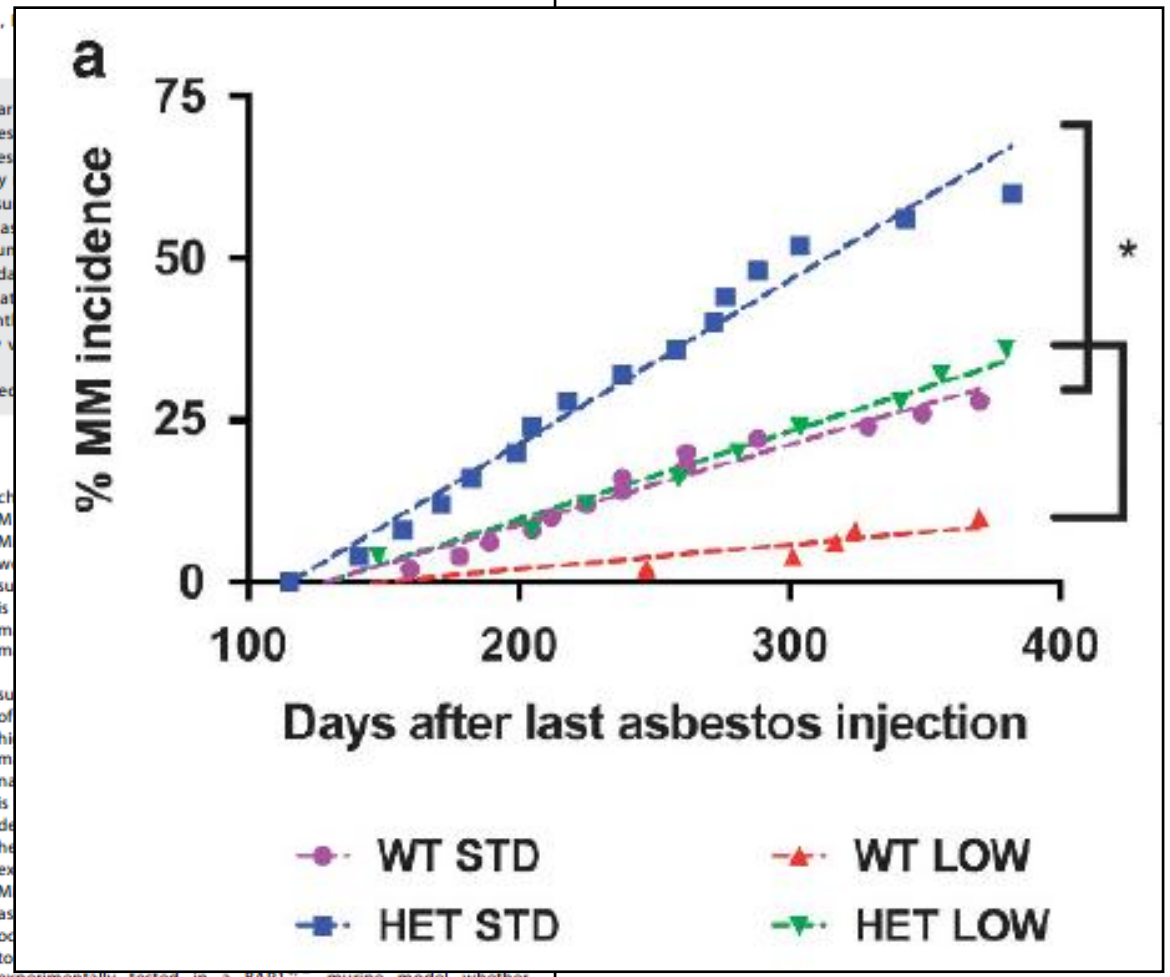
SHORT COMMUNICATION

Minimal asbestos exposure in germline *BAP1* heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma

A Napolitano[1,2], L Pellegrini[1], A Dey[3], D Larson[1], M Tanji[1], EG Flores[1], HI Pass[5], V Dixit[3], H Yang[1] and M Carbone[1]

Germline *BAP1* mutations predispose to several cancers, in particular malignancy generally associated with professional exposure to asbes mesothelioma patients carrying germline *BAP1* mutations were profes *BAP1* mutations might influence the asbestos-induced inflammatory increasing the risk of developing mesothelioma after minimal exposu with their wild-type littermates, BAP1$^{+/-}$ mice exposed to low-dose as inflammatory response, including significantly higher levels of pro-tu levels of several chemokines and cytokines. Consistent with these da mesothelioma after exposure to very low doses of asbestos, doses that suggest that minimal exposure to carcinogenic fibers may significant predisposed individuals carrying germline *BAP1* mutations, possibly

Oncogene (2016) **35,** 1996–2002; doi:10.1038/onc.2015.243; publishe



INTRODUCTION

Malignant mesothelioma (MM) is a deadly cancer usually localized to the pleural and peritoneal linings.[1] In the US and in the UK, ~3200 and ~2500 individuals are diagnosed with and die because of MM each year, respectively.[2,3] About 60–70% of mesotheliomas have been associated with exposure to carcinogenic mineral fibers, mainly asbestos.[1] Nevertheless, the risk of developing MM in high-risk cohorts professionally exposed to asbestos is ~5%, suggesting that other factors contribute to MM pathogenesis.[1] Mineral fibers promote mesothelioma inducing a chronic inflammatory reaction: on one hand, this results in the production of mutagenic oxygen and nitrogen radicals, and on the other hand, it provides damaged mesothelial cells with important survival signals.[4] Although chronic inflammation has been associated with the pathogenesis of several cancers, competent inflammatory cells also provide immunosurveillance, the host's protection process against nascent transformed cells expressing altered antigens.[5] In fact, different functional and phenotypical cell subtypes are associated to anti-tumoral or pro-tumoral immunity.[6] Macrophages (MΦ) can undergo different types of polarization based on the kind and levels of cytokines present in the local tissue environment. Classically activated (M1) MΦ have a pro-inflammatory anti-tumoral phenotype, whereas alternatively activated (M2) MΦ are involved in immunosuppression and tissue repair.[7] Tumor-associated macrophages represent one of the major populations of immune cells infiltrating tumors, and usually acquire functional

experimentally tested in a BAP1$^{+/-}$ murine model whether germline *BAP1* heterozygosity would result in alterations of the asbestos-induced inflammatory response, and whether low doses of asbestos might be sufficient to cause MM.

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Received 14 January 2015; revised 16 March 2015; accepted 20 April 2015; published online 29 June 2015

Kadariya… (2024)

Low Exposures to Amphibole or Serpentine Asbestos in Germline *Bap1*-mutant Mice Induce Mesothelioma Characterized by an Immunosuppressive Tumor Microenvironment

Kadariya, Sementino, Ruan, Cheung, Hadikhani, Osmanbeyoglu, Klein-Szanto, Cai, Testa

CANCER RESEARCH COMMUNICATIONS

AACR American Association for Cancer Research

RESEARCH ARTICLE https://doi.org/10.1158/2767-9764.CRC-23-0423 OPEN ACCESS

Low Exposures to Amphibole or Serpentine Asbestos in Germline *Bap1*-mutant Mice Induce Mesothelioma Characterized by an Immunosuppressive Tumo

Yuwaraj Kadariya[1], Eleonora Sementino[1], Maggie Ruan[1], Mi
Hatice U. Osmanbeyoglu[2,3], Andres J. Klein-Szanto[4], Kathy

ABSTRACT

Asbestos and *BAP1* germline mutations are risk factors for malignant mesothelioma (MM). While it is well accepted that amphibole asbestos is carcinogenic, the role of serpentine (chrysotile) asbestos in MM has been debated. To address this controversy, we assessed whether minimal exposure to chrysotile could significantly increase the incidence and rate of MM onset in germline *Bap1*-mutant mice. With either crocidolite or chrysotile and at each dose tested, MMs occurred at a significantly higher rate and earlier onset time in *Bap1*-mutant mice than in wild-type littermates. To explore the role of gene–environment interactions in MMs from *Bap1*-mutant mice, we investigated proinflammatory and protumorigenic factors and the tumor immune microenvironment (TIME). IHC and immunofluorescence staining showed an increased number of macrophages in granulomatous lesions and MMs. The relative number of CD163-positive (CD163$^+$) M2 macrophages in chrysotile-induced MMs was consistently greater than in crocidolite-induced MMs, suggesting that chrysotile induces a more pro-found immunosuppressive response that creates favorable conditions for evading immune surveillance. MMs from *Bap1*-mutant mice showed up-regulation of CD39/CD73-adenosine and C-C motif chemokine ligand 2 (Ccl2)/C-C motif chemokine receptor 2 (Ccr2) pathways, which together

Introduction

Malignant mesothelioma (MM) is an incurable cancer causally associated with asbestos (1). This inflammation-associated malignancy develops in the mesothelial lining, most often in the pleura and peritoneum, with a latency period of several decades from the initial exposure to asbestos.

Asbestos consists of serpentine (chrysotile) and amphibole minerals. Serpentine fibers have a curved, wavy morphology. In contrast, the amphibole group includes fibers such as crocidolite, which are firm and linear. Amphibole fibers are thought to be much more carcinogenic than chrysotile (2). This is due to the fact that chrysotile is biodegradable and most of it is cleared from the upper respiratory tract, as well as because it has a lower toxicity potential compared

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doi: 10.1158/2767-9764.CRC-23-0423

Results

Mice with Heterozygous Germline Mutations of *Bap1* are Markedly Susceptible to MM Upon Minimal Exposure to Either Crocidolite or Chrysotile Asbestos

MMs developing in *Bap1*$^{+/-}$ and *Bap1*$^{+/+}$ littermates injected with chrysotile or crocidolite typically were diffuse peritoneal lesions sometimes accompanied by ascites. An anatomic image of a chrysotile-induced MM in a *Bap1*$^{+/-}$ mouse is shown in Supplementary Fig. S1.

Betti…(2018)

Sensitivity to asbestos is increased in patients with mesothelioma and pathogenic germline variants in *BAP1* or other DNA repair genes

Betti, Aspesi, Ferrante, Sculco, Righi, Mirabelli, Napoli, Rondón-Lagos, Casalone, Lutati, Paola Ogliara, Bironzo, Gironi, Savoia, Maffè, Ungari, Grosso, Libener, Boldorini, Valiante, Pasini, Matullo, Scagliotti, Magnani, Dianzani

RESEARCH ARTICLE

Sensitivity to asbestos is increased in p
mesothelioma and pathogenic germlin
or other DNA repair genes

Marta Betti[1] | Anna Aspesi[1] | Daniela Ferrante[2] | Ma
Dario Mirabelli[4] | Francesca Napoli[3] | Milena Rondón-La
Francesca Vignolo Lutati[8] | Paola Ogliara[8] | Paolo Biron
Paola Savoia[1] | Antonella Maffè[10] | Silvana Ungari[10] |
Roberta Libener[12] | Renzo Boldorini[13] | Michele Valiant
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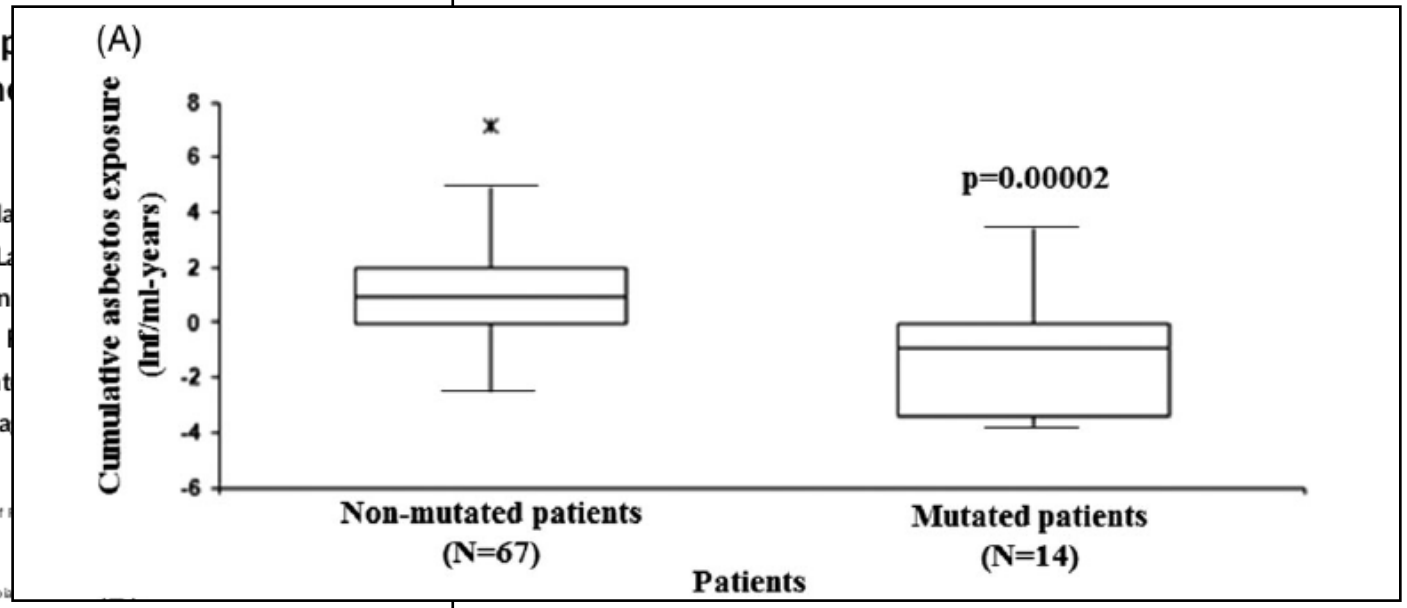
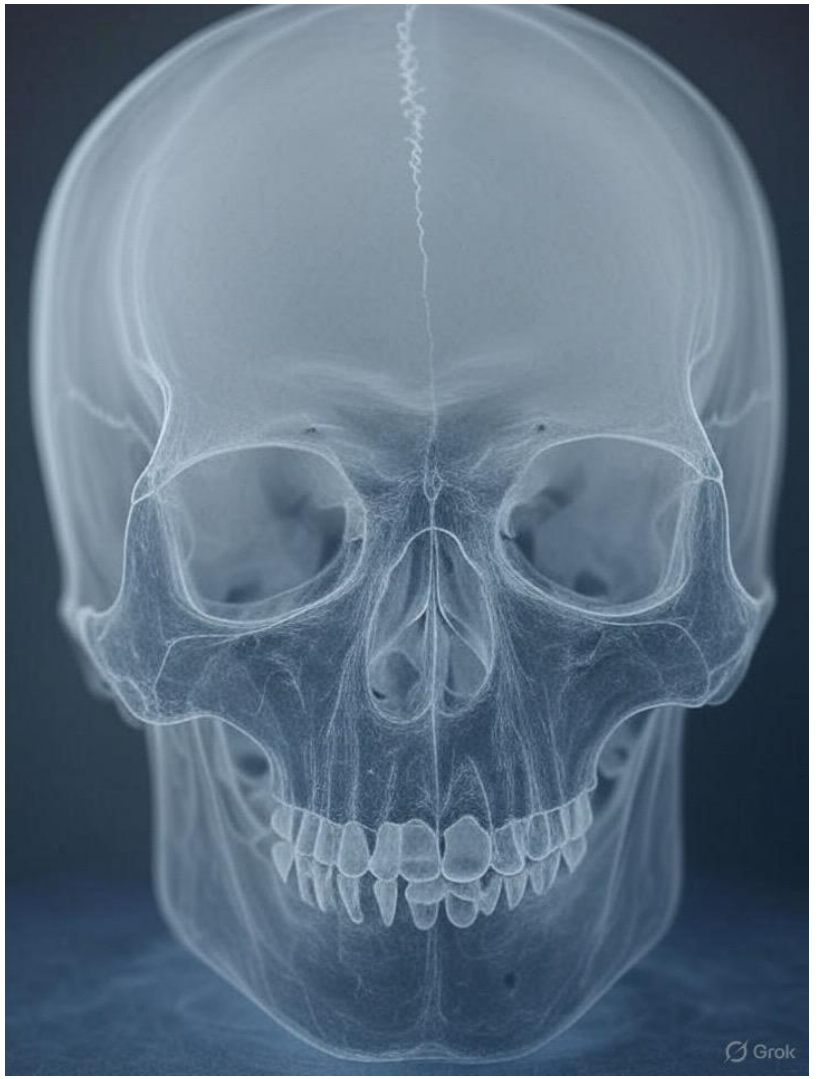
Abstract
Pathogenic germline variants in the *BAP*
called *BAP1* tumor predisposition syndro
tion to mesothelioma, melanoma, renal
Other genes that may predispose to me
tos exposure has often been reported i
and germline variants in *BAP1*, but this e
for germline variants in *BAP1* among 25
marize the prevalence of these variant
tumors recruited over a 5-year period, ar
with MPM and pathogenic germline vari
of 67 patients without germline variants
We report here a new pathogenic germli
pathogenic germline variants in *BAP1* was 7.7% among patients with familial MPM (3/39).

Betti Marta and Aspesi Anna contributed equally to this study

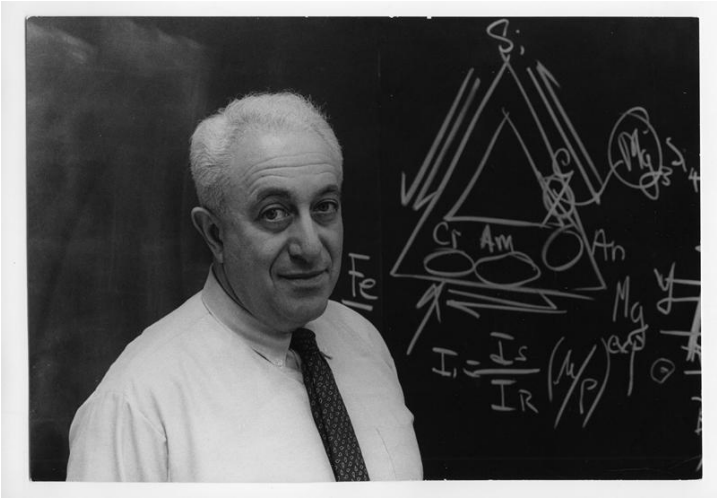


In this article, we report precise quantification of asbestos exposure in four MPM patients with pathogenic germline variants in *BAP1*. Our series showed that these patients had very low cumulative asbestos exposure. When we pooled these patients with patients carrying pathogenic germline variants in other tumor suppressor genes and compared them to patients that did not carry variants in 94 cancer-predisposing genes, we found that patients with pathogenic germline variants had a lower cumulative asbestos exposure than patients without variants (P = .00002).

Highly Susceptible



Highly Susceptible



“Statistics are people with the tears wiped away.”

Nielsen… (2025)

Bayesian analysis of the rate of spontaneous malignant mesothelioma among BAP1 mutant mice in the absence of asbestos exposure

Nielsen, Hsu, Zapata, Ciavarra, and van Zyl

OPEN

Bayesian analysis of the rate of spontaneous malignant mesothelioma among *BAP1* mutant mice in the absence of asbestos exposure

Dahlia M. Nielsen[1✉], Mei Hsu[2], Michael Zapata III[2], Giovanni Ciavarra[3] & Leonel van Zyl[2]

Cancers of the mesothelium, s
solely to exposure to asbestos
that approximately 20% of all
(germline) pathogenic mutati
in humans makes it difficult to
biological effects. This has cre
However, since the molecular
disease, this disconnect betw
inbred mouse strains that har
have focused on the effect of
absence of exposure understu
rate of spontaneous MM amo
of asbestos exposure. We leve
(HCD) to allow us to improve
Our Bayesian analyses indicat
mice is substantially larger th
study findings that mesotheli
independently of asbestos ex

Keywords Mesothelioma, As

Malignant mesothelioma (MM)
known as the mesothelium[1]. In
were reported with 11,747 dea
care annually[3]. Understanding
diagnosis and/or improved trea
mesothelioma, particularly pleu
overall mesothelioma incidence
of easily crushed or crumbled a
U.S.[5–7]. However, despite these
as well as peritoneal mesotheli
reports suggest that exogenous
with most forms of cancer, it is
to the initiation and progression of MM. Germline mutations in key cancer related genes have been shown to play a pivotal role in MM risk in both exposed and non-exposed cases[13–27]. The discovery of the *BAP1* Tumor Predisposition Syndrome[28,29], in particular, was a key step towards understanding the biological basis of MM. Mutations in *BAP1* have been linked to a number of human malignancies, including MMs[10,13,23,28,30–34].

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Study	MM cases	Total # of animals	% MM
*Kadariya et al., 2016[37]	0	43	0.00
Mahler et al., 1996[67]	0	243	0.00
Radaelli et al., 2009[68]	0	64	0.00
Panchenko et al., 2016[69]	0	69	0.00
Huang et al., 2008[70]	0	234	0.00
Giknis and Clifford, 2005[71]	6	6236	0.10
Maita et al., 1988[72]	2	1781	0.11
Total	8	8627	0.09

Giknis and Clifford (2005)

Spontaneous Neoplastic Lesions in the Crl:CD-1(ICR) Mouse in Control Groups from 18 Month to 2 year Studies.

Table 5: Incidence of Neoplasms by Study for Selected Organs / Males

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Study Duration (wks)	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78
LIVER	53	47	50	49	50	59	50	60	50	47	50	50	68	50	59	60	50	50	50	49	50	50	60	50	50	60
Hepatocellular Adenoma	4	7	5	7	3	7	3	3	2	2	5	2	11	3	9	3	12	6	5	2	3	3	3	6	6	8
Hepatocellular Carcinoma	4	6	1	1	2		1	4	1	2	1	1	6	2	2	2	3	4		4	2	2	1		1	2
Hemangioma										1							1									
Hemangiosarcoma	2						2				2			1		1	2		2							
LUNG	53	47	50	49	50	58	50	60	50	48	50	50	69	50	59	60	50	50	50	49	50	50	60	50	50	60
Adenoma, Alveolar/Bronchiolar	6	9	9	10	1	5	6	6		10	3	8	15	6	8	3	13	7	1	2	2	2	4	8	9	7
Adenocarcinoma, Alveolar/Bronchiolar	1	1	3	1	4	2	5	3		**3**			16		1		3	5	6	3	**3**	**3**	4	**3**	1	
Mesothelioma, Malignant																										
WHOLE BODY/MULTIPLE ORGAN	53	47	50	49	50	59	50	60	50	46	50	50	69	50	59	60	50	50	50	50	50	50	50	50	50	60
Lymphoma, Malignant	2	2	1	4	1	**3**	1	2	2	2		1	1	1	2		7		1		1					**3**
Lymphoma, Lymphocytic								2				2	2	1	1							1	1			
Leukemia, Granulocytic																							1			
Hemangiosarcoma																										
Histiocytic Sarcoma							1	1					2		1					1						1
Mast Cell Tumor, Malignant	1						1																			

Table 5: Incidence of Neoplasms by Study for Selected Organs / Males (cont'd)

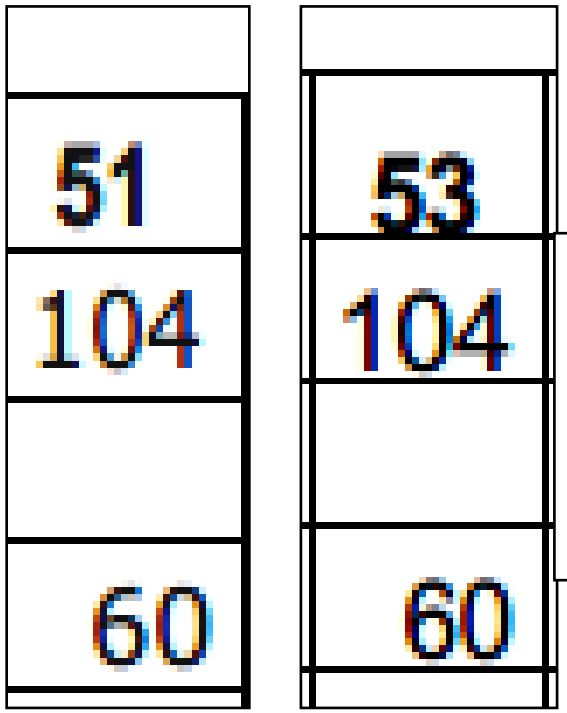
Study Identification	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Study Duration (wks)	97	100	104	104	104	104	104	104													104	104	104	104	104	104
LIVER	50	49	60	67	60	59	70	50													60	60	65	70	60	55
Hepatocellular Adenoma	7	3	3	4	15	4	3	8													7	10	6	2	11	3
Hepatocellular Carcinoma	**3**	5	4	10	2	8	4	3													2	7	6	7	9	2
Hemangioma								2																		
Hemangiosarcoma	2		3	1	1	2	3														3		5	6	4	1
LUNG	50	49	60	69	60	60	70	50													60	60	65	70	60	55
Adenoma, Alveolar/Bronchiolar	14	12	5	11	2	6	8	4													5	11	11	14	5	7
Adenocarcinoma, Alveolar/Bronchiolar	13	6		6	3	6	12	7													8	6	4	8	8	6
Mesothelioma, Malignant																									3	
WHOLE BODY/MULTIPLE ORGAN	49	49	60	70	60	60	70	50	65	50	50	65	65	60	60	60	70	50	50	90	60	60	65	70	60	55
Lymphoma, Malignant	3		4	2	6	13	5		1		2	4	5	3	5	3	2	4	1	5	5	7	2	7	4	2
Lymphoma, Lymphocytic	1	2								1																
Leukemia, Granulocytic	1		1				1								1	1					1			1		
Hemangiosarcoma									3		1	5	3	4	1			6	6							
Histiocytic Sarcoma	2			2			2	2		1	4	1	4	2	2	1	4			1	3	3	2	1	2	
Mast Cell Tumor, Malignant											1						1									

Table 6: Incidence of Neoplasms by Study for Selected Organs / Females

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Study Duration (wks)	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	91	94
LIVER	52	49	50	47	49	60	50	57	49	47	50	49	70	48	59	60	50	49	49	50	50	59	50	50	58	85	59
Hepatocellular Adenoma					1	1	1											1	1	1							
Hepatocellular Carcinoma			1										1			2		1	1		1						1
Undifferentiated Carcinoma																											
Hemangioma																							1				
Hemangiosarcoma	2					1					1	1					1						1				
LUNG	52	49	50	48	49	60	50	57	50	48	50	49	70	49	59	60	50	50	50	50	50	59	50	50	60	89	59
Adenoma, Alveolar/Bronchiolar	3	6	6	5	2	2	5	6		3	5	5	11	3	6	5	8	3	2	2	2	2	6	2	1	2	3
Adenocarcinoma, Alveolar/Bronchiolar		3	4	1	3	2	4	2	4	5		1	7		2		3	6	1	2		5	1	1		3	
Mesothelioma, Benign																											
Mesothelioma, Malignant																											
WHOLE BODY/MULTIPLE ORGAN	52	49	50	48	50	60	50	58	50	47	50	49	70	49	59	60	50	50	50	50	50	59	50	50	60	116	60
Lymphoma, Malignant	2	2	7	6	1	5	7	10	2	5	4	2		3		6	4	3	1	3	**3**	9		5			1
Lymphoma, Lymphocytic								5					9										1				
Histiocytic Sarcoma		1	3	1				1		3	1		2	2	1	2	2		2	1	1	3	1		9		2
Leukemia, Granulocytic														2									2				
Mast Cell Tumor, Malignant																											
Hemangioma													1														1
Hemangiosarcoma													2														1

Table 6: Incidence of Neoplasms by Study for Selected Organs / Females (cont'd)

Study Identification	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Study Duration (wks)	94	97	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
LIVER	75	50	50	60	70	58	117	59	70	50	65	51	50	65	65	60	41	59	70	50	50	60	70	60	65	60	55
Hepatocellular Adenoma	1	1				1	1		1			4	1	1	1	1	3	2		2	1	1	2			1	
Hepatocellular Carcinoma				2	1	2		1	3						1								1			1	
Undifferentiated Carcinoma											1																
Hemangioma		1		1							1					1					1				1		1
Hemangiosarcoma				2	1	1	2	1	3													3		1	4		
LUNG	75	49	50	60	70	60	130	60	70	50	65	51	50	65	65	6							70	60	65	60	55
Adenoma, Alveolar/Bronchiolar	9	6	7			2	9			5	4	2	8	8	10	1							10	10	16	6	10
Adenocarcinoma, Alveolar/Bronchiolar		9	3			5	1			4	6		3	**3**	2								12	4	5	4	2
Mesothelioma, Benign																											
Mesothelioma, Malignant																										2	
WHOLE BODY/MULTIPLE ORGAN	75	50	50	60	70	60	130	60	70	50	65	51	50	65	65	60	60	60	75	50	50	60	70	60	65	60	55
Lymphoma, Malignant	6	2	**3**	12	35	10	11	17	13	7	3		5	8	10	5	8	6		16	6			12	10	14	7
Lymphoma, Lymphocytic			6									14		1									8				
Histiocytic Sarcoma	3		3	5	5	1	9	11	2	3	8	2	4	5	7	4	3			3	6	10	7	4	7	5	2
Leukemia, Granulocytic						1	1							1													
Mast Cell Tumor, Malignant													1									1			1		
Hemangioma	2																										
Hemangiosarcoma										4	2		1			2	4			**3**	6						



Number of Studies (# Studies)

This is the number of studies in which a particular tissue/organ was examined. In this publication, the number of studies is usually 52 for males and 54 for females. It is important for the reader to realize that some of the studies reported in this document were performed in only males or females and occasionally a specific tissue/organ was not examined in a particular study. The study identification number for females does not necessarily correlate with the same study identification number in males.

Kadariya… (2025)

Spontaneous Mesotheliomas in Germline Bap1 Heterozygous Mice from Different Genetic Backgrounds

Kadariya, Zhang, Sementino, Ross, and Testa

cancers

Article

Spontaneous Mesotheliomas in Germ
Mice from Different Genetic Backgr

Yuwaraj Kadariya [1,†], Li Zhang [2,†], Eleonora Sementino [1], Eric Ros

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Simple Summary

Individuals carrying a germline *BAP1* m
lioma. In mice, there is limited inform
Bap1 heterozygous mutations alone ca
susceptible to even minimal asbestos e
neous mesothelioma development ove
and non-mutant, wild-type littermate
mesotheliomas were detected in 2/3
sive analyses were performed using
mice and multiple statistical framewo
in *Bap1*-mutant mice differs from that
significant difference in the probabilitie
and wild-type mice. Thus, we cannot
significantly increased risk of mesothe

check for updates

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Abstract

Background: *BAP1* mutation carriers a
In mice, there is limited data and co
gous mutations alone cause mesothe
lioma incidence is observed in *Bap1*-m
Methods: To address this issue, we inv
over the lifetime of a large cohort of *Ba*
genetic backgrounds. To determine
mice is significantly increased compa
using frequentist and Bayesian frame
probability of disease occurrence, a no
whereas an informative prior for the W
the animals' lifetimes. Multiple strate
and infer the informative prior, inclu
ability of mesothelioma across histori
predictive priors derived from histor
comparison was made using odds ra
taneous mesotheliomas were detecte
various genetic backgrounds. Using four statistical approaches, the results did not detect a
significant difference in the probabilities of mesothelioma occurrence between *Bap1*-mutant

There are several limitations in the assessment by Nielsen et al. [19], including the fact that the WT mice in their HCD were not housed at the exact location or under the same conditions as the animals used for comparison, i.e., the *Bap1*-mutant mice from the report by Kadariya et al. [5]. As reviewed by Everitt [23], the incidence of spontaneous tumors can be influenced by many factors, including genetic background, diet, housing conditions, infection, hormones, age, etc. In addition, all mice used in our report [5] were in an FVB/N background, whereas only 7% of the mice in Nielsen and colleagues' HCD were FVB/N mice, with the remaining 93% being a different strain (CD-1 mice). This is noteworthy because different mouse strains can have significantly different rates and types of spontaneous tumors (reviewed in [24]). Furthermore, in one of the studies included in the HCD used by Nielsen et al. [19], from an extensive report by Giknis and Clifford [25], more than 2716 CD-1 mice were followed for only 78 weeks. No mesotheliomas were observed then, whereas 6 of 3,520 CD-1 mice monitored for up to 104 weeks developed spontaneous mesotheliomas. In another report in the HCD used by Nielsen and colleagues [19], Maita et al. [26] identified mesotheliomas in 2 of 1,781 CD-1 mice used in control groups from eleven 2-year carcinogenicity studies. This research group also reported that the average mortality of male and female CD-1 mice at about 2 years of age was 66.4% and 63.3%, respectively, indicating that about 35% of their CD-1 mice were not followed until the end of life to determine if they might have developed additional spontaneous tumors, including mesotheliomas. Since spontaneous mesotheliomas appear to occur later in life in CD-1 mice [25], the reported incidence of these tumors in the HCD used by Nielsen et al. [19] is likely to be underestimated.

cancers

MDPI

Article

Spontaneous Mesotheliomas in Germline *Bap1* Heterozygous Mice from Different Genetic Backgrounds

Yuwaraj Kadariya [1,†], Li Zhang [2,†], Eleonora Sementino [1], Eric Ross [2] and Joseph R. Testa [1,*]

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† These authors c

Simple Summa

Individuals carr
lioma. In mice,
Bap1 heterozyg
susceptible to ev
neous mesothel
and non-mutan
mesotheliomas
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mice and multi
in *Bap1*-mutant
significant diffe
and wild-type
significantly inc

Abstract

Background: *B*
In mice, there i
gous mutations
lioma incidence
Methods: To ad
over the lifetime of a large cohort of *Bap1*-mutant and wild-type (WT) mice across several genetic backgrounds. To determine if the incidence of mesotheliomas in *Bap1*-mutant mice is significantly increased compared to WT mice, we performed statistical analyses using frequentist and Bayesian frameworks. In the Bayesian framework, to model the probability of disease occurrence, a non-informative prior was used for *Bap1*-mutant mice, whereas an informative prior for the WT group was derived from historical data spanning the animals' lifetimes. Multiple strategies were employed to incorporate historical data and infer the informative prior, including a meta-analysis, assuming a consistent probability of mesothelioma across historical datasets, and applying Bayesian meta-analytic predictive priors derived from historical data. Posterior distribution was used, and a comparison was made using odds ratio, risk difference, and risk ratio. **Results:** Spontaneous mesotheliomas were detected in 2/329 *Bap1*-mutant and 0/227 WT mice from various genetic backgrounds. Using four statistical approaches, the results did not detect a significant difference in the probabilities of mesothelioma occurrence between *Bap1*-mutant

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5. Conclusions

Using multiple statistical approaches, our results did not detect a significant difference between the probabilities of mesothelioma occurrence in *Bap1*-mutant and WT mice. Thus, we cannot conclude that germline *Bap1* heterozygous mice have an increased risk of spontaneous mesothelioma compared to WT mice. However, given that even trace amounts of asbestos induce a high incidence of mesothelioma in *Bap1*-mutant mice compared to WT mice [4,6], this suggests that germline *Bap1* mutations create a highly susceptible setting for a gene-environment interaction with deadly consequences. This aligns with the interplay between mutant cancer predisposition genes and asbestos, particularly low exposures, which have been documented in mesothelioma patients [27,28].

Carbone… (2025)

Clinical and Pathologic Phenotyping of mesotheliomas developing in carriers of Germline BAP1

Michele Carbone, MD, PhD, Michael Minaai, BS, Muaiad Kittaneh, MD, MBA,Thomas Krausz, MD, Markku M. Miettinen, MD, Qiang Pan Hammarström, MD,PhD, Lennart Hammarström, MD, PhD, Hassan Abolhassani, MD, MPH, PhD, IanPagano, PhD, Ronghui Xu, MS, Flavia Novelli, PhD, Giovanni Gaudino, PhD, Sandra Pastorino, PhD, Kavita Y. Sarin, MD, PhD, Robert T. Ripley, MD, Harvey I. Pass, MD,David S. Schrump, MD, MBA, Haining Yang, MD, PhD

Clinical and Pathologic Phenotyping of mesothelioma developing in carriers of Germline *BAP1* Mutations

Journal of Thoracic Oncology

Study design, patients and informed consent.

The first individuals from two families were enrolled in 1999, the remaining individuals/families joined our study from 2000-2023. The inclusion criteria were: (1) first- or second-degree relatives with mesothelioma; (2) proband or one first- or second-degree relative diagnosed with UVM, cutaneous melanoma, and ccRCC—malignancies frequent in carriers of *BAP1*$^{+/-}$; (3) history of multiple cancers (any cancer) in the majority of first- and second-degree relatives; and (4) early MM onset, age <50 years; the incidence of mesothelioma before age 50 is very rare and suggestive of genetic predisposition or environmental exposure since childhood.[5] Some of these patients contacted us directly, some were referred by colleagues and some by the Mesothelioma Association Research Foundation, a nonprofit organization. 84/238 *BAP1*-mutant carriers were diagnosed with mesothelioma. With one exception, none had a work-related or environmental history of asbestos-exposure and the clinical records did not report objective medical evidence of asbestos exposure, i.e., absence of bilateral pleural plaques, absence of bilateral lung fibrosis and absence of ferruginous bodies detected histologically. This objective medical evidence of asbestos exposure is commonly seen in asbestos-exposed individuals.[22,23] We collected the family history, clinical records, and prepared and updated family pedigrees over time. For 23/84 patients diagnosed with mesothelioma, we either diagnosed this malignancy or reviewed the histology and confirmed this diagnosis. Written informed consent was obtained from all patients. Patient information and samples were collected and used in accordance with the Declaration of Helsinki (1995, revised 2013) and approved by the University of Hawaii Institutional Review Board (IRB no. CHS14406).

5. Novelli F, et al. PNAS 2021;118.
6. Bononi A, et al. PNAS 2023;120:e2217840120.


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to keep skin dry & soft
pure cornstarch
silky soft skin

Carbone Deposition

August 21, 2025 at 97

22 **Q.** Okay. Did you ask anyone about talc
23 exposures, whether it be industrial or cosmetic talc?
24 **A.** Absolutely not.

Carbone Deposition

August 21, 2025 at 54

Q. Okay. And would it matter to you in your evaluation of the accuracy of the indications of whether someone was exposed to asbestos or not that these doctors did not ask any of these patients whether or not they were exposed to talcum powder or potentially asbestos-contaminated talcum powder products?

A. Look, to the best of my knowledge, nobody was asked that question, because the issue that talc cause mesothelioma is an issue that belongs to the courtroom. But I've never seen that discussed in any mesothelioma meeting or any paper. So, no, nobody would ask that, I think.

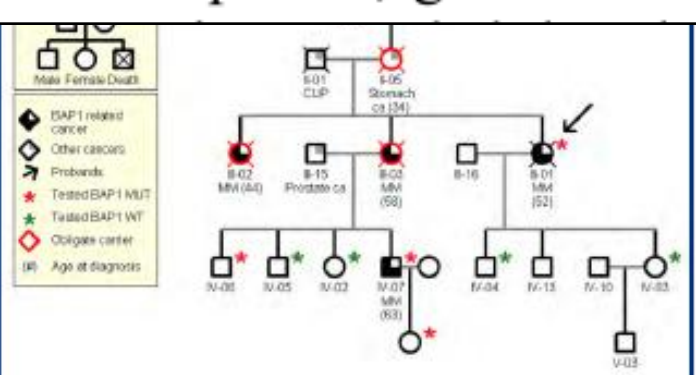
Clinical and Pathologic Phenotyping of mesothelioma developing in carriers of Germline *BAP1* Mutations

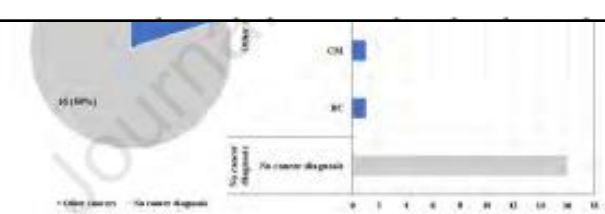
Journal of Thoracic Oncology

Introduction - The *BAP1* Cancer Syndrome and Mesothelioma (MM)

We discovered that familial MM was transmitted in a Mendelian fashion[1]; that germline *BAP1* mutations caused MM[2] and other cancers[3]; and we elucidated mechanisms of BAP1 activity.[4-6]

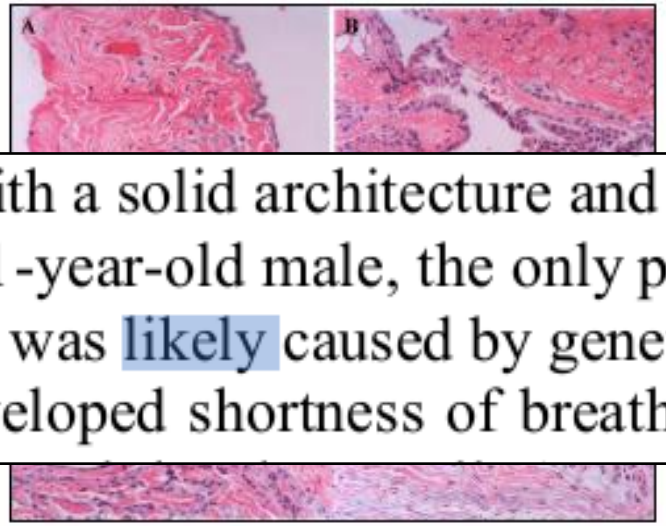
Results





There were 84 cases of MM and 22 cases of UVM among the 238 *BAP1*$^{+/-}$ carriers, 8 of them developed both malignancies. None of the 123 first and second-degree relatives with WT *BAP1*$^{+/+}$ were diagnosed with MM [$\chi^2(1) = 56.6$, $p < 0.0001$], or with UVM [$\chi^2(1) = 92.1$, $p < 0.0001$].

MM in *BAP1* mutant carriers is a different disease compared to asbestos induced MM



Characteristic Histology (A-C), most patients have three-cavitary diffuse mesothelial hyperplasia and (D), focal areas of low-grade germline-mutant-*BAP1*-associated mesothelioma (L-BAM). L-BAM are superficially invasive mesothelial neoplasms that show BAP1 loss. Most microscopic L-BAMs do not progress, if they become visible on imaging these neoplasms should be removed. This patient was treated with extrapleural pneumonectomy at age 43 and died 19.5 years later of a stroke. MM never recurred.

CONCLUSION: Compared to sporadic MM, MM developing in *BAP1*$^{+/-}$ carriers are a different disease, biologically, histologically and clinically: these patients require a tailored clinical approach. Because these patients are at high risk of developing multiple cancers, they benefit from annual screening for early cancer detection that can be life-saving.

IASLC

Carbone M, Minaai M, et al. *J Thorac Onc* (2025)

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2. Testa JR, et al. Nature genetics 2011;43:1022-1025.
3. Carbone M, et al. Cancer discovery 2020;10:1103-1120.
4. Bononi A, et al. Nature 2017;546:549-553.
5. Novelli F, et al. PNAS 2021;118.
6. Bononi A, et al. PNAS 2023;120:e2217840120.

G and H). This mesothelioma was of the epithelioid type with a solid architecture and caused the patient's demise within 5 months. The third patient was a 51-year-old male, the only patient with a work-related history of exposure. Thus, this mesothelioma was likely caused by genetics and by asbestos exposure, gene x environment interaction. He developed shortness of breath and chest

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