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## **Genetic predisposition for malignant mesothelioma: a concise review.**

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## **Abstract**

Malignant mesothelioma (MM) is an aggressive cancer associated with asbestos exposure. Studies of familial malignant pleural mesothelioma (MPM) have suggested the existence of a genetic predisposition. Information on the role of genetic risk factors in the development of MM has been growing in the last years, and both low- and high-risk genetic factors have been identified, but none has ever been shown to induce MM in the absence of asbestos exposure.

Low-risk genetic factors have been identified in studies that systematically analyzed the whole genome. These low-risk factors alone carry a relative risk of MPM that is 10- to 15-fold lower than that carried by asbestos exposure; however, a large number of these factors in combination may increase the impact of asbestos exposure.

High-risk factors are truncating variants in *BAP1* and other genes belonging to DNA repair pathways. Heterozygous germline variants in these tumor suppressor genes may favor carcinogenesis after the occurrence of a second somatic variant that impairs the wild-type allele, causing genetic instability, due to the suppression of a specific DNA repair pathway, and transformation.

This genetic predisposition may have translational consequences, as it may predict patient response to drugs that induce tumor-specific synthetic lethality.

## **Abbreviations**

MM, malignant mesothelioma; MPM, malignant pleural mesothelioma; RR, relative risk; NGS, next generation sequencing; SNPs, single nucleotide polymorphisms; BER, base excision repair; GWAS, genome-wide association study; OR, odds ratios; *BAP1*-TPDS, *BAP1*-Tumor Predisposition Syndrome; MBAITs, Melanocytic *BAP1*-mutated atypical intradermal tumors; NSCLC, non-small cell lung cancer; HRR, homologous recombination repair; HBOC, hereditary breast ovarian cancer syndrome; XP, xeroderma pigmentosum; NER, nucleotide excision repair; MMR, Mismatch DNA Repair; HNPCC, hereditary nonpolyposis colorectal cancer; alt-NHEJ, alternative non-homologous end-joining; NHEJ, non-homologous end-joining; SSB, single strand break; DSB, double strand break; FA, Fanconi Anemia; PTV, pathogenic truncating variant, PARPi, PARP inhibitor.

## **Keywords**

Mesothelioma

Genetic risk factors

DNA repair genes

BAP1

Cancer predisposition syndromes

## **1. Introduction**

MM is an aggressive tumor that affects the lining membrane of the serous cavities of the body, including the pleura, peritoneum, pericardium, and the vaginal tunic of the testicles; the most common is MPM. Most cases of MPM are due to exposure to asbestos, or other fibrous minerals, such as erionite, fluoro-edenite, winchite and richterite [1,2].

A very limited proportion of MPM estimated in Italy in the range from 1.7% to 4.7% is caused by exposure to ionizing radiation for diagnostic or therapeutic purpose [3,4]. Current estimates of the incidence of MM show large variations among the different countries, with the highest incidence rates (Age standardized rates over 30/million) observed in cancer registries from Great Britain, Australia, Germany, Italy and other industrialized countries [5,6]. Recent data show that despite the main risk factor being identified, the reduction in the use of asbestos and considerable efforts made to clear asbestos from the environment starting in some countries since the early 1980s, the incidence of the disease so far has failed to decline because of the extremely long latency. However the first signs of a reduction of incidence are being observed [7].

Asbestos has been widely used for decades all over the world. Indeed, it is very difficult to prove that an individual has never been exposed to asbestos [8]. A direct correlation has been shown between the amount of asbestos exposure, the latency and the risk of MPM [8] Nevertheless, only 10-17% of individuals highly exposed to asbestos develop MPM [9]. This observation has led to the hypothesis of an individual response that modifies the effect of asbestos exposure. The possible role of genetic risk factors was also supported by the description of families with several genetically related cases, including MM and other neoplasms [10]. An early description of familial aggregations of MPM reported a high incidence of mesothelioma in two villages of Cappadocia, whose buildings were built using material from erionite-rich boulders [11,12]. Several clusters have also been described in Italy [13–15]. Such familial aggregation may be due to co-exposure to asbestos, as in the case of “conjugal MPM”, which is attributed to women handling and washing the work clothes of spouses exposed to asbestos at work [14,16].

In the case of MPM, a genetic risk factor is defined as a DNA variant that can modify the effect of asbestos exposure on the risk of MPM. Classically, genetic factors are divided into three types based on their RR: low-risk ( $RR < 1.5$ ), moderate-risk ( $RR 1.5-5$ ) and high-risk ( $RR > 5$ ) factors.

The aim of our study was to conduct a literature review on genetic risk factors predisposing to MM, discussing separately those conferring a low risk and those conferring a moderate/high risk. The literature search was carried out in the NCBI Pubmed database using the keywords “*BAP1* germline mutations/variants and mesothelioma”, “genetic risk factors predisposing to mesothelioma”, “germline mutations predisposing to mesothelioma”.

## **2. Low risk genetic factors**

Low-risk genetic factors are those involved in multifactorial diseases, also called complex diseases [17]. They are DNA variants that show a statistically significant association with the disease in case-control studies. Sometimes the variant can modify the function of a gene in different ways; other times the variant is simply located close to the real pathogenic variant and co-inherited.

In the pre-genomic era, i.e. before the mapping and sequencing of the human genome and the general diffusion of the NGS technique, studies on low-risk genetic factors that could predispose an individual to MPM used a candidate gene approach driven by a biological hypothesis [18–20]. In particular, the observation that patients with inherited defects in DNA repair genes were susceptible to a constellation of tumors, and the identification of reduced DNA repair activity in the lymphocytes of patients with cancer, suggested that DNA repair genes might play a role in one’s predisposition to MM [15]. Thus, SNPs in several DNA repair genes were studied in the germline genome of MPM patients, but resultant associations were inconsistent, probably due to the small number of MPM patients and controls analyzed. An interesting association was observed between MPM and a missense variant in *XRCC1*, a gene encoding for a protein involved in the BER pathway that repairs single-strand breaks due to reactive oxygen species [20]. The BER pathway is directly involved in the repair of genetic lesions due to asbestos fibers. A detailed review of

association studies on genetic SNPs in MPM was previously published [19]. Because of the low RR, studies must have large panels of MPM patients and controls if they are to detect these risk factors. These are often GWAS, in which thousands of variants are simultaneously screened to identify those that are differently represented in MPM patients and controls. To obtain large sample sizes, international collaborations are needed, especially when dealing with rare diseases like MPM. To-date, two GWAS on MPM have been performed: one in the Italian and one in the Australian population [23,24]. The Italian GWAS carried out by our research group included 407 MPM patients and 389 controls from Casale Monferrato, Genoa, and Turin. The Australian GWAS included 428 MPM patients and 778 controls. Each study carefully evaluated asbestos exposure in both groups and used the other for validation. The two studies identified different SNPs associated with MPM status (Table 1a and 1b; Figure 1A), with ORs ranging from 0.54 to 2.37. Each variant alone carries a very low risk, which is 10- to 15-fold lower than that carried by asbestos exposure [8], but interaction was observed between asbestos exposure and several of the SNPs identified in our Italian GWAS and the same study also suggested the joined contribution of different SNPs to the interaction [25]. This interaction analysis was conducted with both additive and multiplicative models, since we did not have experimental or theoretical reasons to choose either. Additive interaction is present when the joint effect of the two risk factors is different from the sum of the individual effects, whereas multiplicative interaction is present when the joint effects of the two risk factors differ from the product of the individual effects [26]. We found that six SNPs (rs1508805, rs2501618, rs4701085, rs4290865, rs10519201, rs763271) deviated from the additive model; interestingly, four of them (rs1508805, rs2501618, rs4701085, rs10519201) also deviated from the multiplicative model. This supports their role in modulating the effects of asbestos exposure. Moreover, rs7632718 is localized within *SLC7A14*, a gene located in a region that has been found to be frequently duplicated in the genome of MPM patients [27]. It is noteworthy that an interaction, although not statistically significant, was also found for rs73034881, which is localized in a region that encompasses *FOXK1*. This gene is a suggestive risk factor because it encodes for a

transcription factor that physically interacts with BAP1 (Figure 1B), the first high-risk genetic factor for MPM. *FOXK1* is located in a region that was identified as associated to MPM both in the Italian and the Australian GWAS [23,24] and was found hypomethylated in MPM tissues [28] (Figure 1B).

### **3. High and moderate risk genetic factors**

The most studied genetic factor carrying a high risk is *BAP1*. Other genes carrying a high or moderate risk are reported in Table 2 and Figure 2A.

#### **3.1 *BAP1*-tumor predisposition syndrome**

Germline variants in *BAP1* characterize *BAP1*-TPDS (MIM#614327), which is an autosomal dominant disease (i.e. each patient is heterozygous for a germline pathogenic mutation) [29,30]. Individuals with *BAP1*-TPDS have a high risk of developing a constellation of tumors, including mesothelioma, cutaneous and uveal melanoma, clear cell renal carcinoma, and basal cell carcinoma (Table 2). Moreover, they develop peculiar skin tumors, called atypical Spitz tumors or MBAIT, which may lead to a diagnosis of *BAP1*-TPDS [31]. Patients with uveal melanoma and germline variants in *BAP1* have a bad prognosis [29,32], whereas patients with mesothelioma and germline variants in *BAP1* seem to have a longer survival than those without these variants [33–35]. So far, only 182 families with *BAP1*-TPDS have been identified, but the penetrance of the defect has not yet been calculated [30–33,35–50]. On the other hand, it is well known that these patients may develop more than one tumor.

Mesothelioma is the second most frequently reported cancer in patient with *BAP1*-TPDS after uveal melanoma [29,40]. So far, 77 families with this tumor have been reported [39,50]. Age at onset of MPM in patients with *BAP1*-TPDS is overall earlier than that in patients without this syndrome, but as observed in environmentally exposed patients, compared to occupationally exposed patients [33,35]. Most patients with *BAP1*-TPDS develop MPM, but peritoneal mesothelioma has also been reported [27,28,30]. Interestingly, peritoneal mesothelioma has been



identified more frequently in women with a germline variant in *BAP1* compared to the general population, in which peritoneal mesothelioma is more likely to occur in men [40].

The prevalence of *BAP1-TPDS* among patients with familial MPM varies between 6% and 7.7% [28,31], which is higher than the prevalence observed in sporadic cases (<1%) [27,32,33]. Other tumors that have been reported in patients with *BAP1-TPDS* include breast cancer [23,25,34,35], cholangiocarcinoma [25,35,36], meningioma [43–46], neuroendocrine tumors [37,40], NSCLC [32,44,47,48], thyroid carcinoma [41,49], and mucoepidermoid carcinoma of the tongue [34] and others. Larger numbers of *BAP1* mutation carriers should be studied to exclude a coincidental association.

### **3.2 The BRCA1 associated protein-1 (*BAP1*)**

*BAP1* (#MIM 603089) is located on 3p21.1 and encodes for a tumor suppressor gene that is frequently mutated in cancer genomes, including mesothelioma [53]. Its protein is a ubiquitin carboxy-terminal hydrolase, a nuclear deubiquitinating enzyme, that catalyzes the cleavage of an ubiquitin residue from several proteins. BAP1 has 729 amino acids and plays an important role in chromatin modulation, transcriptional regulation, cell proliferation, DNA repair, cell death, and glucidic metabolism [54–58]. The BAP1 protein is part of a multiprotein complex that includes FOXK1, HCFC1, ASXL1/2, and OGT [59], and it interacts with BARD1. BAP1 has a ubiquitin C-terminal hydrolase domain, and two nuclear localization sequences.

*Bap1*<sup>+/-</sup> mice show increased sensitivity to asbestos compared with wild-type mice, because they develop MPM when exposed to low amounts of asbestos [60,61]. This may be true also for humans, but quantification of asbestos exposure was reported only for ten subjects with *BAP1-TPDS* [39,62]. Moreover, environmental exposure to carcinogenic mineral fibres is generally involuntary and unknown [63,64].

Follow-up data on *BAP1-TPDS* carriers are also lacking. It is possible that the developed tumor type depends on the carcinogen to which patients are exposed. For example, one individual with

*BAP1*-TPDS, who was not exposed to either domestic or occupational asbestos, died from mucoepidermoid carcinoma of the base of the tongue, whereas his mother, his maternal aunt, and his grandmother who were exposed to domestic asbestos developed MPM [34].

Germline variants are often truncating and generally private, only ten have been identified in more than one patient within apparently non-consanguineous families [40]. Recurrent variants could be due to mutable hot spots within the gene or to the existence of an unknown consanguinity among the families. An example is the case of four American families that shared a common German ancestor nine generation earlier [65]. Moreover, the tumor suppressor gene *BAP1* is frequently deleted in the genome of many tumors, including mesothelioma, as observed in immunohistochemical studies [66]. In the case of tumors that arise in patients with germline variants in *BAP1*, all these patients' cells harbored a single wild-type allele. Further somatic variants affect the wild-type allele, leading to the loss of tumor suppressor function and carcinogenesis. Somatic variants are of different types and include PTVs, large deletions, or chromosomal loss [39,53,67,68]

### **3.3 Other cancer syndromes that predispose to MPM**

Besides *BAP1*, eleven other genes have been identified as involved in predisposition to MPM, i.e. *CDKN2A*, *PALB2*, *BRCA1*, *FANCI*, *ATM*, *SLX4*, *BRCA2*, *FANCC*, *FANCF*, *PMS1*, *XPC*. Except for *CDKN2A*, which is involved in proliferation control, all these genes have a role in DNA repair, most of them in the HRR pathway. Germline variants in these genes are responsible for several cancer syndromes (Table 2), and each syndrome leads to a predisposition to specific tumor types with a high or moderate risk, depending on the gene and the tumor. For example, *BRCA1*, *BRCA2*, and *PALB2* can predispose women to breast and ovarian cancers. *BRCA1* and *BRCA2* are the first genes identified as high-risk factors in the development of HBOC, and they are also its most frequent cause. They are tumor suppressor genes, whose inactivation, due to a somatic variant generated on the wild type allele, induces carcinogenesis in the target tissues of women with a

germline variant. *BRCA1* and *BRCA2* can also predispose to prostate and pancreatic carcinomas [69].

Homozygous germline variants in *BRCA1* and *BRCA2* (also called *FANCS* and *FANCD1*, respectively) are responsible for Fanconi anemia, an autosomal recessive disorder characterized by genetic heterogeneity. This disorder can be caused by at least twenty different genes [70], all of which encode proteins that act in a signaling pathway involved in the response to crosslinking agents. The first step of this pathway is the formation of a multiprotein complex, which includes proteins A, B, C, E, F, G, L, and M, and which has the function of ubiquitin ligase. When the DNA is damaged, the complex interacts with the *FANCD2* and *FANCI* proteins, which are consequently monoubiquitinated and translocated to nuclear foci where they have a role in HRR, in coordination with other proteins, including *BRCA1* (*FANCS*), *BRCA2* (*FANCD1*), *PALB2* (*FANCN*), and *BRIP1* (*FANCJ*). Germline variants have been found in seven FA genes in patients with MPM, i.e. *BRCA1*, *BRCA2*, *PALB2* (*FANCN*), *FANCC*, *FANCF*, *FANCI*, and *SLX4* (*FANCP*).

*XPC* is one of the eight genes responsible for XP (MIM# 278720) and is involved in the NER pathway, a DNA repair system that removes the pyrimidine dimers induced by exposure to ultraviolet radiation. Patients with XP are hypersensitive to ultraviolet radiation and are susceptible to basal cell carcinoma, squamous cell carcinoma, and melanoma [71]. *PMS1* has a role in the MMR pathway, and several genes involved in this pathway predispose to HNPCC or Lynch syndrome [72,73]. Finally, *CDKN2A* plays an important role in cell cycle regulation [74]. Germline variants in this gene predispose to melanoma and pancreatic cancer. It is also interesting to note that anecdotal studies had previously reported MPM in patients with Li-Fraumeni syndrome or neurofibromatosis Type 2, due to germline variants in *TP53* or *NF2* respectively [75,76]. Some of these genes are often somatically mutated or lost in MPM, e.g. *BAP1*, *CDKN2A*, *NF2*, *TP53*, whereas *BRCA2* loss was reported in a single study [53,67,68,77]

The involvement of many DNA repair genes is in line with the important role of *BAP1* as a driver gene in MPM, but it is also in accordance with two (or 3 carbone?) recent independent

studies. The first showed that 12% of 500 patients with different types of metastatic tumors carried germline pathogenic variants, 75% of which are in DNA repair genes [78]. This study shows that our results on MM patients are part of a more general predisposition that includes many metastatic tumor types. The second study reported that 12% of 198 MM patients carried germline mutations in cancer-susceptibility genes, 83% of which were in genes involved in DNA damage sensing and repair genes and 50% in HHR genes [62] (Figure 2). This paper also reports that germline mutations are more common in peritoneal compared with pleural MM [62].

Overall, the observation of a substantial proportion of MM patients carrying germline mutations in DNA repair genes was made in two or three consonant papers, that included 298 patients [79,62,78]. Finally, it is interesting to observe that the patients who carried PTVs in these cancer predisposing genes (i.e. *CDKN2A*, *PALB2*, *BRCA1*, *FANCI*, *ATM*, *SLX4*, *BRCA2*, *FANCC*, *FANCF*, *PMS1*, *XPC* and *BAP1*) were exposed to a lower amount of asbestos as compared to patients who did not carry such variants. The difference is statistically significant [39,79] and this observation was confirmed by Panou et al. [62]. Overall, these data suggest that these patients are more sensitive to asbestos exposure.

#### **4. Translational consequences**

Although the identification of low risk factors has no clinical relevance so far for their carriers, the translational consequences of being a carrier of a mutation in a HHR repair gene are potentially relevant.

It is well known that patients with ovarian cancer and germline variants in *BRCA1* or *BRCA2* respond to PARPi drugs, through a mechanism called synthetic lethality [80,81], a type of genetic interaction characterized by two (or more) defects that are not lethal singularly but are lethal when both are present in a cell [82]. PARP1 is a nuclear enzyme that plays key role in SSBs, BER, and alt-NHEJ [83]. PARP1 binds to SSBs and initiates the PARylation of its substrate proteins, resulting in the formation of polymers of ADP-ribose (PAR). PAR synthesis is required for the

recruitment of SSBs repair scaffolding proteins. PARP1 autoPARylation induces the release of PARP1 from DNA and its inactivation [82]. Treatment with some PARPi (e.g. rucaparib, olaparib, niraparib, and talazoparib) traps PARP1 to the site of DNA damage, interfering with the progression of replication fork. This PARP inhibition causes the accumulation of SSBs that evolve to DSBs through replication fork collapse. HRR and NHEJ are the main pathways used to repair DSBs and restart replication forks stalled by PARPi. If HRR is deficient due to loss of tumor suppressor genes, the damage could also be repaired by alt-NHEJ that is not functional, because it requires PARP1. In the absence of these pathways, cells use classical NHEJ, which leads to chromosomal anomalies, genomic instability, and ultimately cell death [84].

This treatment may be effective also in patients with mesothelioma carrying a germline mutation in *BRCA1* or 2, *BAP1* or possibly other genes affecting HRR (Figure 2B).

In particular, PARPi can be effective in cells that have lost both *BAP1* alleles either because of a germline and somatic variants (like in patients with a genetic predisposition) or because of two somatic variants (like in patients with sporadic cancer). However, while it is difficult to identify the amount of cancer subclones that harbor a biallelic variant, tumors arising in patients with a germline variant in a tumor suppressor gene have a very high likelihood of a second somatic variant on the wild-type allele. Thus, MPM that occurs in patients with a germline variant in *BAP1* could theoretically respond to this treatment. The use of PARPi to treat the MPM patients with *BAP1* loss has been proposed [85], and preventive screening of DNA repair genes might identify a wider group of patients that could benefit of such treatment, i.e. those with a defective HRR.

Another possible treatment that was suggested for patients with *BAP1* loss is the use of EZH2 inhibitors [84]. This approach is supported by the observation that *BAP1* inactivation induces global methylation mediated by the activation of the Polycomb repressive complex 2 (PRC2). The inhibition of EZH2, that encodes for the PRC2 catalytic subunit, has shown excellent results in mesothelioma, both *in vitro* and *in vivo* experiments [86].

## 5. Conclusions

Recent studies have identified germline variants in DNA repair genes in MPM patients. Although papers published more than ten years ago suspected that DNA repair genes played a role in MPM, two issues have hampered the identification of genetic factors with an unequivocal role in cancer development. First, past works focused on frequent variants that needed a very large panel of MPM patients and controls, but enrollment was difficult due to the rarity of the disease. Moreover, an accurate assessment of asbestos exposure was also needed, but this exposure is not routinely assessed with sufficient detail in clinical centers.

Second, analyses focused on the identification of rare variants were more difficult in the past, because high-throughput technologies (e.g. NGS) were not yet available. One example of a variant analyzed in the past is a missense variant in *XRCC1* [20]. *XRCC1* and *PARP1* are proteins involved in the BER pathway. It is likely that patients with variants in *XRCC1* may not only be less efficient in correcting DNA lesions caused by asbestos exposure, but also more sensitive to PARPi. These or other frequent variants may also modulate the risk in patients with a truncating inherited variant in DNA repair genes.

Finally, MM is an aggressive tumor that does not respond to current treatments. Development of new treatments is needed [85,87]. Patients with truncating mutations in HHR genes may represent a subgroup of patients who respond to treatments that induce synthetic lethality.

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## Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

## References

- [1] F. Baumann, J.-P. Ambrosi, M. Carbone, Asbestos is not just asbestos: an unrecognised health hazard, *Lancet Oncol.* 14 (2013) 576–578. doi:10.1016/S1470-2045(13)70257-2.
- [2] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Outdoor Air Pollution., *IARC Monogr. Eval. Carcinog. Risks to Humans.* 109 (2016) 9–444. <http://www.ncbi.nlm.nih.gov/pubmed/29905447> (accessed December 13, 2018).
- [3] C. Magnani, B. Fubini, D. Mirabelli, P.A. Bertazzi, C. Bianchi, E. Chellini, V. Gennaro, A. Marinaccio, M. Menegozzo, E. Merler, F. Merletti, M. Musti, E. Pira, A. Romanelli, B. Terracini, A. Zona, Pleural mesothelioma: epidemiological and public health issues. Report from the Second Italian Consensus Conference on Pleural Mesothelioma., *Med. Lav.* 104 (n.d.) 191–202. <http://www.ncbi.nlm.nih.gov/pubmed/23879063> (accessed December 13, 2018).
- [4] S. Novello, C. Pinto, V. Torri, L. Porcu, M. Di Maio, M. Tiseo, G. Ceresoli, C. Magnani, S. Silvestri, A. Veltri, M. Papotti, G. Rossi, U. Ricardi, L. Trodella, F. Rea, F. Facciolo, A. Granieri, V. Zagonel, G. Scagliotti, The Third Italian Consensus Conference for Malignant Pleural Mesothelioma: State of the art and recommendations., *Crit. Rev. Oncol. Hematol.* 104 (2016) 9–20. doi:10.1016/j.critrevonc.2016.05.004.
- [5] K. Tomasson, G. Gudmundsson, H. Briem, V. Rafnsson, Malignant mesothelioma incidence by nation-wide cancer registry: a population-based study., *J. Occup. Med. Toxicol.* 11 (2016) 37. doi:10.1186/s12995-016-0127-4.
- [6] A. Aspesi, M. Betti, M. Sculco, C. Actis, C. Olgasi, M.W. Wlodarski, A. Vlachos, J.M. Lipton, U. Ramenghi, C. Santoro, A. Follenzi, S.R. Ellis, I. Dianzani, A functional assay for

the clinical annotation of genetic variants of uncertain significance in Diamond-Blackfan anemia, *Hum. Mutat.* (2018). doi:10.1002/humu.23551.

- [7] B. Järholm, A. Burdorf, Emerging evidence that the ban on asbestos use is reducing the occurrence of pleural mesothelioma in Sweden., *Scand. J. Public Health.* 43 (2015) 875–81. doi:10.1177/1403494815596500.
- [8] D. Ferrante, D. Mirabelli, S. Tunesi, B. Terracini, C. Magnani, Pleural mesothelioma and occupational and non-occupational asbestos exposure: a case-control study with quantitative risk assessment., *Occup. Environ. Med.* 73 (2016) 147–53. doi:10.1136/oemed-2015-102803.
- [9] J.T. Hodgson, A. Darnton, The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure., *Ann. Occup. Hyg.* 44 (2000) 565–601.  
<http://www.ncbi.nlm.nih.gov/pubmed/11108782> (accessed April 3, 2017).
- [10] D. Ugolini, M. Neri, M. Ceppi, A. Cesario, I. Dianzani, R. Filiberti, F. Gemignani, S. Landi, C. Magnani, L. Mutti, R. Puntoni, S. Bonassi, Genetic susceptibility to malignant mesothelioma and exposure to asbestos: The influence of the familial factor, *Mutat. Res. Mutat. Res.* 658 (2008) 162–171. doi:10.1016/j.mrrev.2007.08.001.
- [11] M. Carbone, S. Emri, A.U. Dogan, I. Steele, M. Tuncer, H.I. Pass, Y.I. Baris, A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes., *Nat. Rev. Cancer.* 7 (2007) 147–54. doi:10.1038/nrc2068.
- [12] S.A. Emri, The Cappadocia mesothelioma epidemic: its influence in Turkey and abroad., *Ann. Transl. Med.* 5 (2017) 239. doi:10.21037/atm.2017.04.06.
- [13] V. Ascoli, C. Carnovale-Scalzo, F. Nardi, C. Efrati, M. Menegozzo, A one-generation cluster of malignant mesothelioma within a family reveals exposure to asbestos-contaminated jute bags in Naples, Italy., *Eur. J. Epidemiol.* 18 (2003) 171–4.  
<http://www.ncbi.nlm.nih.gov/pubmed/12733840> (accessed March 28, 2017).
- [14] V. Ascoli, D. Cavone, E. Merler, P.G. Barbieri, L. Romeo, F. Nardi, M. Musti, Mesothelioma in blood related subjects: report of 11 clusters among 1954 Italy cases and



- review of the literature., *Am. J. Ind. Med.* 50 (2007) 357–69. doi:10.1002/ajim.20451.
- [15] V. Ascoli, E. Romeo, C. Carnovale Scalzo, I. Cozzi, L. Ancona, F. Cavariani, A. Balestri, L. Gasperini, F. Forastiere, Familial malignant mesothelioma: a population-based study in central Italy (1980-2012)., *Cancer Epidemiol.* 38 (2014) 273–8.  
doi:10.1016/j.canep.2014.02.014.
- [16] D. Ferrante, M. Bertolotti, A. Todesco, D. Mirabelli, B. Terracini, C. Magnani, Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy., *Environ. Health Perspect.* 115 (2007) 1401–5. doi:10.1289/ehp.10195.
- [17] A. Sud, B. Kinnnersley, R.S. Houlston, Genome-wide association studies of cancer: current insights and future perspectives, *Nat. Rev. Cancer.* 17 (2017) 692–704.  
doi:10.1038/nrc.2017.82.
- [18] I. Dianzani, L. Gibello, A. Biava, M. Giordano, M. Bertolotti, M. Betti, D. Ferrante, S. Guarrera, G.P. Betta, D. Mirabelli, G. Matullo, C. Magnani, Polymorphisms in DNA repair genes as risk factors for asbestos-related malignant mesothelioma in a general population study, *Mutat. Res. - Fundam. Mol. Mech. Mutagen.* 599 (2006).  
doi:10.1016/j.mrfmmm.2006.02.005.
- [19] M. Neri, D. Ugolini, I. Dianzani, F. Gemignani, S. Landi, A. Cesario, C. Magnani, L. Mutti, R. Puntoni, S. Bonassi, Genetic susceptibility to malignant pleural mesothelioma and other asbestos-associated diseases., *Mutat. Res.* 659 (2008) 126–36.  
doi:10.1016/j.mrrev.2008.02.002.
- [20] M. Betti, D. Ferrante, M. Padoan, S. Guarrera, M. Giordano, A. Aspesi, D. Mirabelli, C. Casadio, F. Ardisson, E. Ruffini, P.G. Betta, R. Libener, R. Guaschino, G. Matullo, E. Piccolini, C. Magnani, I. Dianzani, XRCC1 and ERCC1 variants modify malignant mesothelioma risk: a case-control study., *Mutat. Res.* 708 (2011) 11–20.  
doi:10.1016/j.mrfmmm.2011.01.001.
- [21] C. Bolognesi, R. Filiberti, M. Neri, E. Perrone, E. Landini, P.A. Canessa, C. Simonassi, P.G.

Cerrano, L. Mutti, R. Puntoni, High frequency of micronuclei in peripheral blood lymphocytes as index of susceptibility to pleural malignant mesothelioma., *Cancer Res.* 62 (2002) 5418–9. <http://www.ncbi.nlm.nih.gov/pubmed/12359747> (accessed December 21, 2017).

[22] V.P. Berwick M, Matullo G, *Studies of DNA repair and human cancer: an update.*, 2002.

[23] G. Matullo, S. Guarrera, M. Betti, G. Fiorito, D. Ferrante, F. Voglino, G. Cadby, C. Di Gaetano, F. Rosa, A. Russo, A. Hirvonen, E. Casalone, S. Tunesi, M. Padoan, M. Giordano, A. Aspesi, C. Casadio, F. Ardisson, E. Ruffini, P.G. Betta, R. Libener, R. Guaschino, E. Piccolini, M. Neri, A.W.B. Musk, N.H. de Klerk, J. Hui, J. Beilby, A.L. James, J. Creaney, B.W. Robinson, S. Mukherjee, L.J. Palmer, D. Mirabelli, D. Ugolini, S. Bonassi, C. Magnani, I. Dianzani, Genetic Variants Associated with Increased Risk of Malignant Pleural Mesothelioma: A Genome-Wide Association Study, *PLoS One.* 8 (2013). doi:10.1371/journal.pone.0061253.

[24] G. Cadby, S. Mukherjee, A.W.B. Musk, A. Reid, M. Garlepp, I. Dick, C. Robinson, J. Hui, G. Fiorito, S. Guarrera, J. Beilby, P.E. Melton, E.K. Moses, D. Ugolini, D. Mirabelli, S. Bonassi, C. Magnani, I. Dianzani, G. Matullo, B. Robinson, J. Creaney, L.J. Palmer, A genome-wide association study for malignant mesothelioma risk., *Lung Cancer.* 82 (2013) 1–8. doi:10.1016/j.lungcan.2013.04.018.

[25] S. Tunesi, D. Ferrante, D. Mirabelli, S. Andorno, M. Betti, G. Fiorito, S. Guarrera, E. Casalone, M. Neri, D. Ugolini, S. Bonassi, G. Matullo, I. Dianzani, C. Magnani, Gene-asbestos interaction in malignant pleural mesothelioma susceptibility, *Carcinogenesis.* 36 (2015). doi:10.1093/carcin/bgv097.

[26] K.J. Rothman, S. Greenland, T.L. Lash, *Modern epidemiology*, Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008. [https://books.google.it/books/about/Modern\\_Epidemiology.html?id=Z3vjT9ALxHUC&redir\\_esc=y](https://books.google.it/books/about/Modern_Epidemiology.html?id=Z3vjT9ALxHUC&redir_esc=y) (accessed February 20, 2018).

- [27] S.G. Gray, D.A. Fennell, L. Mutti, K.J. O'Byrne, In arrayed ranks: array technology in the study of mesothelioma., *J. Thorac. Oncol.* 4 (2009) 411–25.  
doi:10.1097/JTO.0b013e3181951ce8.
- [28] S. Guarrera, C. Viberti, G. Cugliari, A. Allione, E. Casalone, M. Betti, D. Ferrante, A. Aspesi, C. Casadio, F. Grosso, R. Libener, E. Piccolini, D. Mirabelli, I. Dianzani, C. Magnani, G. Matullo, Peripheral blood DNA methylation as potential biomarker of Malignant Pleural Mesothelioma in asbestos-exposed subjects, *J. Thorac. Oncol.* (2018).  
doi:10.1016/j.jtho.2018.10.163.
- [29] R. Pilarski, K. Rai, C. Cebulla, M. Abdel-Rahman, BAP1 Tumor Predisposition Syndrome, 2017. <http://www.ncbi.nlm.nih.gov/pubmed/27748099> (accessed December 27, 2017).
- [30] J.R. Testa, M. Cheung, J. Pei, J.E. Below, Y. Tan, E. Sementino, N.J. Cox, A.U. Dogan, H.I. Pass, S. Trusa, M. Hesdorffer, M. Nasu, A. Powers, Z. Rivera, S. Comertpay, M. Tanji, G. Gaudino, H. Yang, M. Carbone, Germline BAP1 mutations predispose to malignant mesothelioma., *Nat. Genet.* 43 (2011) 1022–5. doi:10.1038/ng.912.
- [31] M. Carbone, L.K. Ferris, F. Baumann, A. Napolitano, C.A. Lum, E.G. Flores, G. Gaudino, A. Powers, P. Bryant-Greenwood, T. Krausz, E. Hyjek, R. Tate, J. Friedberg, T. Weigel, H.I. Pass, H. Yang, BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs., *J. Transl. Med.* 10 (2012) 179. doi:10.1186/1479-5876-10-179.
- [32] C.-N.J. Njauw, I. Kim, A. Piris, M. Gabree, M. Taylor, A.M. Lane, M.M. DeAngelis, E. Gragoudas, L.M. Duncan, H. Tsao, Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families., *PLoS One.* 7 (2012) e35295. doi:10.1371/journal.pone.0035295.
- [33] F. Baumann, E. Flores, A. Napolitano, S. Kanodia, E. Taioli, H. Pass, H. Yang, M. Carbone, Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival., *Carcinogenesis.* 36 (2015) 76–81. doi:10.1093/carcin/bgu227.
- [34] M. Betti, E. Casalone, D. Ferrante, A. Romanelli, F. Grosso, S. Guarrera, L. Righi, S.

- Vatrano, G. Pelosi, R. Libener, D. Mirabelli, R. Boldorini, C. Casadio, M. Papotti, G. Matullo, C. Magnani, I. Dianzani, Inference on germline BAP1 mutations and asbestos exposure from the analysis of familial and sporadic mesothelioma in a high-risk area., *Genes Chromosomes Cancer*. 54 (2015) 51–62. doi:10.1002/gcc.22218.
- [35] J.A. Ohar, M. Cheung, J. Talarchek, S.E. Howard, T.D. Howard, M. Hesdorffer, H. Peng, F.J. Rauscher, J.R. Testa, Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer., *Cancer Res*. 76 (2016) 206–15. doi:10.1158/0008-5472.CAN-15-0295.
- [36] T. Wiesner, A.C. Obenauf, R. Murali, I. Fried, K.G. Griewank, P. Ulz, C. Windpassinger, W. Wackernagel, S. Loy, I. Wolf, A. Viale, A.E. Lash, M. Pirun, N.D. Socci, A. Rütten, G. Palmedo, D. Abramson, K. Offit, A. Ott, J.C. Becker, L. Cerroni, H. Kutzner, B.C. Bastian, M.R. Speicher, Germline mutations in BAP1 predispose to melanocytic tumors., *Nat. Genet*. 43 (2011) 1018–21. doi:10.1038/ng.910.
- [37] M. Betti, E. Casalone, D. Ferrante, A. Romanelli, F. Grosso, S. Guarrera, L. Righi, S. Vatrano, G. Pelosi, R. Libener, D. Mirabelli, R. Boldorini, C. Casadio, M. Papotti, G. Matullo, C. Magnani, I. Dianzani, Inference on germline BAP1 mutations and asbestos exposure from the analysis of familial and sporadic mesothelioma in a high-risk area, *Genes Chromosom. Cancer*. 54 (2015). doi:10.1002/gcc.22218.
- [38] M. Kittaneh, C. Berkelhammer, Detecting germline BAP1 mutations in patients with peritoneal mesothelioma: benefits to patient and family members., *J. Transl. Med*. 16 (2018) 194. doi:10.1186/s12967-018-1559-7.
- [39] M. Betti, A. Aspesi, D. Ferrante, M. Sculco, L. Righi, D. Mirabelli, F. Napoli, M. Rondón-Lagos, E. Casalone, F. Vignolo Lutati, P. Ogliara, P. Bironzo, C.L. Gironi, P. Savoia, A. Maffè, S. Ungari, F. Grosso, R. Libener, R. Boldorini, M. Valiante, B. Pasini, G. Matullo, G. Scagliotti, C. Magnani, I. Dianzani, Sensitivity to asbestos is increased in patients with mesothelioma and pathogenic germline variants in *BAP1* or other DNA repair genes, *Genes*,

Chromosom. Cancer. 57 (2018) 573–583. doi:10.1002/gcc.22670.

- [40] K. Rai, R. Pilarski, C.M. Cebulla, M.H. Abdel-Rahman, Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases., *Clin. Genet.* 89 (2016) 285–94. doi:10.1111/cge.12630.
- [41] T. Popova, L. Hebert, V. Jacquemin, S. Gad, V. Caux-Moncoutier, C. Dubois-d’Enghien, B. Richaudeau, X. Renaudin, J. Sellers, A. Nicolas, X. Sastre-Garau, L. Desjardins, G. Gyapay, V. Raynal, O.M. Sinilnikova, N. Andrieu, E. Manié, A. de Pauw, P. Gesta, V. Bonadona, C.M. Maugard, C. Penet, M.-F. Avril, E. Barillot, O. Cabaret, O. Delattre, S. Richard, O. Caron, M. Benfodda, H.-H. Hu, N. Soufir, B. Bressac-de Paillerets, D. Stoppa-Lyonnet, M.-H. Stern, Germline BAP1 mutations predispose to renal cell carcinomas., *Am. J. Hum. Genet.* 92 (2013) 974–80. doi:10.1016/j.ajhg.2013.04.012.
- [42] R. Pilarski, C.M. Cebulla, J.B. Massengill, K. Rai, T. Rich, L. Strong, B. McGillivray, M.-J. Asrat, F.H. Davidorf, M.H. Abdel-Rahman, Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases., *Genes. Chromosomes Cancer.* 53 (2014) 177–82. doi:10.1002/gcc.22129.
- [43] K.A.W. Wadt, L.G. Aoude, P. Johansson, A. Solinas, A. Pritchard, O. Crainic, M.T. Andersen, J.F. Kiilgaard, S. Heegaard, L. Sunde, B. Federspiel, J. Madore, J.F. Thompson, S.W. McCarthy, A. Goodwin, H. Tsao, G. Jönsson, K. Busam, R. Gupta, J.M. Trent, A.-M. Gerdes, K.M. Brown, R.A. Scolyer, N.K. Hayward, A recurrent germline BAP1 mutation and extension of the BAP1 tumor predisposition spectrum to include basal cell carcinoma., *Clin. Genet.* 88 (2015) 267–72. doi:10.1111/cge.12501.
- [44] M.H. Abdel-Rahman, R. Pilarski, C.M. Cebulla, J.B. Massengill, B.N. Christopher, G. Boru, P. Hovland, F.H. Davidorf, Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers., *J. Med. Genet.* 48 (2011) 856–9. doi:10.1136/jmedgenet-2011-100156.
- [45] M. Cheung, Y. Kadariya, J. Talarchek, J. Pei, J.A. Ohar, O.R. Kayaleh, J.R. Testa, Germline

BAP1 mutation in a family with high incidence of multiple primary cancers and a potential gene-environment interaction., *Cancer Lett.* 369 (2015) 261–5.

doi:10.1016/j.canlet.2015.09.011.

- [46] A. de la Fouchardière, O. Cabaret, L. Savin, P. Combemale, H. Schwartz, C. Penet, V. Bonadona, N. Soufir, B. Bressac-de Paillerets, Germline BAP1 mutations predispose also to multiple basal cell carcinomas., *Clin. Genet.* 88 (2015) 273–7. doi:10.1111/cge.12472.
- [47] K. Wadt, J. Choi, J.-Y. Chung, J. Kiilgaard, S. Heegaard, K.T. Drzewiecki, J.M. Trent, S.M. Hewitt, N.K. Hayward, A.-M. Gerdes, K.M. Brown, A cryptic BAP1 splice mutation in a family with uveal and cutaneous melanoma, and paraganglioma., *Pigment Cell Melanoma Res.* 25 (2012) 815–8. doi:10.1111/pcmr.12006.
- [48] L.G. Aoude, K. Wadt, A. Bojesen, D. Crüger, A. Borg, J.M. Trent, K.M. Brown, A.-M. Gerdes, G. Jönsson, N.K. Hayward, A BAP1 mutation in a Danish family predisposes to uveal melanoma and other cancers., *PLoS One.* 8 (2013) e72144. doi:10.1371/journal.pone.0072144.
- [49] K.J. McDonnell, G.T. Gallanis, K.A. Heller, M. Melas, G.E. Idos, J.O. Culver, S.-E. Martin, D.H. Peng, S.B. Gruber, A novel BAP1 mutation is associated with melanocytic neoplasms and thyroid cancer., *Cancer Genet.* 209 (2016) 75–81. doi:10.1016/j.cancergen.2015.12.007.
- [50] S. Walpole, A.L. Pritchard, C.M. Cebulla, R. Pilarski, M. Stautberg, F.H. Davidorf, A. de la Fouchardière, O. Cabaret, L. Golmard, D. Stoppa-Lyonnet, E. Garfield, C.-N. Njauw, M. Cheung, J.A. Turunen, P. Repo, R.-S. Järvinen, R. van Doorn, M.J. Jager, G.P.M. Luyten, M. Marinkovic, C. Chau, M. Potrony, V. Höiom, H. Helgadottir, L. Pastorino, W. Bruno, V. Andreotti, B. Dalmaso, G. Ciccarese, P. Queirolo, L. Mastracci, K. Wadt, J.F. Kiilgaard, M.R. Speicher, N. van Poppelen, E. Kilic, R.T. Al-Jamal, I. Dianzani, M. Betti, C. Bergmann, S. Santagata, S. Dahiya, S. Taibjee, J. Burke, N. Poplawski, S.J. O’Shea, J. Newton-Bishop, J. Adlard, D.J. Adams, A.-M. Lane, I. Kim, S. Klebe, H. Racher, J.W. Harbour, M.L. Nickerson, R. Murali, J.M. Palmer, M. Howlie, J. Symmons, H. Hamilton, S.

- Warrier, W. Glasson, P. Johansson, C.D. Robles-Espinoza, R. Ossio, A. de Klein, S. Puig, P. Ghiorzo, M. Nielsen, T.T. Kivelä, H. Tsao, J.R. Testa, P. Gerami, M.-H. Stern, B.B. Paillerets, M.H. Abdel-Rahman, N.K. Hayward, Comprehensive Study of the Clinical Phenotype of Germline BAP1 Variant-Carrying Families Worldwide., *J. Natl. Cancer Inst.* (2018). doi:10.1093/jnci/djy171.
- [51] A. Rusch, G. Ziltener, K. Nackaerts, W. Weder, R.A. Stahel, E. Felley-Bosco, Prevalence of BRCA-1 associated protein 1 germline mutation in sporadic malignant pleural mesothelioma cases, *Lung Cancer.* 87 (2015) 77–79. doi:10.1016/j.lungcan.2014.10.017.
- [52] S. Sneddon, J.S. Leon, I.M. Dick, G. Cadby, N. Olsen, F. Brims, R.J.N. Allcock, E.K. Moses, P.E. Melton, N. de Klerk, A.W. (Bill) Musk, B.W.S. Robinson, J. Creaney, Absence of germline mutations in BAP1 in sporadic cases of malignant mesothelioma, *Gene.* 563 (2015) 103–105. doi:10.1016/j.gene.2015.03.031.
- [53] G. Guo, J. Chmielecki, C. Goparaju, A. Heguy, I. Dolgalev, M. Carbone, S. Seepo, M. Meyerson, H.I. Pass, Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma., *Cancer Res.* 75 (2015) 264–9. doi:10.1158/0008-5472.CAN-14-1008.
- [54] S. Daou, I. Hammond-Martel, N. Mashtalir, H. Barbour, J. Gagnon, N.V.G. Iannantuono, N. Sen Nkwe, A. Motorina, H. Pak, H. Yu, H. Wurtele, E. Milot, F.A. Mallette, M. Carbone, E.B. Affar, The BAP1/ASXL2 Histone H2A Deubiquitinase Complex Regulates Cell Proliferation and Is Disrupted in Cancer., *J. Biol. Chem.* 290 (2015) 28643–63. doi:10.1074/jbc.M115.661553.
- [55] H. Yu, H. Pak, I. Hammond-Martel, M. Ghram, A. Rodrigue, S. Daou, H. Barbour, L. Corbeil, J. Hébert, E. Drobetsky, J.Y. Masson, J.M. Di Noia, E.B. Affar, Tumor suppressor and deubiquitinase BAP1 promotes DNA double-strand break repair., *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) 285–90. doi:10.1073/pnas.1309085110.
- [56] Z. Ji, H. Mohammed, A. Webber, J. Ridsdale, N. Han, J.S. Carroll, A.D. Sharrocks, The

forkhead transcription factor FOXK2 acts as a chromatin targeting factor for the BAP1-containing histone deubiquitinase complex., *Nucleic Acids Res.* 42 (2014) 6232–42. doi:10.1093/nar/gku274.

- [57] A. Bononi, H. Yang, C. Giorgi, S. Patergnani, L. Pellegrini, M. Su, G. Xie, V. Signorato, S. Pastorino, P. Morris, G. Sakamoto, S. Kuchay, G. Gaudino, H.I. Pass, A. Napolitano, P. Pinton, W. Jia, M. Carbone, Germline BAP1 mutations induce a Warburg effect, *Cell Death Differ.* 24 (2017) 1694–1704. doi:10.1038/cdd.2017.95.
- [58] I.H. Ismail, R. Davidson, J.-P. Gagné, Z.Z. Xu, G.G. Poirier, M.J. Hendzel, Germline mutations in BAP1 impair its function in DNA double-strand break repair., *Cancer Res.* 74 (2014) 4282–94. doi:10.1158/0008-5472.CAN-13-3109.
- [59] A.E. White, J.W. Harper, Cancer. Emerging anatomy of the BAP1 tumor suppressor system., *Science.* 337 (2012) 1463–4. doi:10.1126/science.1228463.
- [60] A. Napolitano, L. Pellegrini, A. Dey, D. Larson, M. Tanji, E.G. Flores, B. Kendrick, D. Lapid, A. Powers, S. Kanodia, S. Pastorino, H.I. Pass, V. Dixit, H. Yang, M. Carbone, Minimal asbestos exposure in germline BAP1 heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma, *Oncogene.* 35 (2016) 1996–2002. doi:10.1038/onc.2015.243.
- [61] J. Xu, Y. Kadariya, M. Cheung, J. Pei, J. Talarchek, E. Sementino, Y. Tan, C.W. Menges, K.Q. Cai, S. Litwin, H. Peng, J. Karar, F.J. Rauscher, J.R. Testa, Germline mutation of Bap1 accelerates development of asbestos-induced malignant mesothelioma., *Cancer Res.* 74 (2014) 4388–97. doi:10.1158/0008-5472.CAN-14-1328.
- [62] V. Panou, M. Gadiraju, A. Wolin, C.M. Weipert, E. Skarda, A.N. Husain, J.D. Patel, B. Rose, S.R. Zhang, M. Weatherly, V. Nelakuditi, A. Knight Johnson, M. Helgeson, D. Fischer, A. Desai, N. Sulai, L. Ritterhouse, O.D. Røe, K.K. Turaga, D. Huo, J. Segal, S. Kadri, Z. Li, H.L. Kindler, J.E. Churpek, Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma, *J. Clin. Oncol.* 36 (2018) 2863–2871.



doi:10.1200/JCO.2018.78.5204.

- [63] F. Baumann, M. Carbone, Environmental risk of mesothelioma in the United States: An emerging concern—epidemiological issues, *J. Toxicol. Environ. Heal. Part B.* 19 (2016) 231–249. doi:10.1080/10937404.2016.1195322.
- [64] M. Carbone, E.G. Flores, M. Emi, T.A. Johnson, T. Tsunoda, D. Behner, H. Hoffman, M. Hesdorffer, M. Nasu, A. Napolitano, A. Powers, M. Minaai, F. Baumann, P. Bryant-Greenwood, O. Lauk, M.B. Kirschner, W. Weder, I. Opitz, H.I. Pass, G. Gaudino, S. Pastorino, H. Yang, Combined Genetic and Genealogic Studies Uncover a Large BAP1 Cancer Syndrome Kindred Tracing Back Nine Generations to a Common Ancestor from the 1700s., *PLoS Genet.* 11 (2015) e1005633. doi:10.1371/journal.pgen.1005633.
- [65] M. Carbone, E.G. Flores, M. Emi, T.A. Johnson, T. Tsunoda, D. Behner, H. Hoffman, M. Hesdorffer, M. Nasu, A. Napolitano, A. Powers, M. Minaai, F. Baumann, P. Bryant-Greenwood, O. Lauk, M.B. Kirschner, W. Weder, I. Opitz, H.I. Pass, G. Gaudino, S. Pastorino, H. Yang, Combined Genetic and Genealogic Studies Uncover a Large BAP1 Cancer Syndrome Kindred Tracing Back Nine Generations to a Common Ancestor from the 1700s, *PLOS Genet.* 11 (2015) e1005633. doi:10.1371/journal.pgen.1005633.
- [66] L. Righi, E. Duregon, S. Vatrano, S. Izzo, J. Giorcelli, M. Rondón-Lagos, V. Ascoli, E. Ruffini, L. Ventura, M. Volante, M. Papotti, G.V. Scagliotti, BRCA1-Associated Protein 1 (BAP1) Immunohistochemical Expression as a Diagnostic Tool in Malignant Pleural Mesothelioma Classification: A Large Retrospective Study., *J. Thorac. Oncol.* 11 (2016) 2006–2017. doi:10.1016/j.jtho.2016.06.020.
- [67] M. Lo Iacono, V. Monica, L. Righi, F. Grosso, R. Libener, S. Vatrano, P. Bironzo, S. Novello, L. Musmeci, M. Volante, M. Papotti, G. V Scagliotti, Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study., *J. Thorac. Oncol.* 10 (2015) 492–9. doi:10.1097/JTO.0000000000000436.

- [68] R. Bueno, E.W. Stawiski, L.D. Goldstein, S. Durinck, A. De Rienzo, Z. Modrusan, F. Gnad, T.T. Nguyen, B.S. Jaiswal, L.R. Chirieac, D. Sciaranghella, N. Dao, C.E. Gustafson, K.J. Munir, J.A. Hackney, A. Chaudhuri, R. Gupta, J. Guillory, K. Toy, C. Ha, Y.-J. Chen, J. Stinson, S. Chaudhuri, N. Zhang, T.D. Wu, D.J. Sugarbaker, F.J. de Sauvage, W.G. Richards, S. Seshagiri, Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations, *Nat. Genet.* 48 (2016) 407–416. doi:10.1038/ng.3520.
- [69] N. Petrucelli, M.B. Daly, T. Pal, BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer, University of Washington, Seattle, .  
<http://www.ncbi.nlm.nih.gov/pubmed/20301425> (accessed December 29, 2017).
- [70] P.A. Mehta, J. Tolar, Fanconi Anemia, University of Washington, Seattle, 2017.  
<http://www.ncbi.nlm.nih.gov/pubmed/20301575> (accessed December 29, 2017).
- [71] K.H. Kraemer, J.J. DiGiovanna, Xeroderma Pigmentosum, University of Washington, Seattle, 2016. <http://www.ncbi.nlm.nih.gov/pubmed/20301571> (accessed December 29, 2017).
- [72] P. Peltomäki, Lynch syndrome genes., *Fam. Cancer.* 4 (2005) 227–32. doi:10.1007/s10689-004-7993-0.
- [73] Y. Wang, X. Zhou, Y. Song, X. Ji, A. Zhang, G. Zhang, Z. Gao, The mismatch repair gene hPMS1 (human postmeiotic segregation1) is down regulated in oral squamous cell carcinoma., *Gene.* 524 (2013) 28–34. doi:10.1016/j.gene.2013.04.030.
- [74] L.G. Aoude, K.A.W. Wadt, A.L. Pritchard, N.K. Hayward, Genetics of familial melanoma: 20 years after *CDKN2A*, *Pigment Cell Melanoma Res.* 28 (2015) 148–160.  
doi:10.1111/pcmr.12333.
- [75] W.P. Ceelen, T. Van Dalen, M. Van Bockstal, L. Libbrecht, R.H. Sijmons, Malignant peritoneal mesothelioma in a patient with Li-Fraumeni syndrome., *J. Clin. Oncol.* 29 (2011) e503-5. doi:10.1200/JCO.2010.34.1933.

- [76] M.E. Baser, H. Rai, A.J. Wallace, D.G.R. Evans, Neurofibromatosis 2 (NF2) and malignant mesothelioma in a man with a constitutional NF2 missense mutation., *Fam. Cancer*. 4 (2005) 321–2. doi:10.1007/s10689-005-0659-8.
- [77] M. Hylebos, G. Van Camp, G. Vandeweyer, E. Fransen, M. Beyens, R. Cornelissen, A. Suls, P. Pauwels, J.P. van Meerbeeck, K. Op de Beeck, Large-scale copy number analysis reveals variations in genes not previously associated with malignant pleural mesothelioma., *Oncotarget*. 8 (2017) 113673–113686. doi:10.18632/oncotarget.22817.
- [78] D.R. Robinson, Y.-M. Wu, R.J. Lonigro, P. Vats, E. Cobain, J. Everett, X. Cao, E. Rabban, C. Kumar-Sinha, V. Raymond, S. Schuetze, A. Alva, J. Siddiqui, R. Chugh, F. Worden, M.M. Zalupski, J. Innis, R.J. Mody, S.A. Tomlins, D. Lucas, L.H. Baker, N. Ramnath, A.F. Schott, D.F. Hayes, J. Vijai, K. Offit, E.M. Stoffel, J.S. Roberts, D.C. Smith, L.P. Kunju, M. Talpaz, M. Cieřlik, A.M. Chinnaiyan, Integrative clinical genomics of metastatic cancer., *Nature*. 548 (2017) 297–303. doi:10.1038/nature23306.
- [79] M. Betti, E. Casalone, D. Ferrante, A. Aspesi, G. Morleo, A. Biasi, M. Sculco, G. Mancuso, S. Guarrera, L. Righi, F. Grosso, R. Libener, M. Pavesi, N. Mariani, C. Casadio, R. Boldorini, D. Mirabelli, B. Pasini, C. Magnani, G. Matullo, I. Dianzani, Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma, *Cancer Lett*. 405 (2017) 38–45. doi:10.1016/j.canlet.2017.06.028.
- [80] P.C. Fong, D.S. Boss, T.A. Yap, A. Tutt, P. Wu, M. Mergui-Roelvink, P. Mortimer, H. Swaisland, A. Lau, M.J. O'Connor, A. Ashworth, J. Carmichael, S.B. Kaye, J.H.M. Schellens, J.S. de Bono, Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers., *N. Engl. J. Med*. 361 (2009) 123–34. doi:10.1056/NEJMoa0900212.
- [81] E.M. Swisher, K.K. Lin, A.M. Oza, C.L. Scott, H. Giordano, J. Sun, G.E. Konecny, R.L. Coleman, A. V Tinker, D.M. O'Malley, R.S. Kristeleit, L. Ma, K.M. Bell-McGuinn, J.D. Brenton, J.M. Cragun, A. Oaknin, I. Ray-Coquard, M.I. Harrell, E. Mann, S.H. Kaufmann, A. Floquet, A. Leary, T.C. Harding, S. Goble, L. Maloney, J. Isaacson, A.R. Allen, L. Rolfe,

- R. Yelensky, M. Raponi, I.A. McNeish, Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial., *Lancet. Oncol.* 18 (2017) 75–87. doi:10.1016/S1470-2045(16)30559-9.
- [82] C.J. Lord, A. Ashworth, PARP inhibitors: Synthetic lethality in the clinic, *Science* (80-. ). 355 (2017) 1152–1158. doi:10.1126/science.aam7344.
- [83] J.S. Brown, B. O’Carrigan, S.P. Jackson, T.A. Yap, Targeting DNA Repair in Cancer: Beyond PARP Inhibitors, *Cancer Discov.* 7 (2017) 20–37. doi:10.1158/2159-8290.CD-16-0860.
- [84] A. Ohmoto, S. Yachida, Current status of poly(ADP-ribose) polymerase inhibitors and future directions., *Onco. Targets. Ther.* 10 (2017) 5195–5208. doi:10.2147/OTT.S139336.
- [85] T.A. Yap, J.G. Aerts, S. Popat, D.A. Fennell, Novel insights into mesothelioma biology and implications for therapy, *Nat. Rev. Cancer.* 17 (2017) 475–488. doi:10.1038/nrc.2017.42.
- [86] L.M. LaFave, W. Béguelin, R. Koche, M. Teater, B. Spitzer, A. Chramiec, E. Papalexii, M.D. Keller, T. Hricik, K. Konstantinoff, J.-B. Micol, B. Durham, S.K. Knutson, J.E. Campbell, G. Blum, X. Shi, E.H. Doud, A. V Krivtsov, Y.R. Chung, I. Khodos, E. de Stanchina, O. Ouerfelli, P.S. Adusumilli, P.M. Thomas, N.L. Kelleher, M. Luo, H. Keilhack, O. Abdel-Wahab, A. Melnick, S.A. Armstrong, R.L. Levine, Loss of BAP1 function leads to EZH2-dependent transformation., *Nat. Med.* 21 (2015) 1344–9. doi:10.1038/nm.3947.
- [87] A. Bononi, A. Napolitano, H.I. Pass, H. Yang, M. Carbone, Latest developments in our understanding of the pathogenesis of mesothelioma and the design of targeted therapies., *Expert Rev. Respir. Med.* 9 (2015) 633–54. doi:10.1586/17476348.2015.1081066.
- [88] M. Betti, A. Aspesi, A. Biasi, E. Casalone, D. Ferrante, P. Ogliara, L.C. Gironi, R. Giorgione, P. Farinelli, F. Grosso, R. Libener, S. Rosato, D. Turchetti, A. Maffè, C. Casadio, V. Ascoli, C. Dianzani, E. Colombo, E. Piccolini, M. Pavesi, S. Miccoli, D. Mirabelli, C. Bracco, L. Righi, R. Boldorini, M. Papotti, G. Matullo, C. Magnani, B. Pasini, I. Dianzani, CDKN2A and BAP1 germline mutations predispose to melanoma and mesothelioma, *Cancer*

Lett. 378 (2016). doi:10.1016/j.canlet.2016.05.011.

## **Legends to figures**

### **Figure 1: Low- risk genetic factors: possible effects**

A: Low- risk factors predisposing to mesothelioma are represented by specific SNPs in the reported genes. A single SNP confers a very low risk, but interaction among different SNPs may cause synergistic effects. B: FOXX1 (whose gene is located in a region that includes *SDK1*) is an interactor of BAP1: we speculate that the associated SNPs may modify BAP1 function and favor carcinogenesis.

### **Figure 2: High- and moderate- risk genetic factors: possible role in carcinogenesis and treatment**

A: High- and moderate-risk factors predisposing to mesothelioma are represented by pathogenic truncating variants in genes involved in autosomal dominant or recessive cancer-predisposition syndromes. B: Their presence may favor treatments based on synthetic lethality.

**Table 1-** Low-risk genetic factors for malignant pleural mesothelioma**Table 1a -** Matullo et al. study: 407 cases vs 389 controls [23]

<b>Locus</b>	<b>SNP</b>	<b>Gene</b>	<b>Gene Name</b>	<b>Context</b>	<b>Biological Process</b>	<b>Left Gene</b>	<b>Right Gene</b>
6p21	rs742109	-		Intergenic	-	<i>PRDM1</i>	<i>ATG5</i>
3q26.2	rs7632718	<i>SLC7A14</i>	Solute carrier family 7 member 14	Intronic	Amino acid transport	<i>CLDN11</i>	<i>RPL22L1</i>
3p24.2	rs9833191	<i>THRB</i>	Thyroid hormone receptor beta	Intronic	Transcription regulation	<i>NR1D2</i>	<i>MIR4792</i>
5q23.1	rs1508805	-		Intergenic	-	<i>PRR16</i>	<i>FTMT</i>
1q25.2	rs2501618	<i>CEP350</i>	Centrosome-associated protein 350	Intronic	Microtubule anchoring	<i>TORIAIP1</i>	<i>QSOX1</i>
5q35.3	rs4701085	<i>ADAMTS2</i>	A disintegrin and metalloproteinase with thrombospondin motifs 2	Intronic	Collagen degradation	<i>ZNF354C</i>	<i>AX747985</i>
4q22.1	rs4290865	-		Intergenic	-	<i>FAM190A</i>	<i>GRID2</i>
13q14.3	rs9536579	-		Intergenic	-	<i>OLFM5</i>	<i>MIR1297</i>
7p21.2	rs3801094	<i>ETV1</i>	ETS translocation variant 1	Intronic	Transcription regulation	<i>ARL4A</i>	<i>DGKB</i>
8q24.21	rs7841347	<i>PVT1</i>	Pvt1 oncogene (non-protein coding)	Intronic	Cancer pathophysiology	<i>MYC</i>	<i>TMEM75</i>
15q21.1	rs10519201	<i>SHC4</i>	SHC-transforming protein 4	Intronic	Apoptotic process, intracellular signal transduction, cell proliferation, regulation of gene expression	<i>EID1</i>	<i>SECISBP2L</i>
22q12.3	rs5756444	-		Intergenic	-	<i>CSF2RB2</i>	<i>C22orf33/TEX33</i>

**Table 1b –** Cadby et al. study: 428 cases vs 778 controls [24]

<b>Locus</b>	<b>SNP</b>	<b>Gene</b>	<b>Gene Name</b>	<b>Context</b>	<b>Biological Process</b>	<b>Left Gene</b>	<b>Right Gene</b>
11q24.1	rs17338032	<i>CRTAM</i>	Cytotoxic and regulatory T-cell molecule	Intronic	Adaptive immune response	<i>UBASH3B</i>	<i>JHY</i>
2p12	rs11126513	-		Intergenic	-	<i>C2orf3</i>	<i>LRRTM4</i>
5q13	rs1379270	<i>RASGRF2</i>	Ras-specific guanine nucleotide-releasing factor 2	Intronic	Apoptotic process, regulation of Rho protein signal transduction, regulation of small GTPase mediated signal transduction	<i>MSH3</i>	<i>CKMT2</i>
7p22.2	rs12540101	<i>SDK1</i>	Protein sidekick-1	Intronic	Cell-cell junction organization	<i>CARD11</i>	<i>CYP3A54P</i>
6q15	rs4707427	-		Intergenic	-	<i>AKIRIN2</i>	<i>SPACA1</i>

8p21.3	rs10089418	-		Intergenic	-	<i>LZTS1</i>	<i>LINC02153</i>
13q13.3	rs9548166	-		Intergenic	-	<i>LINC02334</i>	<i>LINC00571</i>
5q23.1	rs4895337	-		Intergenic	-	<i>FTMT</i>	<i>SRFBP1</i>
9p21.1	rs13287752	-		Intergenic	-	<i>MIR873</i>	<i>C9orf72</i>
4q12	rs282718	-		Intergenic	-	<i>IGFBP7</i>	<i>LINC02380</i>
7p22.2	rs12701229	<i>SDK1</i>	Protein sidekick-1	Intronic	Cell-cell junction organization	<i>CARD11</i>	<i>CYP3A54P</i>

**Table 2 - High- and moderate -risk genetic factors for malignant pleural mesothelioma**

Reference	Gene	MIM #	Function	Tumors	Autosomal Dominant Syndrome	Autosomal Recessive Syndrome
[30–33,35–50,62]	<i>BAP1</i>	603089	DNA repair (HRR)	Mesothelioma Cutaneous melanoma Uveal melanoma Renal cell carcinoma Basal cell carcinoma Melanocytic <i>BAP1</i> -mutated atypical intradermal tumors (MBAITs)	<i>BAP1</i> -Tumor Predisposition Syndrome ( <i>BAP1</i> -TPDS)	-
[79,62]	<i>BRCA1</i> ( <i>FANCS</i> )	113605	DNA repair (HRR)	Breast cancer Ovarian cancer Prostate cancer Pancreatic cancer Melanoma	Hereditary Breast and Ovarian Cancer (HBOC)	Fanconi anemia
[79,62]	<i>BRCA2</i> ( <i>FANCD1</i> )	600185	DNA repair (HRR)	Breast cancer Ovarian cancer Prostate cancer Pancreatic cancer Melanoma	Hereditary Breast and Ovarian Cancer (HBOC)	Fanconi anemia
[79]	<i>XPC</i>	613208	DNA repair (NER)	Basal cell carcinoma Squamous cell carcinoma Melanoma	-	Xeroderma pigmentosum (XP)
[88,62]	<i>CDKN2A</i>	600160	Cell cycle control	Melanoma Pancreatic cancer	Familial Atypical Multiple Mole Melanoma-Pancreatic Carcinoma Syndrome (FAMMPC)	-
[79]	<i>PALB2</i> ( <i>FANCN</i> )	610355	DNA repair (HRR)	Breast cancer Pancreatic cancer	-	Fanconi anemia
[79]	<i>PMS1</i>	600258	DNA repair (MMR)	-	-	-
[79]	<i>FANCC</i>	613899	DNA repair (HRR)	Head and neck squamous cell carcinoma Pancreatic cancer	-	Fanconi anemia
[79]	<i>FANCF</i>	603467	DNA repair (HRR)	Head and neck squamous cell carcinoma Pancreatic cancer	-	Fanconi anemia



[79]	<i>FANCI</i>	611360	DNA repair (HRR)	Head and neck squamous cell carcinoma Pancreatic cancer	-	Fanconi anemia
[79]	<i>SLX4</i> ( <i>FANCP</i> )	613278	DNA repair (HRR)	Head and neck squamous cell carcinoma Pancreatic cancer	-	Fanconi anemia
[79,62]	<i>ATM</i>	607585	DNA repair (HRR)	Breast cancer	Lymphoma, Leukemia *	Ataxia telangiectasia
[62]	<i>MSH6</i>	600678	DNA repair (MMR)	Colorectal cancer	-	-
[62]	<i>MRE11A</i>	600814	DNA repair (HRR)	Breast cancer	-	Ataxia telangiectasia
[62]	<i>TMEM127</i>	613403	-	Pheochromocytoma	-	-
[62]	<i>TP53</i>	191170	DNA repair (HRR)	Breast cancer Ovarian cancer Melanoma Colorectal cancer Osteosarcoma Glioma	Li-Fraumeni	-
[62]	<i>SDHA</i>	600857	-	Paranglioma	-	-

\*Heterozygous carriers show a moderate risk for breast and gastrointestinal cancer.