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Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival

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BRCA1-associated protein-1 (*BAP1*) mutations cause a new cancer syndrome, with a high rate of malignant mesothelioma (MM). Here, we tested the hypothesis that MM associated with germline *BAP1* mutations has a better prognosis compared with sporadic MM. We compared survival among germline *BAP1* mutation MM patients with that of all MM (*N* = 10 556) recorded in the United States Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2010. We identified 23 MM patients—11 alive—with germline *BAP1* mutations and available data on survival. Ten patients had peritoneal MM, ten pleural MM and three MM in both locations. Thirteen patients had one or more malignancies in addition to MM. Actuarial median survival for the MM patients with germline *BAP1* mutations was 5 years, as compared with <1 year for the median survival in the United States SEER MM group. Five-year survival was 47%, 95% confidence interval (24–67%), as compared with 6.7% (6.2–7.3%) in the control SEER group. Analysis of the pooled cohort of germline *BAP1* mutation MM showed that patients with peritoneal MM (median survival of 10 years, *P* = 0.0571), or with a second malignancy in addition to MM (median survival of 10 years, *P* = 0.0716), survived for a longer time compared with patients who only had pleural MM, or MM patients without a second malignancy, respectively. In conclusion, we found that MM patients with germline *BAP1* mutations have an overall 7-fold increased long-term survival, independently of sex and age. Appropriate genetic counseling and clinical management should be considered for MM patients who are also *BAP1* mutation carriers.

Introduction

Malignant mesothelioma (MM) is a devastating and lethal cancer associated with exposure to mineral fibers. It arises from the mesothelial cells of the pleura (80–90%), peritoneum (10–15%) and more rarely pericardium (<5%) (1). MM is rare: annually ~1–2 cases are diagnosed per million inhabitants in countries without significant use of asbestos (1). In the USA the incidence of MM varies from 5.8 to 16.5 cases per million inhabitants, depending on the extent of commercial asbestos use and the presence of natural mineral deposits (2). Although MM incidence was predicted to decrease following the ban of asbestos (1,3), it is still increasing worldwide (4), and it has remained stable at ~3200 cases/year in the USA since 2003 (2). There are several reasons that may account for the persistent increase or at least lack of reduction of MM worldwide and in the USA, respectively. Worldwide, the use of asbestos continues to increase, especially in developing countries (5). In Europe and in the USA the ban on asbestos has eliminated or drastically reduced its use; however, asbestos is a very durable material, which is the very reason it has been used so extensively. Therefore, millions of tons of asbestos that have been used during the past decades remain in place and continue to pose a risk to millions of people. In other words, although the amount of occupational exposure has diminished, the number of people exposed to low amounts of asbestos or other carcinogenic fibers has increased. For example, it has been estimated that over 20 million homes in the USA contain asbestos or have roofs made of asbestos (6). As times passes, asbestos deteriorates and the risk of exposure to asbestos dust increases. In addition, asbestos is a commercial name that was given to six mineral fibers because they were used commercially from the mid-19th century (5). There are, however, ~400 additional mineral fibers in nature, and although these fibers are not called 'asbestos' their potential to induce MM is similar to the six fibers that were included in the 'asbestos' definition. Erionite, antigorite, winchite and richterite are four of such fibers that have been shown to cause MM (5). As rural areas in the USA and in Europe are developed, the likelihood of human exposure to such fibers increases, as documented, for example in North Dakota (USA) for erionite, New Caledonia for antigorite and Libby Montana (USA) for winchite and richterite (5). Together, asbestos in place, increased exposure to other types of carcinogenic mineral fibers, inherited mutations of the BRCA1-associated protein-1 (*BAP1*) gene (7), and possible additional causes that at this time are not yet defined, likely account for the continued high incidence of MM.

MM occurs after a median latency period of 30–50 years from initial exposure to mineral fibers (8). The mean age at diagnosis is 70–74 years (1) and due to occupational exposure the male to female sex ratio is generally 4:1–8:1 (9). Because the diagnosis is often made at a late stage, MM prognosis is very poor, with a median survival of 6–12 months and a 5-year survival of <5% (10). Epithelial MM is the most common histological subtype and is associated with better survival (11.1 months) than other subtypes, as follows: sarcomatoid (4.5 months), biphasic (7.2 months) and undifferentiated MM (2.7 months) (11,12). Women have a better survival compared with men, independent of age, stage and treatment (13).

Occupational exposure to asbestos appears to account for ~50–80% of male and ~15–20% of female MM cases (14). Actually, environmental exposure to mineral fibers present in the natural environment poses a risk similar to occupational exposure to asbestos (5). Recently, we discovered that germline mutations of the *BAP1* gene cause a hereditary cancer syndrome characterized by a very high incidence of MM and uveal melanoma in families that were not occupationally exposed to asbestos (7,15). Several other studies have confirmed and expanded our findings (16–31).

BAP1 is a nuclear deubiquitinylase and is usually found as part of multiprotein complexes that regulate key cellular pathways, including the cell cycle, cellular differentiation, cell death, gluconeogenesis and the DNA damage response. *BAP1* is located on chromosome 3p21 in a region that often shows loss or deletion in various cancers (7).

We have been studying two families with germline *BAP1* mutations for over 10 years (7). Several family members developed MM, and we noted that some of them had prolonged survival. Thus, in this study we tested the hypothesis that MM occurring in germline *BAP1* mutation carriers (hereafter referred to as 'BAP1 MM cohort') has a better

Abbreviations: BAP1, BRCA1-associated protein-1; CI, confidence interval; MM, malignant mesothelioma; SEER, Surveillance, Epidemiology, and End Results.

survival compared with sporadic MM. This is the first study of MM survival among patients with germline *BAP1* mutation.

Materials and methods

A systematic search of the PubMed databases was conducted to identify all appropriate family studies on germline *BAP1* mutations for pooled analysis inclusion, using the search terms 'germline' and 'BAP1', or 'family' and 'BAP1'. The inclusion criteria were (i) family studies on BAP1, (ii) one positive germline *BAP1* mutation found in at least one member of the family, (iii) MM diagnosed in at least one member of the family. Predefined exclusion criteria were assigned for studies that did not include the minimal information: *BAP1* status, age at diagnosis, gender, age at death or status at end of follow-up, site of MM. If any of this information was missing the MM case was not included in our study. Eighteen papers were initially selected (15,17–25,27–34), and four of them satisfied the inclusion and exclusion criteria, with a total of six selected families (15,18–20) (Table I).

Twenty-three germline *BAP1* mutation carrier MM patients were identified aged 34–87 years old that met the inclusion and exclusion criteria (see above). Sixteen of them were from families we are studying: 10 from two BAP1 families we studied for many years (15); and six were from six separate families that we screened recently because of a history of MM and other malignancies. In these 16 MM patients, *BAP1* mutation status was assessed by extracting genomic DNA from whole blood followed by bidirectional sequencing of the *BAP1* gene (15). Seven additional MM that developed in germline *BAP1* mutation carriers were from four families that were published by others; the details of genetic testing are described in those publications (17–20).

The population-based comparison group was of all MM cases recorded at the Surveillance, Epidemiology, and End Results (SEER) program from 1973 to 2010 (hereafter referred to as 'SEER MM cohort'). The diagnoses of these MMs were histologically confirmed, and MM patients 35–84 years old were selected to match the BAP1 MM cohort. The SEER is a program of the National Cancer Institute that gathers records of incidence, survival and prevalence of cancer from several United States state cancer registries following strict quality rules, and covering 26% of the United States population. A total of 10 556 MM cases were included, 8167 in male and 2389 in female (M:F sex ratio = 3.42). The median MM survival was 8.6 months. Because available data on survival were given in years in our BAP1 MM cohort and in months in the SEER MM cohort, we could not directly compare survival between the two cohorts. Nevertheless, data from the control SEER MM cohort allowed us to compare the observed survival in the cohort of MM patients with germline *BAP1* mutations with a theoretical median survival of 1 year.

Comparison of continuous variables was performed using the *t*-test, the Welch variant of *t*-test when the variances were significantly unequal and the Mann–Whitney non-parametric test when the distribution of the data was not normal. For the comparison of categorical variables the chi-squared or Fisher's exact test were used. Survival analysis was carried out using the Kaplan–Meier method; the Wilcoxon test was used to compare survival curves, which is more powerful in detecting differences early in time, rather than the log-rank test, which is more sensitive in detecting differences late in time (35). Five-year survival, and median survival time with 95% confidence interval (CI) were calculated according to demographic and clinical studied factors. A multivariate stepwise Cox regression analysis was performed to evaluate independent prognostic factors (age at diagnosis, sex, MM site, unique or multiple cancers), and their interactions. All tests were two tailed and the significance limit was set for $P \leq 0.05$. All analyses were realized using STATA version 12.0.

Results

The characteristics of the 23 participants included in the pooled cohort are described in Table II. Among them, 14 were female (60.9%). The mean age at MM diagnosis was 56.3 years and median age was 55 years, ranging from 34 to 87 years. Ten patients had peritoneal MM, 10 had pleural MM, and three had both. The histological subtype was known for only 12 patients (52.2%); all of them were of the epithelioid subtype. Eleven patients (47.8%) are presently alive. Thirteen patients (56.5%) had one or several other cancers in addition to MM. There was no correlation between sex, site of cancer, mean age at diagnosis and proportion of other cancers (Table II).

The two studied cohorts presented several significant differences: the mean age at MM diagnosis was of 56.3 years in the BAP1 MM cohort, and 72 years in the SEER MM cohort; the M:F ratio was 0.73:1 in the BAP1 MM cohort, and 3.42:1 in the SEER MM cohort ($P \leq 0.0001$). Moreover, the percentage of peritoneal MM was higher in the BAP1 MM cohort (50.0%) than in the control SEER MM cohort (14.2%, $P \leq 0.0001$).

In the BAP1 MM cohort, the 5-year survival rate was 47% (95% CI: 24–67%) compared with 6.7% (95% CI: 6.2–7.3%) in the control SEER MM cohort, and the median survival from MM diagnosis was 5 years (95% CI: 3 years; -), compared with <1 year in the control SEER MM cohort (Figure 1). When MM survival was analyzed according to clinical characteristics of the patients with germline *BAP1* mutations (Table III, Figure 2), females had a 5-year survival of 49 versus 42% in males ($P = 0.3442$). Similar differences in survival between genders were observed in the SEER MM cohort: women had a 5-year survival of 13.3% (95% CI: 11.9–14.8%) compared with men (4.8%, 95% CI: 4.3–5.3%). In the SEER MM cohort, survival was also better in the youngest group (median survival of 13.25 months and 5-year survival rate of 17.4% for patients younger than 55 years; median survival of 8.11 months and 5-year survival rate of 5.1% for patients aged 55 and older). Instead, survival was not related to age in the BAP1 MM cohort: among those aged <55 years, 5-year survival was 45% compared with 51% among those ≥55 years ($P = 0.3658$). In the BAP1 MM cohort survival was longer in patients with a peritoneal MM (median survival of 10 years) compared with pleural MM (median survival of 2 years, $P = 0.0571$). The median survivals were comparable between peritoneal and pleural MM in the SEER MM cohort: 8.69 and 8.55 months, respectively. Peritoneal MM had a significantly worse 5-year survival compared with pleural MM in the SEER MM cohort (Table III). In the BAP1 MM cohort the presence of a second malignancy was associated with a better survival, although not significant because of the small number of patients, compared with MM patients without a second malignancy: median survival of 10 years, 95% CI (4 –) versus 3 years, 95% CI (1 –); $P = 0.0716$.

In the multivariate analysis, only the presence of another cancer in addition to MM (hazard ratio = 0.384, 95% CI: 0.120–1.234, $P = 0.1053$) was retained in the final model, but the small numbers did not lead to a significant result. No interaction between the studied factors (age, sex, MM site and other cancer) was significant.

Discussion

Here we tested the hypothesis that MM arising in carriers of germline *BAP1* mutations have better prognosis compared with sporadic MM. The results showed that germline *BAP1* mutation carriers with MM had roughly seven times longer survival than the control cohort,

Table I. Published germline *BAP1* mutations among MM patients

References	Family	Study description	Number of MM with *BAP1* mutation	Age range (years)	Sex M/F
Testa *et al.* (15)	LOU	Familial mesothelioma	6	37–66	2/4
	WIS		4	43–58	1/3
Wadt *et al.* (20)	II	Familial melanoma	1	84	0/1
	III		1	47	1/0
Wiesner *et al.* (18,19)	F2	Familial melanoma	1	52	0/1
	F3		4	34–87	1/3

Table II. BAP1 MM cohort patient characteristics

Variable	*N*	Male/female	Age at MM (years): mean (range)	>1 cancer (%)	MM first cancer (%)	% Alive
All	23	9/14	56.3 (34–87)	56.5	73.7	47.8
Sex						
Female	14		56.4 (34–84)	57.1	75.0	50.0
Male	9		56.3 (37–87)	55.6	71.4	44.4
Age group (years)						
34–54	10	4/6	—	60.0	71.4	50.0
55–87	13	5/8	—	53.8	75.0	46.1
Site						
Pleural	10	4/6	56.2 (43–87)	40.0	87.5	40.0
Peritoneal	10	5/5	58.3 (37–84)	60.0	62.5	50.0
Both	3	0/3	50.7 (34–63)	100	66.7	66.7

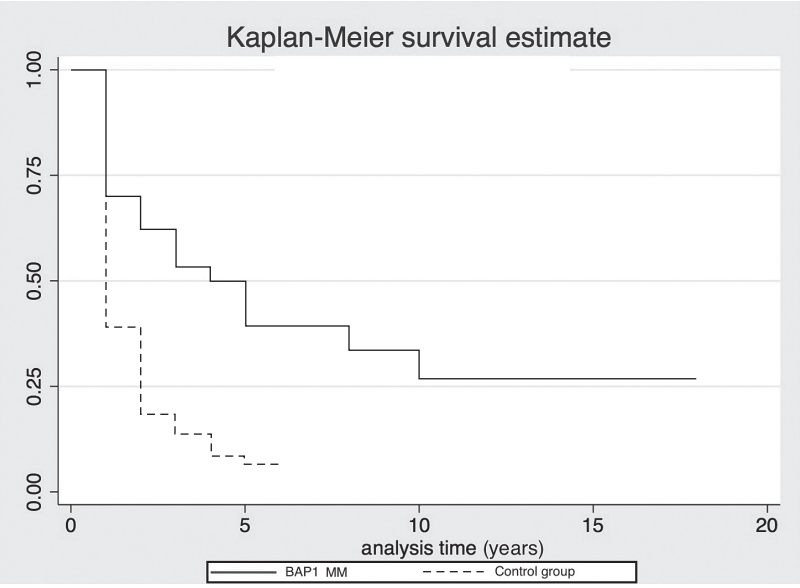

Fig. 1. Kaplan–Meier survival curves of the BAP1 MM cohort patients ($N = 23$) and of the SEER MM cohort ($N = 10\,556$). The survival curve for the control group was based on the survival data rounded to the years.

which represented a population sample of United States MM from the SEER database.

Compared with the SEER MM cohort, the BAP1 MM cohort had several significant clinical differences: (i) earlier mean age at MM diagnosis (56.3 versus 72 years); (ii) lower M:F ratio (0.73:1 versus 4:1); and (iii) higher percentage of peritoneal MM (50 versus 14.2%). Collectively, a younger age at diagnosis, a M:F sex ratio close to 1:1 as well as a pleural:peritoneal ratio close to 1:1, are typical of MMs developing in cohorts without occupational exposure to asbestos fibers and instead help to identify cohorts with genetic predisposition to MM or environmentally exposed to carcinogenic mineral fibers from early age (36). Among the individuals forming the cohort with germline *BAP1* mutations and MM, none had occupational exposure to asbestos, suggesting that either a low background amount of exposure to mineral fibers might be sufficient to trigger MM, or alternatively that these MM are totally unrelated to exposure to carcinogenic mineral fibers.

Since the pooled BAP1 MM cohort and the SEER MM cohort were matched for the period of time of MM diagnosis, therapeutic options available to patients should be similar in the two cohorts and should not affect survival significantly. Moreover, current therapies only extend the ~1 year MM survival by ~11 weeks (10), whereas carriers of germline *BAP1* mutations had an average survival of 5 years, an amount of time that significantly exceeded the benefit of any available therapy.

We tested and disproved the hypothesis that the patient characteristics in the BAP1 MM cohort might be related to the extended survival. MM in women has been related to better survival (13), particularly for peritoneal MM (37). However, in the BAP1 MM cohort the 5-year survival was four times better in females and nine times better in males compared with the SEER MM group. Thus, the increased proportion of women in the BAP1 MM cohort alone could not explain the better survival in this cohort, as males did better than females (Table III). Similarly, the younger age of the BAP1 MM cohort was not associated with better survival as older patients in this cohort appeared to do as well or better than younger ones, although the low number of patients precludes studies of significance (Table III). In contrast to the SEER MM cohort, in the BAP1 MM cohort median survival was 10 years for peritoneal MM compared with 2 years for pleural MM (Table III). In the general population, peritoneal MM has a very poor prognosis with a median survival of 6–12 months from diagnosis (38). Only recent therapies, available in specific experienced centers, have improved the prognosis of peritoneal MM in selected patients (39–42).

Histology was available for review for 12 MM in the germline *BAP1* mutation carrier cohort. All of them were of the epithelial subtype a less aggressive variant compared with other histological subtypes. However, the 5-year median survival we observed in these patients far exceeded the 1-year median survival observed in epithelial MM (10). Interestingly, germline *BAP1* mutations have also been associated with well-differentiated papillary mesothelioma (23), a rare variant of epithelioid mesothelioma clinically indolent with long survival (these 'benign' MMs were excluded from our analysis).

Table III. Median and 5-year MM survival by clinical characteristics in sporadic and *BAP1* mutation-carrying MM patients

	MM patients with germline *BAP1* mutations				SEER control group		
Variable / Category	*N*	Median survival (95% CI)	Wilcoxon *P* value between categories	5-year survival (95% CI)	*N*	Median survival [months (95% CI)]	5-year survival (95% CI)
All patients	23	5 years (3 –)	—	47% (24–67%)	10556	<1 year [9 months (9–9)]	6.7% (6.2–7.3%)
Sex							
Female	14	5 years (3 –)		49% (23–73%)	2389	<1 year [10 months (11–13)]	13.3% (11.9–14.8%)
Male	9	4 years (1 –)	0.3442	42% (10–71%)	8167	1 year [8 months (8–9)]	4.8% (4.3–5.3%)
Age							
<55 years	10	5 years (1 –)		45% (12–73%)	1360	1 year [13 months (13–14)]	17.4% (15.3–19.6%)
≥55 years	13	10 years (3 –)	0.3658	51% (20–74%)	9196	<1 year [8 months (8–9)]	5.1% (4.6–5.6%)
Site							
Pleural	10	2 years (1 –)		38% (10–66%)	9247	<1 year [9 months (8–9)]	16.0% (13.7–18.3%)
Peritoneal	10	10 years (1 –)	Pleural only versus peritoneal only, 0.1210	53% (18–77%)	1309	<1 year [9 months (8–9)]	5.2% (4.7–5.7%)
Both	3	— (5 –)	Pleural only versus peritoneal/both, 0.0571	67% (5–95%)	—	—	—
+ Other cancer							
No	10	3 (1 –)		24% (4–58%)	—	—	—
Yes	13	10 (4 –)	0.0716	64% (30–85%)	—	—	—

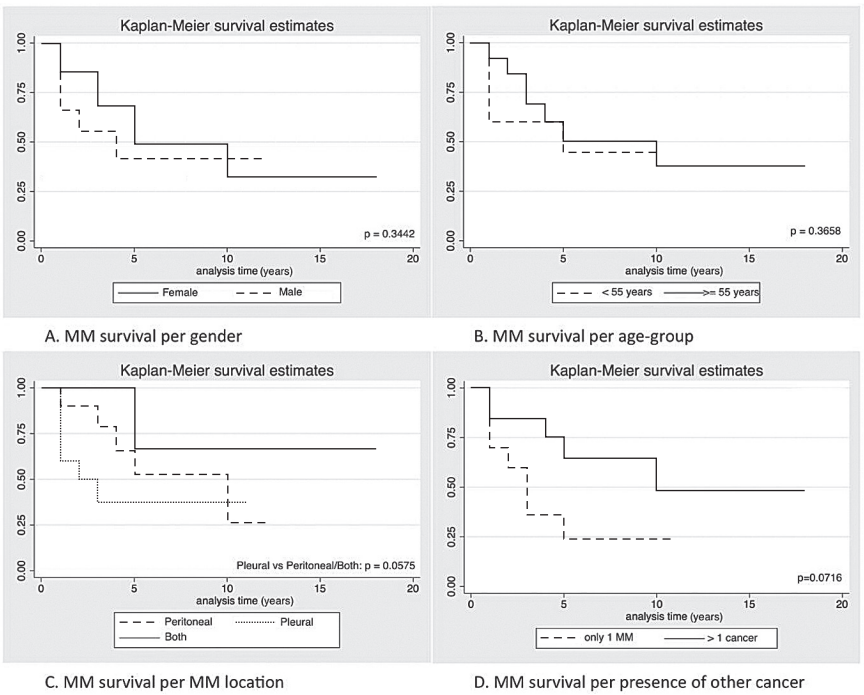

Fig. 2. Kaplan–Meier survival curves of the BAP1 MM cohort according to sex, age, MM site and presence of other cancers.

In summary, the clinical characteristics cannot explain the 7-fold increased survival we observed in the cohort of MM patients with germline *BAP1* mutations.

Within this BAP1 MM cohort, both the univariate and multivariate analyses showed a non-significant trend of improved survival in patients with multiple cancers and/or peritoneal MM. A limitation of our study is the small number of cases, which may prevent detecting significant differences between the two compared cohorts. Among the 13 individuals with MM and at least one other cancer, six developed at least one malignancy before developing MM. In these individuals, a first diagnosis of cancer might have increased the frequency of medical follow-ups and the chances for early detection of MM. In addition, because members of families carrying germline BAP1 mutations are at high risk of MM and other cancers, it is possible that they may seek medical evaluation earlier than the general population and be diagnosed at an earlier stage. Early MM detection is associated with better survival; however, only ~5% of MM are diagnosed in stage I (43). Data on the stage of disease at diagnosis were not available in the present study. However, although early detection in some of these patients may have contributed to the improved prognosis, it was probably not the only factor, as the cohort we studied includes MM patients that were diagnosed before we discovered the BAP1 cancer syndrome, and thus before any medical protocol for regular screening was put in place. Because early detection is linked to improved prognosis, since 2013 we yearly screen BAP1 family members for melanoma, and most of them are also enrolled in a biomarker clinical trial for early detection of MM and other cancers.

Acquired somatic *BAP1* mutations have been reported in 22–23% of United States MM biopsies (7,15,44) and in 61% of Japanese MM biopsies (45). The apparent discrepancy between the United States and Japanese results may be related to methodological or

ethnical differences: these hypotheses are currently being investigated in a joint effort between our laboratory and some of the Japanese investigators. However, there are no apparent distinct clinical phenotypes for MM with somatic *BAP1* mutations (44). This is in contrast with what was observed in renal cell carcinoma (46–49) and in uveal melanoma (50), where somatic *BAP1* mutations are associated with a much more aggressive tumor phenotype and metastases.

MM survival of 5 years or more is exceedingly rare, yet we observed it in more than half of the MM that occurred in a cohort carrying germline *BAP1* mutations. It would be an extraordinary coincidence if less aggressive cases would cluster in this way following only a selection bias. Our data, instead, indicate that MM arising in the context of germline *BAP1* mutations is clinically less aggressive and frequently associated with prolonged survival. This information should be taken into account to provide appropriate genetic counseling and clinical management to MM patients with germline *BAP1* mutations.

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Conflict of Interest Statement: M. Carbone has pending patent applications on BAP1 and provides consultation for mesothelioma expertise and diagnosis. The remaining authors declare no competing financial interests.

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