Incidence and survival of peritoneal malignant mesothelioma between 1989 and 2015: A population-based study

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Abstract

Background: Peritoneal malignant mesothelioma is a rare disease for which few population-based studies are available. The aim of this study was to describe the evolution of the

incidence and survival of peritoneal malignant mesothelioma in France between 1989 and 2015, using data derived from the French network of cancer registries.

Methods: Age world-standardized incidence rates and overall survival were calculated using data from 16 French cancer registries. Log-linear Poisson regression analysis was used to estimate the average annual percentage change in incidence rates. Overall survival was performed using age-adjusted Cox proportional hazards model.

Results: In French men, the incidence has increased quietly over the reporting period from 0.07 to 0.10 with a maximum of 0.16 per 100,000 persons-years in 2001–2003. For women, the increase in incidence has been lower than for men over the period 1989–2015, ranging from 0.04 to 0.11. A better prognosis was associated with a diagnosis made after 2000 (HR = 1.76; p = 0.013), the epithelioid histological type (p = 0.003), and the fact of being a woman, which has a 5-year risk of death half that of men (HR = 0.55; p = 0.001), regardless of age, diagnosis period or histology.

Conclusion: Our results are similar to those currently available for other countries. In France, peritoneal mesothelioma remains a rare and fatal cancer with a small increase in the incidence rate since 1989 and a median survival of 1 year; it seemed to develop equally in women and men over this period of time.

Keywords: Malignant peritoneal mesothelioma, incidence, time trends, survival

1. Introduction

Malignant mesothelioma is a rare disease that results from the transformation of mesothelial cells that line the serosal surfaces. It represents 0.2% of all cancers [1] and has a dismal prognosis with few therapeutic options. Mesothelioma is much more frequent in men than in women (ratio 3.7:1) [2]. It is strongly associated with asbestos exposure (up to 90% of male cases [3]), and can develop in the pleura (the most frequent location, 90%), the peritoneum (10%), and rarely in the tunica vaginalis testis and pericardium [4].

Due to its rarity, trends in peritoneal mesothelioma among men and women are not as extensively described as for pleural mesothelioma. Between 1971 and 1995, the incidence of peritoneal mesothelioma was estimated to 0.02–0.3 cases per 100,000 persons-years in the US and Europe. Age world-standardized rates per 100,000 persons-years range from 0.05–0.3

cases in men to 0.02–0.2 in women [5]. A study carried out in 2011, the RARECARE study, estimated the incidence between 1995 and 2002 at 0.12 cases per 100,000 persons-years in Europe [6].

The 5-year overall and relative survivals reported by the RARECARE study between 1995 and 2002 and were 9.8% and 11.4%, respectively [6]. The mechanisms of carcinogenesis in peritoneal malignant mesothelioma have not been definitively elucidated [7], limiting the therapeutic options. Nevertheless, the combined treatment of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy can offer prolonged survival for selected patients, increasing the 5-year overall survival to 47% [8].

Taking advantage of the French National Database MESOPATH, which systematically certifies the pathological diagnosis of mesothelioma, together with the French Network of Registries (FRANCIM), this study describes for the first time the French incidence and survival of malignant peritoneal mesothelioma from population-based data available between 1989 and 2015.

2. Material and methods

2.1. Data sources

FRANCIM provided incidence and follow-up data from local cancer registries operating at the 'department' level (French administrative area). All of these registries follow the rules of the European Network of Cancer Registries for recording and coding, and cancers were defined according to the International Classification of Diseases for Oncology, 3rd edition (ICDO-3). Local data were checked and standardized before inclusion in the common database [9].

Data were available from 16 registries of this network, with at least 5 years of information for the areas covered by the cancer registries, which in total represent 20% of the French metropolitan population (Table 1). The included invasive tumors corresponded to ICDO-3 C48.0–8 topographies and 9050/3–9053/3 morphologies, diagnosed between 1989 and 2015.

A standardized procedure of certification for the pathological diagnosis is applied to all reported mesothelioma cases in France. The pathological diagnosis certification is provided by expert pathologists in the field covering all the French departments, the Referent National Center MESOPATH [10,11]. The cases were recorded according to the three histological types (epithelioid, biphasic and sarcomatoid) as defined by the WHO 2015 classification. The well-

differentiated papillary mesotheliomas, multicystic peritoneal mesotheliomas, and adenomatoid tumors were all excluded from the study because they were clinically and prognostically separate entities from diffuse epithelioid malignant mesothelioma. They were indolent tumors associated with very long survival.

The population data estimated for each department each year for each age group were provided by the National Institute for Statistics and Economic Studies.

All registries carried out an active search for the vital status of the patients using a single standardized procedure via an electronic request to the 'National directory identifying private persons' and from the medical patient's files on June 30th 2013. For patients still alive, an update of the survival was made from the patient's medical files on September 30th 2018. The search for the context of asbestos exposure is not part of the collected data from the registries, and is not exhaustively reported in MESOPATH database.

2.2. Statistical analysis

All statistical analyses were performed using Stata Statistical Software: Release 13.0 (College Station, Texas, USA: Stata Corporation). Potential differences in individual and morphological characteristics were investigated by period using Pearson's chi-square and Mann–Whitney's tests.

The incidence rates by gender were estimated as the number of incident cases occurring each year divided by the total annual persons-years the same year in the general population in the same geographical area. Age-specific rates were calculated using 10-year age groups and 3-year period groups. Age world-standardized rates were standardized by the direct method using the World population age structure proposed by Segi's reference [12] and were expressed for 100,000 persons-years. Changes in time trends were analyzed using age-adjusted log-linear Poisson regression.

For patients diagnosed between 1989 and 2012, we calculated the overall survival (OS) defined as the time between the date of diagnosis and the date of last follow-up, at 1, 3 and 5 years using the Kaplan–Meier method. Curves resulting from univariate analysis were compared by using the log-rank test. For multivariate analysis, the age-adjusted Cox proportional hazards model was used, significant variables in univariate analysis being entered (p <0.15).

For incidence and survival, rates and hazard ratios (HRs) are given with 95% confidence intervals (95%CIs).

3. Results

3.1. Incidence

A total of 349 malignant peritoneal mesotheliomas diagnosed between January 1st 1989 and December 31st 2015 were used to calculate the incidence (Table 1). We found an almost equal incidence in men and women, with a ratio of men to women of 1.3 (195/154). The median age of onset was 66 years; there was no significant difference between men (67 years) and women (65 years). The gender distribution (p = 0.51) and age of patients (p = 0.27) were the same in each diagnosis period. The diagnosis was more precise after 2000 due to the improving pathological knowledge of mesothelioma and the establishment of the pathological diagnosis certification, resulting in a significant decrease in the not-otherwise-specified mesothelioma percentage between 1989 and 2015 (Table 2).

Although the incidence rates for peritoneal mesothelioma increased over the period, no significant change in incidence was observed between 1989 and 2015. In men, the world age-standardized incidence rate increased weakly by +0.94% (–1.04%; 1.40%) per year over the overall period from 0.07 in 1989 to 0.10 in 2015. In women, with an incidence of 0.04 in 1989 against 0.07 in 2015, an increase of +0.74% (–1.20%; 1.37%) per year is reported (Figure 1, Table 3). It should be noted that between 2004 and 2015 the trends in male and female incidence rates were very similar (Figure 1).

3.2. Survival

A total of 282 malignant peritoneal mesotheliomas diagnosed between January 1st 1989 and December 31st 2012 were used to calculate the survival (Table 1). The proportion of lost-to-follow-up cases was 1.7%. The total population presented a median OS of 11.4 months and a 5-year OS of 21% (95%CI 17–26).

In the univariate analysis, the 5-year OS was significantly lower for patients older than 66 years (11%; 95%CI 5–19; p <0.0001). Women had a better survival than men, with a 5-year OS of 33% against 12% in men (p <0.0001). A non-epithelioid histology was associated with a worse prognosis with a 5-year OS of 8%. Epithelioid type and not-otherwise-specified mesothelioma had a survival of 23% at 5 years. Patients diagnosed in the more recent period

had a better survival at 5 years: 31% in the period 2010–2012 against 18% in the periods 1989–1999 and 2000-–2009 (Table 4). Survival at 5 years improved—especially during the last diagnostic period—in women (51% in 2010–2012, 26% in 1989–2009), in patients under 66 years of age (40–60% in 2010–2012, 14–31% in 1989–2009) and by histological type (Table 5).

The multivariate analysis adjusted by age confirmed the results of the univariate analysis. Women had a 5-year risk of death half that of men (HR = 0.55; $p = 0.001$), regardless of age, diagnosis period or histology. A diagnosis made after 2000 also had half the 5-year risk of death (HR = 1.76; $p = 0.013$). Biphasic or fibrous (sarcomatoid) mesotheliomas had for their part a risk at 5 years two-fold greater than that of epithelioid or not-otherwise-specified mesothelioma ($p = 0.003$) (Table 4).

4. **Discussion**

In this study we report for the first time the patients' characteristics and long-term trends in the incidence and survival of peritoneal malignant mesothelioma in France from the population-based cancer registries, using data available since 1989. Peritoneal mesothelioma is a rare disease that histologically mimics other cancers, causing frequent misdiagnosis that may result in epidemiological discordances. Thanks to advances in biological and histological knowledge of this tumor and the establishment in France in 1998 of a standardized procedure for certification of the diagnosis of mesothelioma, diagnostic accuracy has improved, as has in consequence the coding and assessment of incidence, reducing epidemiological bias [9]. In our series, the risk of misclassification is minimal.

We found that, contrary to pleural malignant mesothelioma (ratio of men to women of about 4:1 between 1989 and 2003 and 3:1 since 2003 [3,9,10,13-15]), peritoneal mesothelioma develops almost equally in both men and women. In French men, the incidence has been slowly increasing since 1989 from 0.07 per 100,000 persons-years in the period 1989–1991 to 0.10 in 2012–2015, with a maximum rate of 0.16 in 2001–2003. For women, this rate increased faster than for men over the period 1989–2015, fluctuating between 0.04 and 0.11. These findings were consistent with results recently published in Europe [16]; in particular, the male incidence per 100,000 persons-years in Lombardy had two peaks, one in 2001 (0.17) and one in 2010 (0.19) [15], and this has also been observed in France.

If we compare our results with those obtained in a parallel study of the pleural counterpart in similar population settings and data sources [9], we notice that the clinical behavior of these two mesothelioma localizations is clearly different. The median OS is 11.7 months in peritoneum and 10.6 months in pleura. Only 4% of men and 11% of women affected by pleural mesothelioma are alive 5 years after diagnosis, against 13% of men and 34% of women with peritoneal mesothelioma. The 1-year survival rate is similar for both diseases, reflecting the high lethality of these diseases regardless of their location; however, the proportion of long-term survivors is larger in peritoneal mesothelioma cases [17,18]. The main individual characteristics associated with 5-year survival, regardless of age, are: female gender, epithelioid morphology, and diagnosis after 2000. Regarding the results for the histological type, the devastating prognosis of biphasic or sarcomatoid types (also called fibrous for cancer registries) is well established [17-19].

Due to the appointment of a pathologists' panel at national level to perform a pathological review, we could rule out that diagnosis misclassification occurred selectively in women and is responsible for the difference in survival between genders. Several studies have reported the role of gender in prognosis [17,20], which may reflect a biological difference. Recent molecular studies have provided new insights, in particular regarding the loss-of-function mutations in *CDKN2A* (p16), *NF2* and *BAP1* previously reported in pleural malignant mesothelioma [21-23]. The prognostic impact of these alterations was investigated in peritoneal mesothelioma [24-26]; it was found that the presence of a *BAP1* mutation is a long-term survival factor, while the presence of homozygous *CDKN2A* deletion or hemizygous *NF2* loss results in poor survival. Singhi *et al.* [25], in a series of 86 patients with peritoneal mesothelioma who benefited from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy between 2001 and 2014, showed that peritoneal cancer index, extent of invasion, and combination of *CDKN2A* deletion and *NF2* loss were prognostic factors independent of age. Gender and completeness of cytoreduction were not significant. However, there were no significant differences in the frequency of *CDKN2A* deletions, *NF2* loss, and BAP1 expression between the 60 men and 26 women included in this study.

The diagnosis period also seems to play an important role in the prognosis. Continuous advances in the knowledge of mesothelioma, and therefore in medical imaging, immunohistochemical and molecular biology techniques allow for more efficient and earlier detection of this disease. With the introduction of cytoreductive surgery and hyperthermic

intraperitoneal chemotherapy, studies from the literature have reported significant improvement in survival for patients treated for a peritoneal mesothelioma [8,27,28]. In France, this heavy treatment has been performed on selected peritoneal mesothelioma patients since the early 1990s. Moreover, the French National Cancer Institute (INCa) supports the establishment of the RENAPE Network of expert and specialized centers in the management of this rare peritoneal disease in 2009. We may hypothesize that this policy leading to early diagnosis and better therapeutic management may explain the better prognosis in the most recent population (from 2010 to 2012). The RENAPE database [28,29] reported a median survival of 61 months and a 5-year OS of 53% on a series of 126 eligible cases with a median age of 56–59 years diagnosed between 1991 and 2014. According to the multivariate analysis performed, the only independent prognostic factors were the completeness of cytoreduction and the administration of neoadjuvant chemotherapy [30]. This study did not take into account molecular markers.

5. Conclusions

Our results are similar to those currently available for other countries. In France, peritoneal mesothelioma remains a rare and fatal cancer with a small increase in the incidence rate since 1989 and a median survival of 1 year. Noticeably, our results provide evidence that peritoneal mesothelioma develops equally in women and men over this period of time. More extensive epidemiological studies on larger cohorts would be needed for a better understanding of the trends in mesothelioma in relation to biological, occupational and non-occupational etiological factors.

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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Sep 12.

[2] Abdel-Rahman O. Global trends in mortality from malignant mesothelioma: Analysis of WHO mortality database (1994-2013). *Clin Respir J*. 2018; 12(6): 2090-2100.

[3] Marinaccio A, Corfiati M, Binazzi A, Di Marzio D, Scarselli A, Ferrante P, Bonafede M, Verardo M, Mirabelli D, Gennaro V, Mensi C, Schallemberg G, Mazzoleni G, Merler E, Girardi P, Negro C, D'Agostin F, Romanelli A, Chellini E, Silvestri S, Pascucci C, Calisti R, Stracci F, Romeo E, Ascoli V, Trafficante L, Carrozza F, Angelillo IF, Cavone D, Cauzillo G, Tallarigo F, Tumino R, Melis M, Iavicoli S; ReNaM Working Group. The epidemiology of malignant mesothelioma in women: gender differences and modalities of asbestos exposure. *Occup Environ Med*. 2018; 75(4): 254-262.

[4] Galateau-Sallé F, Brambilla E, Cagle P, et al. Pathology of malignant mesothelioma; an update of the international mesothelioma panel. London: *Springer*, 2006. p. 29.

[5] Boffetta P, Epidemiology of peritoneal mesothelioma: a review, *Ann. Oncol*. 2007; 18: 985–990.

[6] Gatta G, van der Zwan JM, Gasali PG, Siesling S, Dei Tos AP, Kunkler I, et *al*. Rare cancers are not so rare: the rare cancer burden in Europe, *Eur J Cancer.* 2011; 47: 2493–2511. doi: 10.1016/j.ejca.2011.08.008.

[7] Judge S, Thomas P, Govindarajan V, Sharma P, Loggie B. Malignant peritoneal mesothelioma: characterization of the inflammatory response in the tumor microenvironment, *Ann Surg Oncol*. 2016; 23: 1496–1500. doi: 10.1245/s10434-015-4965-6.

[8] Yan TD, Deraco M, Baratti D et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multiinstitutional experience. *J Clin Oncol* 2009; 27: 6237–6242. doi: 10.1200/JCO.2009.23.9640.

[9] Cowppli-Bony A, Uhry Z, Remontet L, Voirin N, Guizard AV, Trétarre B, Bouvier AM, Colonna M, Bossard N, Woronoff AS, Grosclaude P; French Network of Cancer Registries (FRANCIM). Survival of solid cancer patients in France, 1989-2013: a population-based study. *Eur J Cancer Prev*. 2017; 26(6): 461-468. doi: 10.1097/CEJ.0000000000000372.

[10] Le Stang N, Belot A, Gilg Soit Ilg A, Rolland P, Astoul P, Bara S, Brochard P, Danzon A, Delafosse P, Grosclaude P, Guizard AV, Imbernon E, Lapôtre-Ledoux B, Ligier K, Molinié F, Pairon JC, Sauleau EA, Trétarre B, Velten M, Bossard N, Goldberg M, Launoy G, Galateau-Sallé F. Evolution of pleural cancers and malignant pleural mesothelioma incidence in France between 1980 and 2005. *Int J Cancer*. 2010; 126(1): 232-8.

[11] Galateau-Sallé F, Gilg Soit Ilg A, Le Stang N, Brochard P, Pairon JC, Astoul P, Frenay C, Blaizot G, Chamming's S, Ducamp S, Rousvoal T, de Quillacq A, Abonnet V, Abdalsamad I, Begueret H, Brambilla E, Capron F, Copin MC, Danel C, de Lajartre AY, Foulet-Roge A, Garbe L, Groussard O, Giusiano S, Hofman V, Lantuejoul S, Piquenot JM, Rouquette I, Sagan C, Thivolet-Bejui F, Vignaud JM, Scherpereel A, Jaurand MC, Jean D, Hainaut P, Chérié-Challine L, Goldberg M, Luce D, Imbernon E. The French mesothelioma network from 1998 to 2013. *Ann Pathol*. 2014; 34(1): 51-63. doi: 10.1016/j.annpat.2014.01.009.

[12] Segi M, Fukushima I, Kurihara M. A proposal on a calculation method to be applied by geographical comparison of cancer mortality. *Tohoku J Exp Med*. 1954; 60(3-4): 307-10.

[13] Gilg Soit Ilg A, Ducamp S, Gramond C, Audignon S, Chamming's S, de Quillacq A, et *al*. Programme national de surveillance du mésothéliome (PNSM). Actualisation des principaux résultats. *Bull Epidémiol Hebd*. 2015; (3-4): 28-37. http://www.invs.sante.fr/beh/2015/3-4/2015_3-4_1.html

[14] Salo SAS, Ilonen I, Laaksonen S, Myllärniemi M, Salo JA, Rantanen T. Epidemiology of malignant peritoneal mesothelioma: A population-based study. *Cancer Epidemiol*. 2017; 51: 81-86. doi: 10.1016/j.canep.2017.10.008. Epub 2017 Nov 5. PubMed PMID: 29080447.

[15] Mensi C, Mendola M, Dallari B, Sokooti M, Tabibi R, Riboldi L, Consonni D. Differences between peritoneal and pleural mesothelioma in Lombardy, Italy. *Cancer Epidemiol*. 2017; 51: 68-73. doi: 10.1016/j.canep.2017.10.003.

[16] Siesling S, van der Zwan JM, Izarzugaza I, Jaal J, Treasure T, Foschi R, Ricardi U, Groen H, Tavilla A, Ardanaz E; RARECARE Working Group. Rare thoracic cancers, including peritoneum mesothelioma. *Eur J Cancer*. 2012; 48(7): 949-60. doi: 10.1016/j.ejca.2012.02.047.

[17] Mirabelli D, Roberti S, Gangemi M, Rosato R, Ricceri F, Merler E, Gennaro V, Mangone L, Gorini G, Pascucci C, Cavone D, Nicita C, Barbieri PG, Marinaccio A, Magnani C, Montanaro F. Survival of peritoneal malignant mesothelioma in Italy: a population-based study. *Int J Cancer*. 2009; 124(1): 194-200. doi: 10.1002/ijc.23866.

[18] Montanaro F, Rosato R, Gangemi M, Roberti S, Ricceri F, Merler E, Gennaro V, Romanelli A, Chellini E, Pascucci C, Musti M, Nicita C, Barbieri PG, Marinaccio A, Magnani C, Mirabelli D. Survival of pleural malignant mesothelioma in Italy: a population-based study. *Int J Cancer*. 2009; 124(1): 201-7. doi: 10.1002/ijc.23874. PubMed PMID: 18792097.

[19] Soeberg MJ, Leigh J, Driscoll T, Armstrong B, Young JM, van Zandwijk N. Incidence and survival trends for malignant pleural and peritoneal mesothelioma, Australia, 1982-2009. *Occup Environ Med*. 2016; 73(3): 187-94. doi: 10.1136/oemed-2015-103309.

[20] Cao C, Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH; Peritoneal Surface Malignancy Group. Importance of gender in diffuse malignant peritoneal mesothelioma. *Ann Oncol*. 2012; 23(6): 1494-8. doi: 10.1093/annonc/mdr477.

[21] Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, Gnad F, Nguyen TT, Jaiswal BS, Chirieac LR, Sciaranghella D, Dao N, Gustafson CE, Munir KJ, Hackney JA, Chaudhuri A, Gupta R, Guillory J, Toy K, Ha C, Chen YJ, Stinson J, Chaudhuri S, Zhang N, Wu TD, Sugarbaker DJ, de Sauvage FJ, Richards WG, Seshagiri S.

Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet*. 2016; 48(4): 407-16. doi: 10.1038/ng.3520.

[22] Guo G, Chmielecki J, Goparaju C, Heguy A, Dolgalev I, Carbone M, Seepo S, Meyerson M, Pass HI. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. *Cancer Res*. 2015; 75(2): 264-9. doi: 10.1158/0008-5472.CAN-14-1008.

[23] De Rienzo A, Archer MA, Yeap BY, Dao N, Sciaranghella D, Sideris AC, Zheng Y, Holman AG, Wang YE, Dal Cin PS, Fletcher JA, Rubio R, Croft L, Quackenbush J, Sugarbaker PE, Munir KJ, Battilana JR, Gustafson CE, Chirieac LR, Ching SM, Wong J, Tay LC, Rudd S, Hercus R, Sugarbaker DJ, Richards WG, Bueno R. Gender-Specific Molecular and Clinical Features Underlie Malignant Pleural Mesothelioma. *Cancer Res*. 2016; 76(2): 319-28. doi: 10.1158/0008-5472.CAN-15-0751.

[24] Singhi AD, Krasinskas AM, Choudry HA, Bartlett DL, Pingpank JF, Zeh HJ, Luvison A, Fuhrer K, Bahary N, Seethala RR, Dacic S. The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma. *Mod Pathol*. 2016; 29(1): 14-24. doi: 10.1038/modpathol.2015.121.

[25] Leblay N, Leprêtre F, Le Stang N, Gautier-Stein A, Villeneuve L, Isaac S, Maillet D, Galateau-Sallé F, Villenet C, Sebda S, Goracci A, Byrnes G, McKay JD, Figeac M, Glehen O, Gilly FN, Foll M, Fernandez-Cuesta L, Brevet M. BAP1 Is Altered by Copy Number Loss, Mutation, and/or Loss of Protein Expression in More Than 70% of Malignant Peritoneal Mesotheliomas. *J Thorac Oncol*. 2017; 12(4): 724-733. doi: 10.1016/j.jtho.2016.12.019.

[26] Baumann F, Flores E, Napolitano A, Kanodia S, Taioli E, Pass H, Yang H, Carbone M. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis*. 2015; 36(1): 76-81. doi: 10.1093/carcin/bgu227.

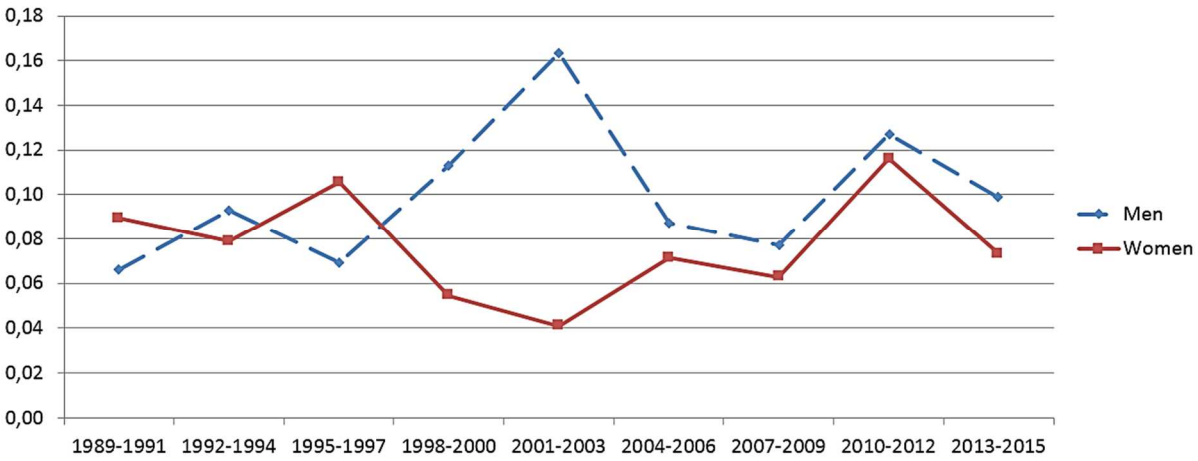
[27] Malgras B, Gayat E, Aoun O, Lo Dico R, Eveno C, Pautrat K, Delhorme JB, Passot G, Marchal F, Sgarbura O, Ferron G, Goéré D, Andre T, Pocard M; RENAPE Network. Impact of Combination Chemotherapy in Peritoneal Mesothelioma Hyperthermic Intraperitoneal Chemotherapy (HIPEC): The RENAPE Study. *Ann Surg Oncol*. 2018; 25(11): 3271-3279. doi: 10.1245/s10434-018-6631-2.

[28] Villeneuve L, Passot G, Glehen O, Isaac S, Bibeau F, Rousset P, Gilly FN; RENAPE Network. The RENAPE observational registry: rationale and framework of the rare peritoneal tumors French patient registry. *Orphanet J Rare Dis*. 2017;12(1):37. doi: 10.1186/s13023-017-0571-y.

[29] Villeneuve L, Isaac S, Glehen O, Capovilla M, Chevallier A, Croce S, Dartigues P, Fontaine J, Kaci R, Lang-Averous G, Laverriere MH, Leroux-Broussier A, Mery E, Poizat F, Valmary-Degano S, Verriele-Beurrier V, Gilly FN, Bibeau F. The RENAPE network: towards a new healthcare organization for the treatment of rare tumors of the peritoneum. Description of the network and role of the pathologists. *Ann Pathol*. 2014;34(1):4-8. doi: 10.1016/j.annpat.2014.01.008.

[30] Kepenekian V, Elias D, Passot G, Mery E, Goere D, Delroeux D, Quenet F, Ferron G, Pezet D, Guilloit JM, Meeus P, Pocard M, Bereder JM, Abboud K, Arvieux C, Brigand C, Marchal F, Classe JM, Lorimier G, De Chaisemartin C, Guyon F, Mariani P, Ortega-Deballon P, Isaac S, Maurice C, Gilly FN, Glehen O; French Network for Rare Peritoneal Malignancies (RENAPE). Diffuse malignant peritoneal mesothelioma: Evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE Database: Multi-Institutional Retrospective Study. *Eur J Cancer*. 2016; 65: 69-79. doi: 10.1016/j.ejca.2016.06.002.

Figure 1. Trends in malignant peritoneal mesothelioma in world age-standardized incidence rates per 100,000 persons-years.


0,18
0,16
0,14
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1989-1991
1992-1994
1995-1997
1998-2000
2001-2003
2004-2006
2007-2009
2010-2012
2013-2015
Men
Women

Table 1. Data sources of incidence and survival of peritoneal malignant mesothelioma.

Geographical coverage	Incidence			Survival	
	Population (estimates 2015)	Diagnosis period	Number of cases	Diagnosis period	Number of cases
Bas-Rhin	1,116,658	1989–2015	31	1989–2012	29
Calvados	639,938	1989–2015	42	1989–2012	37
Doubs	536,959	1989–2015	26	1989–2012	21
Gironde	1,548,478	2005, 2008–15	16	2005, 2008–12	10
Haut-Rhin	762,607	1989–2015	16	1989–2012	15
Haute-Vienne	375,795	2009–2015	2	2009–2012	1
Hérault	1,120,190	1989–2015	33	1989–2012	24
Isère	1,251,060	1989–2015	50	1989–2012	40
Lille et sa région	793,603	2005, 2008–15	7	2005, 2008–12	4
Loire-Atlantique	1,365,227	1998–2015	38	1998–2012	30
Manche	499,287	1994–2015	19	1994–2012	15
Poitou-Charentes	1,802,873	2008–2015	18	2008–2012	15
Somme	571,879	1989–2015	16	1989–2012	15
Tarn	386,543	1989–2015	14	1989–2012	12
Territoire de Belfort	144,483	2007–2015	3	2007–2012	2
Vendée	666,714	1998–2015	18	1998–2012	12
Total			**349**		**282**

Table 2. Patients' characteristics according to the diagnosis period.

Variables	1989–2015 n = 349	1989–1999 n = 86	2000–2009 n = 125	2010–2015 n = 138	Comparison test
Gender					p = 0.51[a]
Men	195 (56%)	44 (51%)	74 (59%)	77 (56%)	
Women	154 (44%)	42 (49%)	51 (41%)	61 (44%)	
Age					p= 0.27[b]
Median	66 y	65 y	70 y	65 y	
Range	[20;91]	[26;88]	[20;91]	[21;87]	
Age of men					p = 0.91[b]
Median	67 y	65 y	69 y	66 y	
Range	[21;88]	[26;88]	[22;88]	[21;86]	
Age of women					p = 0.18[b]
Median	65 y	64 y	70 y	64 y	
Range	[20;91]	[30;83]	[20;91]	[31;87]	
Histology					**P <0.0001[a]**
Epithelioid (9052/3)	228 (65%)	41 (48%)	79 (63%)	108 (78%)	
Biphasic (9053/3)	232 (7%)	5 (6%)	7 (5%)	11 (8%)	
Fibrous (9051/3)	8 (2%)	0 (0%)	6 (5%)	2 (2%)	
NOS (9050/3)	90 (26%)	40 (46%)	33 (27%)	17 (12%)	

NOS, not otherwise specified.

[a] Pearson χ^2 test.

[b] Mann–Whitney test.

Table 3. World age-standardized incidence rates (with 95%CIs) of malignant peritoneal mesothelioma per 100,000 persons-years between 1989 and 2015.

Gender	Period	1989–1991	1992–1994	1995–1997	1998–2000	2001–2003	2004–2006	2007–2009	2010–2012	2013–2015
Men	Rate	0.07	0.09	0.07	0.11	0.16	0.09	0.07	0.13	0.10
	95%CI rate	[0.01–0.13]	[0.03–0.16]	[0.02–0.12]	[0.05–0.17]	[0.07–0.24]	[0.04–0.13]	[0.03–0.12]	[0.06–0.20]	[0.05–0.15]
Women	Rate	0.09	0.08	0.10	0.05	0.04	0.07	0.06	0.11	0.07
	95%CI rate	[0.01–0.17]	[0.03–0.14]	[0.03–0.18]	[0.01–0.10]	[0.01–0.07]	[0.02–0.11]	[0.02–0.10]	[0.05–0.18]	[0.04–0.11]

Table 4. Results of univariate and multivariate analysis in overall survival.

	Univariate analysis					Age-adjusted Cox model	
	n	1-year OS [95%CI]	3-year OS [95%CI]	5-year OS [95%CI]	Log-rank test	HR [95%CI]	p-value
Age (years)					p<0.0001	–	
<55	73	76 [64–84]	51 [39–62]	38 [27–49]		–	
55–65	66	56 [43–67]	35 [24–46]	26 [16–37]		–	
66–74	74	37 [26–48]	18 [10–27]	11 [5–19]		–	
≥75	65	23 [14–34]	12 [6–22]	9 [4–18]		–	
Gender					p<0.0001		**p = 0.001**
Men	158	40 [33–48]	21 [14–27]	12 [8–18]		1.00[a]	–
Women	121	59 [50–67]	41 [32–49]	33 [25–42]		0.55 [0.39–0.77]	
Diagnosis period					p=0.07		
1989–1999	86	41 [30–52]	25 [16–35]	18 [10–27]		1.76 [1.13–2.74]	**p = 0.013**
2000–2009	124	48 [38–56]	29 [21–37]	18 [12–25]		1.16 [0.80–1.67]	p = 0.22
2010–2012	72	58 [46–68]	35 [24–46]	31 [21–42]		1.00[a]	
Epithelioid					p=0.03		
No	25	31 [15–49]	19 [7–36]	8 [1–22]		2.00 [1.27–3.15]	**p = 0.003**
Yes	176	53 [45–60]	32 [25–39]	23 [17–29]		1.00*	
NOS	77	45 [34–55]	27 [18–37]	23 [14–33]		1.00	

HR, hazard ratio; NOS, not otherwise specified; OS, overall survival.

[a] Reference class,

Table 5. Overall survival at 1, 3 and 5 years by diagnosis period (in percentages).

	1989–1999				2000–2009				2010–2012			
	n	1-year OS	3-year OS	5-year-OS	n	1-year OS	3-year OS	5-year OS	n	1-year OS	3-year OS	5-year-OS
Gender												
Men	43	29 [16–43]	14 [6–27]	10 [3–21]	74	42 [31–53]	25 [15–35]	12 [6–21]	41	49 [33–63]	20 [9–33]	15 [6–27]
Women	39	55 [38–69]	37 [22–52]	26 [13–41]	50	55 [40–68]	35 [22–48]	26 [15–39]	35	69 [50–81]	54 [36–69]	51 [33–66]
Age (y)												
<55	21	62 [38–79]	43 [22–62]	29 [12–48]	32	75 [56–87]	47 [29–63]	31 [16–47]	21	90 [67–98]	66 [41–82]	60 [36–78]
55–65	25	52 [31–69]	32 [15–50]	24 [10–42]	22	48 [26–67]	29 [12–48]	14 [4–32]	20	70 [45–85]	45 [23–65]	40 [19–60]
66–74	19	28 [10–49]	11 [2–30]	6 [0–22]	36	42 [26–57]	25 [12–40]	14 [5–27]	19	37 [17–57]	11 [2–28]	11 [2–28]
≥75	17	12 [2–33]	6 [0–25]	6 [0–25]	34	27 [14–43]	15 [5–29]	12 [4–26]	16	31 [11–54]	25 [8–47]	19 [5–40]
Epithelioid type												
No	5	20 [1-58]	–	–	13	23 [5–47]	23 [5–47]	–	8	50 [15–77]	25 [4–56]	25 [4–56]
Yes	39	41 [25–56]	30 [16–45]	19 [8–33]	79	56 [45–67]	32 [22–42]	20 [12–30]	59	56 [42–67]	33 [21–45]	28 [17–40]
NOS	38	45 [29–60]	24 [12–38]	18 [8–32]	32	35 [19–52]	23 [10–38]	19 [8–35]	9	78 [36–94]	56 [20–80]	56 [20–80]

NOS, not otherwise specified; OS, overall survival.