Cancer Epidemiology 51 (2017) 81–86

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Epidemiology of malignant peritoneal mesothelioma: A population-based study

Silja A.S. Salo[a], Ilkka Ilonen[b,c], Sanna Laaksonen[b,d], Marjukka Myllärniemi[b,d], Jarmo A. Salo[b,c], Tuomo Rantanen[a,e,*]

[a] Department of Surgery, Institute of Clinical Medicine, University of Eastern Finland, Finland
[b] Department of Surgery, Clinicum, Faculty of Medicine, University of Helsinki, Finland
[c] Department of General Thoracic and Esophageal Surgery, Heart and Lung Center, Helsinki University Hospital, Finland
[d] Department of Pathology, University of Helsinki and HUSLAB, Helsinki University Hospital, Finland
[e] Department of Surgery, Kuopio University Hospital, Finland

ARTICLE INFO

Keywords:
Mesothelioma
Peritoneal mesothelioma
Epidemiology
Finland
Asbestos
Survival
HIPEC

ABSTRACT

Background: Malignant peritoneal mesothelioma (MPeM) is a rare cancer of the mesothelial cells in the peritoneum with poor prognosis. Earlier reports from other countries indicate an incidence of 0.2–3 new cases per million per year. No previous studies have examined the national epidemiology of MPeM in Nordic countries. This study aimed to clarify the epidemiology of MPeM in Finland over a 12-year period.

Methods: The data consisted of cancer notifications, laboratory notifications, and death certificate information in the Finnish Cancer Registry (FCR) and Statistics Finland (SF) of all MPeM patients from 2000 to 2012 in Finland. We also collected data on occupational disease compensations from the Workers' Compensation Center (WCC) of Finland. Any missing information was collected from the respective patient's file of every patient obtained from health institutions that had treated the patients.

Results: Between January 1, 2000 and December 31, 2012, 90 new MPeM cases (56 males, 34 females) occurred in Finland. Median annual incidence was four new cases, which corresponded to 0.74 new cases per million per year. MPeM was deemed an occupational disease in 21 patients (23.3%). 71 patients (78.9%) of whom had a known cause of death, with a median survival of 4 months. The number of deaths linked to other disease than mesothelioma was 28/74 (37.8%).

Conclusions: Our study indicates that MPeM in Finland is rare and fatal, which is in accordance with previous reports from other countries. MPeM is also a fatal disease, since most of the patients died due to MPeM.

1. Introduction

Malignant peritoneal mesothelioma (MPeM) is a rare cancer of mesothelial cells in the peritoneum [1–3]. Beyond the peritoneum, mesothelial cells are found in the pleura, pericardium and tunica vaginalis of the testes [1,4]. The incidence of MPeM is reportedly 0.2 to 3 cases per million people per year [1,5]. The RARECARE database indicates an incidence of MPeM in Europe, from 1995 to 2002, of 1.2 to 1.3 cases per million people per year [6]. The little information available suggests that MPeM is reportedly more common among men [2,5,7]. The most significant risk factor for MPeM is exposure to asbestos [7,8]. In Finland, cytoreductive surgery (CRS) and hyperthermic intra-abdominal chemotherapy (HIPEC) have been performed to MPeM and pseudomyxoma peritonei since 2007. Performing HIPEC is centralized to two centers in Finland.

Due to the rarity of the disease knowledge of the treatment of MPeM is limited. Mainly due to the same reason the knowledge of the oncogenesis and the microenvironment of the cancer is limited [1]. Little is known about the epidemiology of MPeM at the national level in recent years. In addition, few epidemiological studies of MPeM worldwide are available and most of them are epidemiological cohort studies of work-related asbestos exposure [9].

To date no studies have examined the national epidemiology of MPeM in the Nordic countries. This population-based cohort study will clarify the epidemiology of MPeM in Finland.

Our aim was to report the incidence, epidemiology and expression of MPeM in Finland between January 1st, 2000 and December 31st, 2012.

* Corresponding author at: Department of Surgery, Kuopio University Hospital, Puijonlaaksontie 2, 70210 Kuopio, Finland.
E-mail address: tuomo.rantanen@kuh.fi (T. Rantanen).

http://dx.doi.org/10.1016/j.canep.2017.10.008
Received 23 July 2017; Received in revised form 8 October 2017; Accepted 10 October 2017
Available online 05 November 2017
1877-7821/

2. Methods

This was a retrospective population-based study. The data consisted of cancer notifications, laboratory notifications, and information on death certificates in the Finnish Cancer Registry (FCR) and Statistics Finland (SF) of all patients diagnosed with MPeM between 2000 and 2012. We also collected information on work-related disease compensations from the Workers' Compensation Center (WCC) of Finland. All Finnish hospitals, laboratories and doctors are obliged to notify the FCR on all new or suspected cancer cases. The FCR has maintained a registry of all cancers diagnosed in Finland since 1953 and the FCR's coverage of solid tumors is reportedly as high as 99% [10]. Additional and missing information was collected from the respective patient's files, obtained from the health institutions where the patients received treatment. We produced the database and verified patient survivals in February 2013.

We collected the following patient data: date of birth, gender, profession at time of diagnosis, date of diagnosis, morphology of the cancer, primary site of the cancer, method of diagnosis, staging of the cancer, type and duration of treatments received, beginning date of treatment, present status of the patient, date of death, cause of death (main or other) according to the diagnoses in the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD10), municipality of stay, reason for not receiving active cancer treatment, and confirmed or suspected occupational diseases. The ICD10-codes used in the searching process were C45.1 for MPeM, C45.7 for mesothelioma of another site, C45.9 for unspecified mesothelioma, C45.0 for pleural mesothelioma, and C80 for unspecified malignant neoplasm.

2.1. Ethics

This study was approved by the Heart and Lung Center of Helsinki University Hospital, the National Institute of Health and Welfare, Statistics Finland, and as well by the Ethical Committee of Helsinki and Uusimaa Hospital District.

3. Results

During the study period 94 patients (60 males, 34 females) were diagnosed with MPeM per FCR clinical notifications. However, four patients were excluded from the data after going through the patients' files: two patients had tunica vaginalis testis and one patient pleura as the actual location of their mesothelioma, whereas one patient with adenocarcinoma was first misdiagnosed with MPeM. The final data included 90 patients (56 males, 34 females) who were diagnosed with MPeM. The mean incidence was 6,9 new cases per year (male 4.31, female 2.62). The median annual incidence was four new cases, which corresponds to 0.74 new cases per million per year in Finland. Fig. 1 shows the number of new MPeM cases in Finland from 2000 to 2012. The mean age during diagnosis was 67.4 years (male 66.7 years, range 37–92 and female 68.4 years, range 24–88).

The patientś professions have been divided into six different categories according to their characteristics. The most common professions were technical and household workers, and clerical workers (Table 1).

MPeM was deemed an occupational disease in 21 patients (23.3%) (male 19, female 2) and suspected in three patients (3.2%) (male 1, female 2). Additionally, in seven cases (7.4%) an occupational disease was related to another disease. Fig. 2 shows the number of new MPeM cases on patients with an occupational disease in Finland from 2000 to 2012. The median annual age at diagnosis of the patients classified with occupational disease was 66 years.

The diagnosis was made histologically from the primary tumor either by ultra-sound-guided thick needle biopsy, laparotomy or laparoscopy (60 cases, 66.7%) or from a metastasis (6 cases, 6.7%). In 23 cases (25.6%) MPeM was diagnosed microscopically only at autopsy. In one case (1.1%) the diagnosis was made clinically and involved a biopsy taken from the primary tumor; histological analysis served to confirm the diagnosis.

The histological subtype of the MPeM was reported in 34 (37.8%) cases (male 24, female 10). The most common histological subtype was epithelial (26 cases, 28.9%) (male 18/56, 32.1%, female 8/34, 23.5%) followed by biphasic (5 cases, 5.6%) (male 4/56, 7.1%, female 1/34, 2.9%) and sarcomatoid (3 cases, 3.3%) (male 2/56, 3.6%, female 1/34, 2.9%).

In the majority of the cases MPeM had spread beyond the regional lymph nodes (Table 2). 81 patients (90.0%) died, 74 (91.4%) of whom had a known cause of death. All of these 74 patients died of or with cancer.

Surgical treatment was given to 14 out of 90 patients (15.6%). 6 patients (6.7%) were radically operated whereas 8 patients (8.9%) got palliative surgical treatment.

Chemotherapy was given to 37/90 patients (41.1%). In 2 cases (2.2%) there was no certain information whether the patient had got chemotherapy or not. Radiotherapy was given to 14/90 patients (15.6%). In 2 cases (2.2%) there was no certain information whether the patient had got radiotherapy or not.

The survival time after the diagnosis was known on 79/90 patients (87.8%). The mean of the survival was 12.47 months and the median was 4.0 months (range from 0 months to 92 months). Fig. 3 shows the survival among men and women as a Kaplan-Meier figure.

The median survival of radically operated patients was 59.5 months (range 57 − 62 months). Respectively, on patients with a palliative operation, the median survival was 1.0 months (1–6 months), on patients who got chemotherapy 9.0 months (1–92 months) and on patients who got radiotherapy 2.0 months (2–15 months). Fig. 4 shows the different survivals among patients divided in groups by their treatment.

In 33/74 deaths the patients' death certificates indicated MPeM (IDC10 code C45.1) as the main cause of death. In four out of 74 deaths (5.4%), the main causes of death were mesothelioma of another site (ICD10 code C45.7), also in five (6.8%) unspecified malignant neoplasm (ICD10 code C80), and in two (2.7%) unspecified mesothelioma (ICD10 code C45.9). In these 11 cases, however, the patients' files and FCR notifications suggested that the main cause of death was actually MPeM. In two of the 74 deaths pleural mesothelioma (ICD10 code C45.0) was indicated as the main cause of death. Based on the patients' files and cancer notifications, however, both of the patients had really MPeM as their diagnosis.

As many as 28 out of 74 deaths (37.8%) were linked to some other disease than mesothelioma; 18 to pulmonary diseases, seven to cardiovascular ones, and three to others (Table 3).

4. Discussion

With only 90 new MPeM cases in Finland's population of 5.5 million over a 12-year period (a median annual incidence of 0.74 cases per million inhabitants), MPeM is a rare disease in Finland. Its incidence in Finland, reported here for the first time, is well in accordance with earlier reports from other countries [1,5].

This study also shows that MPeM is more common among men in Finland, which also supports earlier results on MPeM's distribution by sex worldwide [2,5,7]. Some researchers have suggested that MPeM's higher incidence among men is linked to either genetic factors or more frequent asbestos exposure [11]. Fig. 3 shows that the survival is better among female patients. The better survival among women has been stated also earlier in the literature [12].

One fourth of the MPeM cases occurred in patients diagnosed with an occupational disease. Occupational diseases were more common among men than among women which may be a consequence of men working more often in jobs with asbestos exposure such as technical and household workers. A Swedish study linking occupational data to

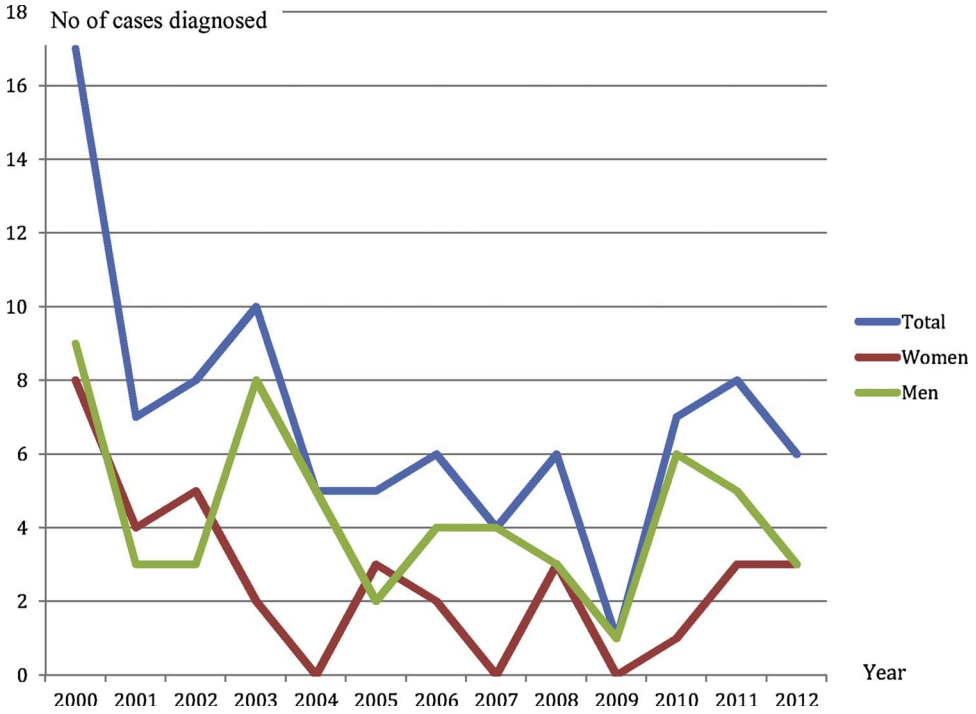

Fig. 1. The incidence of MPeM in Finland 2000–2012.

cancer registry data between 1961 and 2009 reported similar results. Plumbers and pipe workers, bricklayers, painters and insulators were at higher risk for MPeM [13]. The use of asbestos was completely prohibited in Finland in 1994 and in the European Union in 2005, and after that asbestos demolition has required a special permission and a proper protection, and can be done only by professionals. Therefore, due to MPeM's long latency time its incidence can be expected to remain at the same level for several years.

Most of the patients died of or with MPeM; only one patient died disease-free, indicating that MPeM is a fatal disease. Previous studies have shown similar findings [3–5,14]. As stated in several studies, CRS combined with HIPEC, and the combination of chemotherapy, radiotherapy and immunotherapy seems to be the only possibility to long term survival [14,15]. The effectiveness of CRS and HIPEC was seen also in our study. However, radical surgery was performed only to 6 patients in Finland during the study time. The causes for small number of radical operations may be the rarity of MPeM and performing HIPEC in Finland not until 2007.

More than one fourth of the cases were diagnosed microscopically only during autopsy indicating that the diagnostics of MPeM are quite demanding due to the disease's long latency period and obscure symptoms [8,16]. In addition our results indicate that more than half of the MPeM cases had spread beyond the regional lymph nodes at the time of diagnosis. Only a few cases were diagnosed as local and had not spread which supports the above-mentioned assessment that the diagnostics of MPeM are demanding.

However, our finding contradicts those of earlier reports on the distribution of MPeM. Several studies state that MPeM seldom spreads beyond the peritoneum area [2,17,18]. The reasons for this difference between Finland and other countries remain unknown, but could be attributed to Finland's relatively small population which can further complicate the diagnostics of MPeM.

As stated in the earlier literature [19] epithelial MPeM was the most common histological subtype while the sarcomatoid subtype the rarest. However, our data set was quite small and less than a third of the histological subtypes of the MPeM cases were marked in the FCR notification forms. Although FCR is considered valid and reliable the FCR notification forms may, in some cases, have been incomplete, thereby leading to a lack of important information and factors about MPeM patients. Also, in cases not linked to an occupational disease, the patient's profession may have been omitted.

Our study shows that MPeM is a fatal disease and resistant to most of the treatments. Nonetheless, patients who received both radical surgery and chemotherapy or HIPEC had a noticeable response to their treatments.

One limitation of this study is that the occupation was known for only half of the patients. The occupation provided was the patients' occupation at the time of cancer diagnosis, and the duration of the exposure could not be clarified.

Because of the challenges in diagnosing MPeM the incidence of MPeM cases may be higher than that found in this study; in fact, over one third of the cases were diagnosed at autopsy. More focus on the

Table 1
Professions of patients with MPeM in Finland 2000–2012.

Profession group	Men	Women	Total (%)	Occupational diseases
Technical and household workers and clerical workers	21	5	26 (28.2%)	12 (57.1%)
Science and art workers and clerical workers	5	3	8 (8.9%)	0 (0%)
Commercial workers and clerical workers	1	3	4 (4.4%)	0 (0%)
Agriculture and forestry workers and clerical workers	3	3	6 (6.7%)	0 (0%)
Traffic workers and clerical workers	4	1	5 (5.6%)	1 (4.8%)
Social and health workers and clerical workers	0	4	4 (4.4%)	0 (0%)
Unknown	22	15	37 (41.1%)	8 (38.0%)
Total	56	34	90 (100%)	21 (100%)

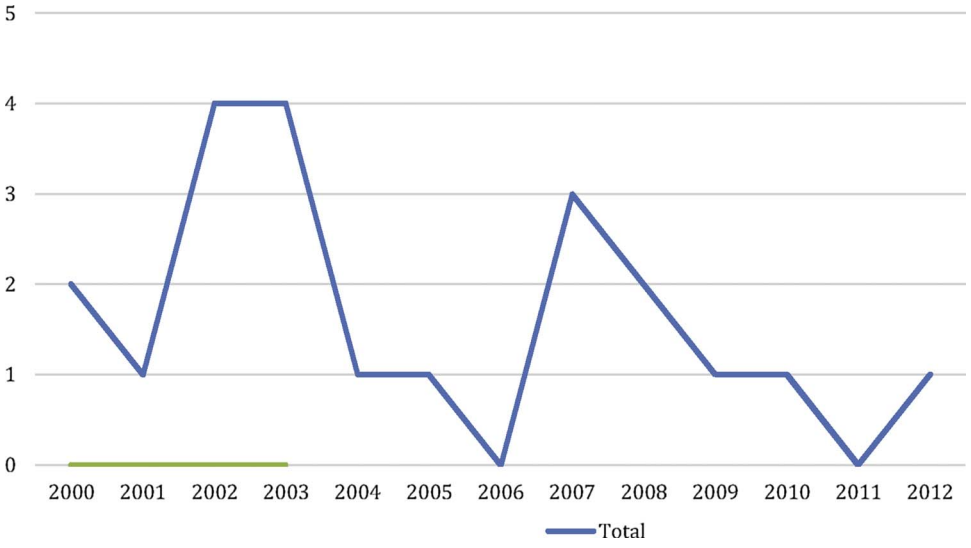

Fig. 2. The incidence of MPeM among patients diagnosed with an occupational disease in Finland 2000–2012.

Table 2
Stages of distribution of MPeM in Finland 2000–2012.

Stage of distribution	Men	Women	Total (%)
Local, not spread	2	1	3 (3.3%)
Spread to the regional lymph nodes	0	1	1 (1.1%)
Spread beyond the regional lymph nodes	34	18	52 (57.8%)
Distant metastases	1	0	1 (1.1%)
Spread, but the stage of distribution was unclear	7	6	13 (14.4%)
Unknown	12	8	20 (22.2%)
Total	56	34	90 (100%)

diagnostics of MPeM – especially in patients that have been exposed to asbestos – should be put.

Despite the small number of MPeM patients during this 13-year study period our data can be considered reliable and significant, because the FCR and Finnish hospital records are well organized and comprehensive. Completion of the FCR cancer notifications is obligatory for all Finnish doctors, hospitals and laboratories.

5. Conclusions

We report here for the first time the epidemiology of MPeM in Finland. Our results, which are in line with reports from other

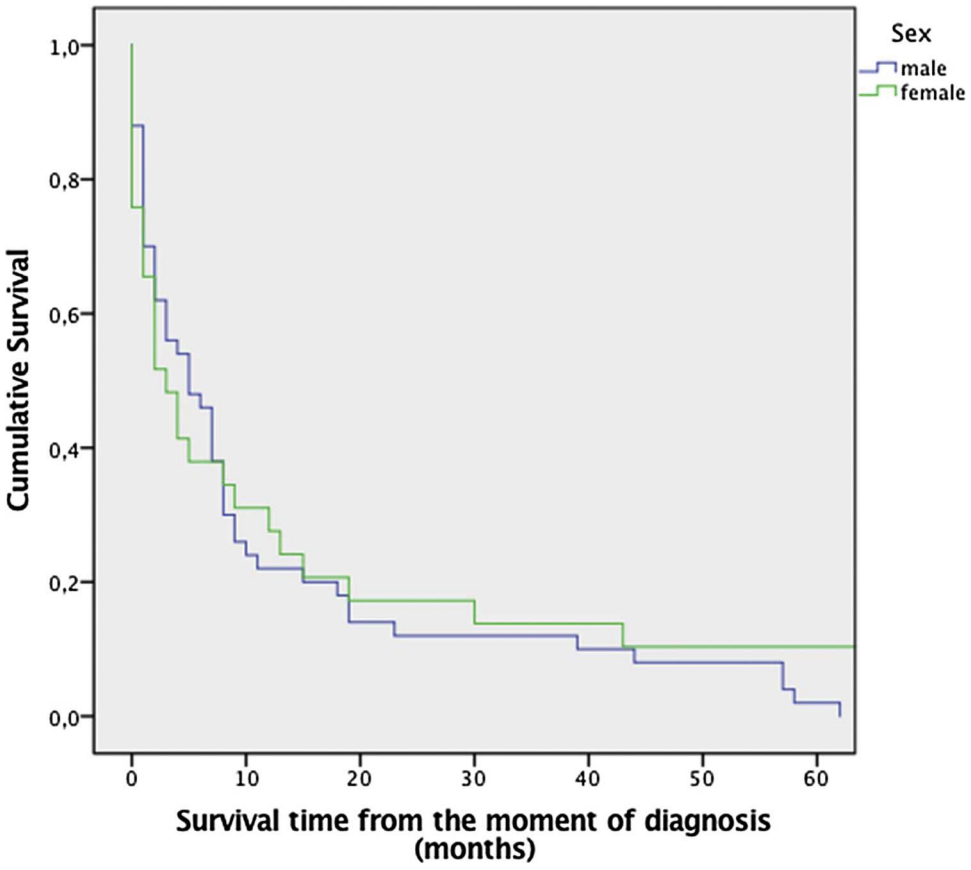

Fig. 3. A Kaplan-Meier – survival figure of the survival time from the moment of diagnosis among men and women.

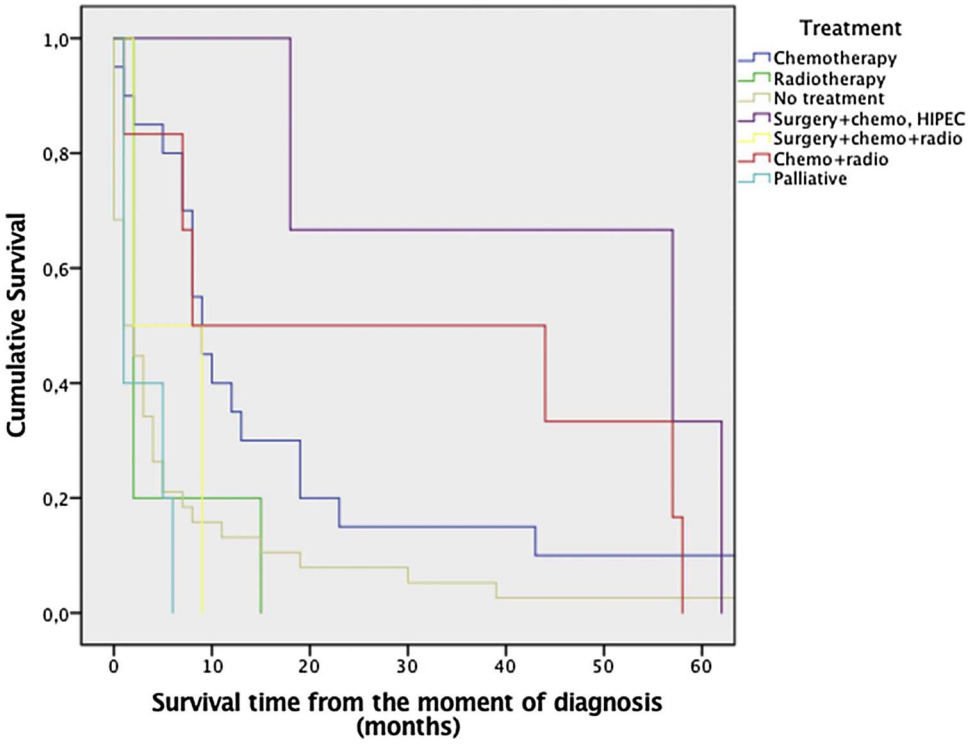

Fig. 4. A Kaplan-Meier – survival figure of the survival time from the moment of diagnosis. Patients divided into groups by their treatment.

Table 3
Deaths linked to other disease than cancer among patients suffering from MPeM in Finland 2000–2012.

Group	Total	Cause of death	Total
Pulmonary diseases	18		
		Pneumonia or bronchitis	17
		Other specified pleural conditions	1
Cardiovascular diseases	7		
		Pulmonary embolism without mention of acute cor pulmonale	3
		Atherosclerotic disease	3
		Cardiogenic shock	1
Other diseases	3		
		Acute peritonitis	1
		Unspecified sepsis	1
		Small cell B-lymphoma, unspecified site	1
Total	28		28

countries, indicate that MPeM is a rare and fatal disease. However, a deeper analysis will require more information about the characteristics of MPeM in Finland.

Author contribution

Authorship among all authors are based on 1) substantial contributions to conceptions and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

Conflicts of interest

None.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The study was supported by the Cancer Society of Finland and the Finnish Work Environment Fund.

The authors thank Yvonne Sundström for skillful secretarial assistance.

References

[1] S. Judge, P. Thomas, V. Govindarajan, P. Sharma, B. Loggie, Malignant peritoneal mesothelioma: characterization of the inflammatory response in the tumor microenvironment, Ann. Surg. Oncol. 23 (2016) 1496–1500.
[2] S.N. Gilani, R. Gridley, G. Searle, A. Jegannathen, Malignant peritoneal mesothelioma (MPM) who responded to rechallenge with cisplatin and pemetrexed with current literature review, BMJ Case Rep. (2013), http://dx.doi.org/10.1136/bcr-2012-007786.
[3] A. Raza, W.-C. Huang, K. Takabe, Advances in the management of peritoneal mesothelioma, World J. Gastroenterol. 20 (2014) 11700–11712.
[4] P.H. Sugarbaker, T.D. Yan, O.A. Stuart, D. Yoo, Comprehensive management of diffuse malignant peritoneal mesothelioma, EJSO 32 (2006) 686–691.
[5] P. Mirarabshahii, K. Pillai, T.C. Chua, M.H. Pourgholami, Diffuse malignant peritoneal mesothelioma – an update on treatment, Cancer Treat. Rev. 38 (2012) 605–612.
[6] G. Gatta, J.M. van der Zwan, P.G. Gasali, S. Siesling, A.P. Dei Tos, I. Kunkler, et al., Rare cancers are not so rare: the rare cancer burden in Europe, Eur. J. Cancer 47 (2011) 2493–2511.
[7] P. Boffetta, Epidemiology of peritoneal mesothelioma: a review, Ann. Oncol. 18 (2007) 985–990.
[8] M. Kaspar, Peritoneal mesothelioma: an unusual cause of high-protein ascites, ACG Case Rep. J. 3 (2015) 71–73.
[9] S. Conti, G. Minelli, V. Ascoli, A. Marinaccio, M. Bonafede, V. Manno, et al., Peritoneal mesothelioma in Italy: trends and geography of mortality and incidence, Am. J. Ind. Med. 58 (2015) 1050–1058.
[10] L. Teppo, E. Pukkala, M. Lehtonen, Data quality and quality control of a population-based cancer registry. Experience in Finland, Acta Oncol. 33 (1994) 365–369.
[11] Z. Gao, K. Hiroshima, X. Wu, J. Zhang, D. Shao, H. Shao, et al., Asbestos textile production linked to malignant peritoneal and pleural mesothelioma in women: analysis of 28 cases in Southeast China, Am. J. Ind. Med. 58 (2015) 1040–1049.
[12] C. Cao, T.D. Yan, M. Deraco, D. Elias, O. Glehen, E.A. Levine, et al., Importance of gender in diffuse malignant peritoneal mesothelioma, Ann. Oncol. 23 (June (6)) (2012) 1494–1498.
[13] N. Plato, J.I. Martinsen, P. Sparén, G. Hillerdal, E. Weiderpass, Occupation and mesothelioma in Sweden: updated incidence in men and women in the 27 years after the asbestos ban, Epidemiol. Health 38 (2016) e2016039, http://dx.doi.org/10.4178/epih.e2016039 Published online 2016 Sep 20.
[14] S. Cao, S. Jin, J. Cao, J. Shen, J. Hu, D. Che, et al., Advances of malignant peritoneal mesothelioma, Int. J. Colorectal Dis. 30 (2015) 1–10.

[15] P.H. Sugarbaker, K.K. Turaga, H.R. Alexander Jr., M. Deraco, M. Hesdorffer, Management of malignant peritoneal mesothelioma using cytoreductive surgery and perioperative chemotherapy, J. Oncol. Pract. 12 (October (10)) (2016) 928–935.
[16] S. Toyokuni, Iron overload as a major targetable pathogenesis of asbestos-induced mesothelial carcinogenesis, Redox Rep. 19 (1) (2014) 1–7.
[17] B.S. Zha, M. Flanagan, C. Coulson, K.W. Garvin, Difficult to identify: malignant primary peritoneal mesothelioma, Am. J. Med. 128 (2015) 1191–1194.
[18] M. Deraco, D. Nonaka, D. Baratti, P. Casali, J. Rosai, R. Younan, et al., Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion, Ann. Surg. Oncol. 13 (2006) 229–237.
[19] S. Liu, P. Staats, M. Lee, H.R. Alexander, A.P. Burke, Diffuse mesothelioma of the peritoneum: correlation between histological and clinical parameters and survival in 73 patients, Pathology (Phila.) 46 (2014) 604–609.