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Use of variability in national and regional data to estimate the prevalence of lymphangioleiomyomatosis

E.C. HARKNETT[1], W.Y.C. CHANG[1], S. BYRNES[2], J. JOHNSON[3], R. LAZOR[4,5,6], M.M. COHEN[7], B. GRAY[8], S. GEILING[9], H. TELFORD[10], A.E. TATTERSFIELD[11], R.B. HUBBARD[12] and S.R. JOHNSON[1]

From the [1]Division of Therapeutics and Molecular Medicine and Respiratory Biomedical Research Unit, University of Nottingham, Nottingham UK, NG72UH, [2]The LAM Foundation, 4015 Executive Park Dr, Suite 320, Cincinnati, OH 4524, USA, [3]LAM Action, Clinical Science Building, City Hospital, Nottingham, NG51PB, UK, [4]Clinic for Interstitial and Rare Lung Diseases, Dept of Respiratory Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [5]Reference Center for Rare Pulmonary Diseases, Claude Bernard University, Lyon, France, [6]On behalf of the Swiss Group for Interstitial and Orphan Lung Diseases, [7]LAM Canada, 38 Avenue Road, Suite 612, Toronto, ON, M5R 2G2, Canada, [8]The New Zealand LAM Charitable Trust, 8 Paget Street, Freemans Bay, Auckland, New Zealand, [9]LAM Selbsthilfe Deutschland e.V, Postfach 31 07 39, D- 04211 Leipzig, Germany, [10]LAM Australasia Research Alliance, PO Box 363, Bondi Junction, NSW 1355, Australia, [11]Division of Respiratory Medicine, University of Nottingham and [12]Division of Public Health and Respiratory Biomedical Research Unit, University of Nottingham, Nottingham UK, NG51PB

Address correspondence to S.R. Johnson, Division of Therapeutics and Molecular Medicine and Respiratory Biomedical Research Unit, University of Nottingham, Nottingham UK, NG72UH.
email: simon.johnson@nottingham.ac.uk

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Summary

Background: Understanding the true prevalence of lymphangioleiomyomatosis (LAM) is important in estimating disease burden and targeting specific interventions. As with all rare diseases, obtaining reliable epidemiological data is difficult and requires innovative approaches.
Aim: To determine the prevalence and incidence of LAM using data from patient organizations in seven countries, and to use the extent to which the prevalence of LAM varies regionally and nationally to determine whether prevalence estimates are related to health-care provision.
Methods: Numbers of women with LAM were obtained from patient groups and national databases from seven countries ($n = 1001$). Prevalence was calculated for regions within countries using female population figures from census data. Incidence estimates were calculated for the USA, UK and Switzerland. Regional variation in prevalence and changes in incidence over time were analysed using Poisson regression and linear regression.
Results: Prevalence of LAM in the seven countries ranged from 3.4 to 7.8/million women with significant variation, both between countries and between states in the USA. This variation did not relate to the number of pulmonary specialists in the region nor the percentage of population with health insurance, but suggests a large number of patients remain undiagnosed. The incidence of LAM from 2004 to 2008 ranged from 0.23 to 0.31/million women/per year in the USA, UK and Switzerland.

Conclusions: Using this method, we have found that the prevalence of LAM is higher than that previously recorded and that many patients with LAM are undiagnosed.

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease, which predominantly affects the lungs, kidneys and lymphatics. Patients are almost exclusively women and the age of onset is generally between the menarche and the menopause.[1–3] Dyspnoea and pneumothorax result from cystic destruction of the lungs due to the growth of immature smooth muscle-like cells (LAM cells), which infiltrate the lung parenchyma.[1,4] LAM is generally progressive and can lead to respiratory failure.[5] The disease can occur sporadically or as part of tuberous sclerosis complex (TSC)[6] with both forms of LAM being associated with mutations in TSC1 or more commonly TSC2, the genes known to cause TSC.[7,8]

The prevalence of LAM was estimated at 2.6 cases/million women aged 20–69 years in France in 1997[9] and as 1/1.1 million of the total population of the UK in 2000.[10] After these studies, several factors, and particularly the increased use of high-resolution computerised tomography (CT) scanning, have contributed to increasing awareness of LAM and earlier diagnosis.[11–13]

Obtaining prevalence data on rare diseases is difficult, but important for a better understanding of the natural history of the disease. LAM is not specifically named in the WHO International Classification of Disease 10 (ICD-10), making it difficult to estimate prevalence and incidence for epidemiological analyses. The awareness of rare diseases, such as LAM, among physicians has increased through patient groups that raise awareness and provide support specifically for patients with LAM and organizations that promote rare diseases (e.g. Orphanet).[14] The established groups are easily accessible to patients and keep records on their members.

Anecdotal evidence from patient groups and specialist centres suggest that the prevalence of LAM may be greater than previously reported, and rates of diagnosis may vary between countries. In this study, we used data from patient groups in the USA, UK, Canada, Australia, New Zealand, Switzerland and Germany to examine the current prevalence and incidence of LAM.

Methods

Countries were included in the study, if they had LAM organizations with a database of patients, were not restricted to one region of the country and had been established for at least 5 years. Registries and patient groups provided anonymous data on date of birth and date and region of diagnosis for all living patients with physician diagnosed LAM. No distinction was made between sporadic and TSC-associated LAM.

Patient identification

The number of patients with LAM and their county, state, region or canton at the time of diagnosis was obtained from LAM Action and the national LAM register (UK), the LAM Foundation (USA), LAM Canada, The New Zealand LAM Charitable Trust, LAM Selbsthilfe (Germany) and LAM Australasia Research Alliance. Swiss data were obtained from the Swiss Registries for Interstitial and Orphan Lung Diseases (SIOLD), a recruitment tool for research on rare pulmonary disorders. Data on patients diagnosed in one canton was unobtainable and prevalence figures were adjusted to account for this. Data on ethnic origin and lung transplantation was also available from the UK LAM register. The UK, USA and Swiss registries also provided data on incident cases. The UK LAM register is approved by the UK multicentre research ethics committee and patients sign informed consent. For patients outside the UK, ethical permissions were not required as only patient numbers were used.

Population and health services data

The female population for each state or canton in the USA, Germany and Switzerland was acquired from the 2008 census,[15–17] for Canadian provinces from the 2007 census,[18] for New Zealand districts and territory in Australia from the 2006 census[19,20] and for counties in the UK, including ethnic distribution, from the 2001 census.[21]

The number of pulmonary doctors in each US state was acquired from the American Board of Internal Medicine and the number of respiratory consultants in each UK county from the 2008 British Thoracic Society directory of Training Posts and Services in Adult Respiratory Medicine. Academic respiratory centres in the UK were defined as University hospitals with at least one professor and five consultants in respiratory medicine. The health insurance coverage of each state of the USA was obtained from the 2008 census.[22] The Gini index, a measure of the inequality in distribution of household income within a country, was

obtained from The World Factbook from the Central Intelligence Agency, USA.[23] The higher the Gini index of a country, the more unequal its income distribution. Most countries have a Gini index lying between 25 and 50.

Analysis

The prevalence of patients with LAM per million female population was estimated for each country and region. The incidence (number of new LAM cases diagnosed per million female population per year) was calculated over the 5-year period from 2004 to 2008. A crude estimate of median survival for patients with LAM from the date of diagnosis was estimated by dividing the prevalence by the mean yearly incidence over this period.

To examine if significant variation in the prevalence of diagnosed LAM exists between regions or countries, Poisson regression was performed on prevalence data and a likelihood ratio test carried out. Associations between prevalence of diagnosed LAM and numbers of pulmonary physicians per million women (USA and UK), academic centres (UK), wealth distribution (between countries) or health insurance coverage (USA only) were tested by Poisson regression.

An estimate for the number of potentially undiagnosed cases of LAM was obtained from the observed variations in prevalence, by assuming that the lower prevalence in some countries or regions compared with other countries or regions is explained by geographical variation in confirming a diagnosis. Using a conservative estimate that the true prevalence of LAM lies between the median and maximum values for the countries studied, we estimated a possible true prevalence range by applying the mean and maximum prevalence figures for all seven countries to individual countries.

All analyses were conducted using STATA version 10.1 (StataCorp LP, Texas, USA).

Results

A total of 1001 patients with physician diagnosed LAM were identified in the seven countries. Of them, 17 were withdrawn as the original diagnosis was made in a country not included in the study, leaving 984 patients for analysis. From the UK where extra data were available, 88% of patients were of white UK origin and the remainder of other European, Asian and Chinese origin. This ethnic distribution did not differ from that of the UK population as a whole. Of them, 17 (9%) patients in the UK had undergone lung transplantation.

Prevalence

The median prevalence of diagnosed LAM for all countries was 4.9 cases/million female population (range 3.35–7.76). The differences in prevalence between countries were significant ($P < 0.01$, Table 1).

The prevalence of LAM also varied between regions within countries and these regional differences were significant in the USA and Canada (Table 1 and Supplementary Figures E1–E4). We examined the reasons for this variation within the USA and UK, where 523 and 148 women, respectively, had been diagnosed with LAM. Prevalence across all 52 US states ranged from 0.0 to 9.13 cases/million female population (mean 3.35, median 3.15, Figure 1 and Table 2). Prevalence across UK counties ranged from 0.0 to 15.5 cases/million female population (mean 4.9, median 4.6). Although the overall variation in the UK was not significant, there were differences between the highest and lowest values ($P < 0.001$, Figure 2 and Supplementary Table E1).

We tested to see if the differences observed related to regional differences in access to pulmonary specialists or health insurance. There was no relationship between the prevalence of LAM with the number of pulmonary doctors nor the proportion of patients with health insurance in individual states (Supplementary Figure E5). Similarly, the number of respiratory consultants was not related to the prevalence of LAM in counties of the UK (Supplementary Figure E6). Twenty seven centres in the UK fitted our criteria for academic respiratory centres. The presence of an academic respiratory centre was not associated with the prevalence of LAM across individual counties ($P = 0.57$). The prevalence of LAM was not related to the Gini coefficient for the seven countries ($P = 0.93$, Supplementary Figure E7). There was a trend towards countries with smaller populations having higher prevalence rates, but this was not significant (Supplementary Figure E8, $R^2 = 0.43$, $P = 0.11$).

Incidence

The mean standard deviation (SD) incidence of LAM per million female population between 2004 and 2008 was 0.31 (0.058) cases/year in the USA, 0.23 (0.076) in the UK and 0.37 (0.26) in Switzerland. The incidence did not vary significantly from year-to-year over this period (Figure 3, $P = 0.89$).

Combining our data on the prevalence and incidence of LAM, a crude estimate of the median survival from diagnosis was 12 years across all countries.

Table 1 Prevalence of LAM in seven countries

Country	Female population	LAM patients	Prevalence	Maximum regional prevalence	*P*-value*
USA	156 191 761	523	3.35	9.13	0.012
Germany	41 818 073	155	3.77	14.70	0.17
Canada	16 643 900	69	4.15	64.91	0.0041
UK	30 280 000	148	4.89	15.47	0.20
Australia	10 056 041	52	5.17	18.25	0.56
Switzerland	3 240 073	21	6.48	20.42	0.27
New Zealand	2 062 053	16	7.76	20.19	0.27

Prevalence figures are patients per million women of the population.
**P*-values are for comparison between regions within a single country.

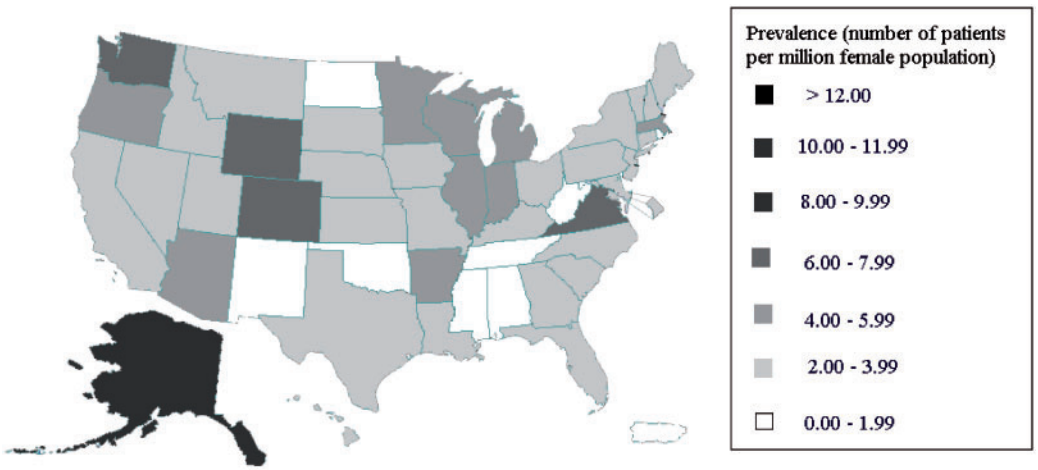

Figure 1. Prevalence of LAM across the USA. Prevalence across states ranged between 0.00 and 9.13 cases/million female population (median 3.15). This regional variation is significant ($P = 0.012$).

Estimates of true prevalence of LAM

The median and maximum values of prevalence for the countries we studied were 4.89 and 7.76 patients/million women. Applying these values to the year 2000 world female population of 3 billion' to make clearer. We estimate that they are between 15 000 and 23 000 patients with LAM worldwide. We applied the same method to the USA, the country with the lowest prevalence and largest population studied. This predicts that there may be between 764 and 1212 patients in the USA; suggesting that 241–689 patients are undiagnosed. These estimates for other countries are provided in Supplementary Table E2.

Discussion

Using details obtained predominantly from patient organizations, we found a prevalence of LAM between 3.35 and 7.76 cases/million women in seven countries. This is higher than previous estimates of 2.6 cases/million women aged 20–69 years in France[9] and 1/1.1 million of the total population in the UK.[10] These studies, published in 1997 and 2000, respectively, were smaller and relied on data from respiratory physicians only. It is possible that the prevalence of LAM has increased since 2000 but much more likely that this rise is due to better identification of patients and supports our contention that patient organizations can provide useful data to study rare diseases.

Regional variation in prevalence of LAM

Variation in prevalence was observed between the seven countries and between states of the USA and Canada. It is possible that the true prevalence of LAM varies between separate regions or countries, although the magnitude of the differences between adjacent, geographically and culturally similar regions suggest that variation in diagnostic

Table 2 USA regional prevalence data

State	Female population	LAM patients	Prevalence	IRR (95% confidence interval)]
Delaware	449 756	0	0	
New Mexico	1 006 030	0	0	
North Dakota	319 548	0	0	
Puerto Rico	2 056 641	1	0.49	2.89 (0.85–9.86)
Oklahoma	1 843 520	1	0.54	2.00 (0.73–5.49)
West Virginia	925 772	1	1.08	3.93 (1.31–11.75)
Alabama	2 403 813	4	1.66	1.68 (0.45–6.24)
Rhode Island	542 083	1	1.84	0.00 (0.00)
Tennessee	3 185 773	6	1.88	1.93 (0.22–17.24)
Mississippi	1 514 777	3	1.98	1.68 (0.58–4.80)
Montana	482 955	1	2.07	1.47 (0.47–4.54)
North Carolina	4 705 427	10	2.13	1.88 (0.34–10.27)
Louisiana	2 269 998	5	2.20	2.38 (0.53–10.64)
Utah	1 355 163	3	2.21	2.66 (0.94–7.58)
Texas	12 183 416	28	2.30	2.60 (0.86–7.90)
Nevada	1 275 577	3	2.35	1.98 (0.53–7.36)
Georgia	4 920 769	12	2.44	1.70 (0.43–6.82)
South Dakota	403 333	1	2.48	1.65 (0.47–5.86)
South Carolina	2 298 522	6	2.61	1.32 (0.36–4.93)
Kentucky	2 181 103	6	2.75	1.78 (0.33–9.73)
Connecticut	1 793 842	5	2.79	2.07 (0.65–6.59)
Florida	9 323 058	26	2.79	2.87 (0.96–8.60)
Kansas	1 410 313	4	2.84	2.60 (0.90–7.55)
Maine	674 087	2	2.97	2.75 (0.89–8.53)
New Hampshire	666 722	2	3.00	1.19 (0.27–5.32)
Hawaii	638 679	2	3.13	2.39 (0.77–7.39)
Vermont	315 547	1	3.17	1.24 (0.14–11.13)
District of Columbia	311 953	1	3.21	2.01 (0.45–8.96)
Iowa	1 519 683	5	3.29	1.41 (0.32–6.32)
California	18 368 644	61	3.32	reference
Nebraska	899 152	3	3.34	2.31 (0.78–6.85)
Maryland	2 906 274	10	3.44	0.00 (0.00)
Ohio	5 882 142	21	3.57	2.28 (0.81–6.38)
Pennsylvania	6 388 109	23	3.60	1.28 (0.40–4.07)
New York	10 028 234	38	3.79	0.00 (0.00)
New Jersey	4 430 879	17	3.84	2.15 (0.74–6.25)
Idaho	757 236	3	3.96	0.33 (0.04–2.92)
Missouri	3 023 698	12	3.97	2.84 (0.87–9.21)
Arizona	3 243 489	13	4.01	2.16 (0.75–6.26)
Wisconsin	2 830 318	12	4.24	0.29 (0.03–2.61)
Indiana	3 234 282	14	4.33	1.11 (0.12–9.92)
Michigan	5 079 493	22	4.33	1.57 (0.44–5.56)
Illinois	6 541 657	29	4.43	1.49 (0.17–13.33)
Minnesota	2 620 494	12	4.58	1.13 (0.32–4.01)
Oregon	1 907 329	9	4.72	1.38 (0.48–3.94)
Massachusetts	3 344 791	16	4.78	1.33 (0.30–5.94)
Arkansas	1 456 755	7	4.81	1.90 (0.21–17.04)
Virginia	3 952 047	21	5.31	3.19 (1.10–9.30)
Washington	3 279 299	19	5.79	3.48 (1.18–10.23)
Colorado	2 448 415	16	6.53	0.65 (0.07–5.81)
Wyoming	262 478	2	7.62	2.55 (0.82–7.90)
Alaska	328 686	3	9.13	4.58 (0.84–25.00)

There are 523 living patients with LAM in the USA (female population of 156 million.) The overall prevalence of LAM across the USA is 3.35 cases/million women. Variation between states is statistically significant ($P = 0.012$). IRR, incidence-rate ratio for LAM. Prevalence figures are patients per million women of the population.

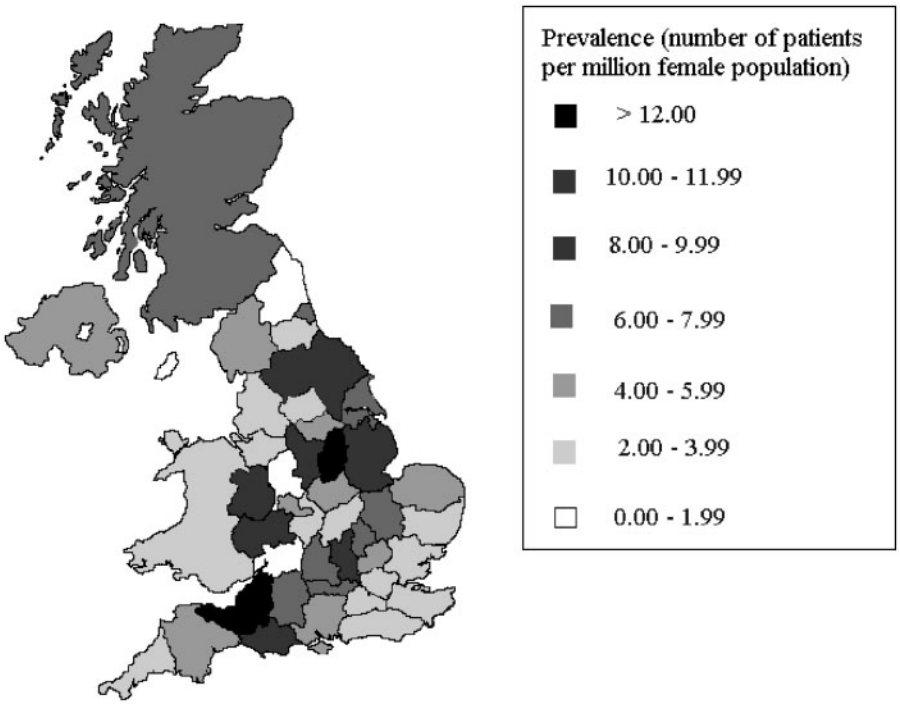

Figure 2. Prevalence of LAM across the UK. Prevalence across counties ranged between 0.00 and 15.47 cases/million female population (median 4.6). This regional variation is not significant ($P = 0.20$).

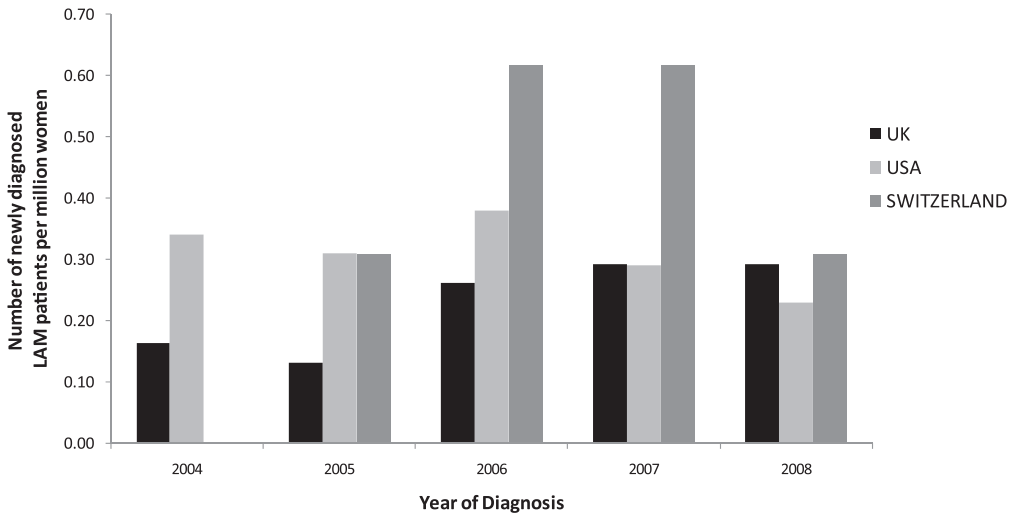

Figure 3. Incidence of LAM from 2004 to 2008 in three countries. The incidence of LAM between 2004 and 2008 per million female population per year. The incidence did not change significantly over time ($P = 0.89$).

ascertainment is more likely to occur. Surprisingly, no association was observed between the prevalence of LAM and the number of pulmonary specialists, academic respiratory centres, nor with access to health insurance. The observed regional variation may still be attributable to factors related to recognition of LAM as we were unable to test whether prevalence figures were higher in regions with physicians with particular expertise in LAM as this is not possible to identify in all cases.

Incidence of LAM

Although the prevalence of LAM is higher in our study than that previously recorded, the incidence had not increased over 5 years. There have been no

major developments in the methods used to diagnose LAM over the last 5 years and it is likely that any increase in incidence due to increased recognition occurred prior to this when the availability of CT scanning was increasing. Early diagnosis of patients will result in an increased prevalence of LAM and would explain the rise in prevalence with no overall rise in incidence.

The only previous estimate of the incidence of LAM was 0.23 patients/million females/year in France between 1991 and 1996 (reported as 0.4 cases/million women aged 20–69 years/year).[9] The mean incidence between 2004 and 2008 in our study, 0.3/million women/year, is similar despite the differences in data collection methods between the two studies.

It is now recognized that a number of patients with LAM live for over 20 years from the onset of symptoms.[24,25] Estimates of survival performed between 1990 and 2004 range from 71% to 91% at 10 years from symptom onset.[5,24] These figures may have improved due to earlier diagnosis and the increasing use of lung transplantation over this period. The true median survival is difficult to estimate as this would require a large, representative cohort of incident cases followed-up for at least 20 years. The value obtained by our method is less than clinical experience and observational studies would suggest. The approach we used to calculate median survival is less prone to survivor bias than other studies, but is very reliant on the number of cases identified. The low estimate here is likely to be a consequence of a greater number of unrecognised cases of LAM in areas reporting low prevalence.

Predicted number of missing cases

We estimated that in the USA alone, there may be as many as 689 patients living with LAM with no details registered with the LAM Foundation. These patients have either been diagnosed with LAM, but chose not to register with the patient group, or have not yet been diagnosed with LAM. As the LAM Foundation is the longest established and highest profile patient group for LAM worldwide, it is unlikely that they only have details on 40% of patients in the US living with LAM. We predict, therefore, that a significant number of patients with symptomatic LAM remain undiagnosed. Making a correct diagnosis would have potential benefits for these patients. Simple interventions that can benefit patients with LAM include avoidance of oestrogens, careful consideration of pregnancy and early surgical treatment of pneumothorax.[26]

Our study has a number of limitations. Obtaining accurate data on patients with rare diseases is difficult and differences in data ascertainment may have biased our findings. As patients self-register with these organizations, individual diagnoses are neither independently verified nor are patient deaths always recorded. However, these potential errors are likely to represent only a small portion of cases and are not likely to differ significantly between groups. We have attempted to minimize these sources of variation by selecting similar patient groups with respect to how well-established they are in their country and that they were well recognized by physicians and patients alike. We are aware that not all patients diagnosed with LAM will have registered with their national patient group, but this is also likely to be true of other registry techniques. This is particularly likely to apply to patients with TSC. The prevalence of TSC is not thought to vary significantly between regions including Europe and the USA with a reported prevalence of 8.8 and 10.6/100 000, respectively.[27,28] About 40% of the women with TSC have LAM when studied by chest CT and it is possible that these patients have not been screened, or if diagnosed, continue to associate with TSC groups rather than LAM organizations.

Conclusions

We have used incidence and prevalence data from patient groups for the first time to study 984 patients, and provide a clearer picture of the epidemiology of LAM. The estimated prevalence of LAM in seven countries was between 3.35 and 7.76 cases/million women with an incidence of 0.23–0.31/million women/year. Combining data sets is an important way forward for rare diseases where numbers of patients in individual countries are small. Further research to explain the variation in prevalence of LAM requires comprehensive research networks, and could eventually improve recognition and hence management of this rare disease.

Supplementary Data

Supplementary Data are available at *QJMED* Online.

Acknowledgements

E.C.H. analysed all data and co-wrote the paper. W.Y.C.C. helped collate and analyse data. J.J., R.L., S.B., M.M.C., B.G., S.G. and H.T. extracted and collated source data. R.B.H. helped design the

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