» **Original Article** «

Mortality from Pulmonary Heart Disease in Japan, 1979–2006

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Objective: In Japan, there have been no reports on the time-trends of mortality rates from pulmonary heart disease without pulmonary embolism (PHD). Our aim was to examine the annual changes of mortality in Japan.

Materials and Methods: Annual age-adjusted and age-specific PHD mortality for Japanese residents during 1979–2006 were calculated from “Vital statistics of Japan” and census data and population estimates for intercensal years.

Results: The number of age-adjusted deaths from PHD continued to decrease throughout the study period. The age-specific mortality from PHD increased throughout the life span except below 1 year old and decreased in recent years. Male mortality was greater at most ages. In Poisson regression analysis, the relative risk of death from PHD was increased in males and the aged except below 1 year-age, and decreased in recent years. The annual number of deaths from idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension (IPAH/HPAH) continued to increase throughout the study period. The number of annual new cases with IPAH/HPAH was estimated to be about 400 in a recent period of 10 years.

Conclusion: The annual number of deaths from PHD decreased, and those from IPAH/HPAH increased significantly during 1979–2006 in Japan.

Key words: mortality, pulmonary hypertension, idiopathic pulmonary arterial hypertension, pulmonary circulation

INTRODUCTION

The accumulation of evidence on the basic mechanism of occurrence of pulmonary hypertension and the appearance of new therapeutic agents has led to a revision of the classification of pulmonary hypertension and treatment strategies.^{1–4)} The prognosis has been dramatically improved especially in idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension (IPAH/HPAH).^{5–8)} Recently, guidelines for the treat-

ment of pulmonary hypertension^{9, 10)} have been published in Japan, and concern about pulmonary hypertension is increasing.

Surveillance in Western countries has revealed that the number of deaths from PH has increased among females, and decreased among males.¹¹⁾ The number of clinical cases with IPAH/HPAH is high in the third and fourth decade.^{12, 13)} However, age-specific mortality showed a high rate among infants below 1 year old, a low rate in childhood, and an ascending rate through the remainder of life in the United States.¹⁴⁾

There have been no reports on the time-trend of mortality from pulmonary heart disease without pulmonary embolism (PHD) or IPAH/HPAH in Japan. PHD includes Group 3 (pulmonary hypertension owing to lung disease and/or hypoxia), Group 1.1 (IPAH), and Group 1.2 (HPAH) in Dana Point classification of pulmonary hypertension.⁴⁾ The causes of pulmonary hypertension in Group 3 are chronic obstructive pulmonary diseases,

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Fig. 1 Deaths from PHD by gender, 1979–2006. PHD: pulmonary heart disease without pulmonary embolism

interstitial lung disease, other pulmonary diseases with mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, and developmental abnormalities.⁴⁾ Our aims were to examine the annual changes of mortality in Japan.

METHODS

Data on deaths and population for the period 1979–2006 were obtained from “Vital statistics of Japan,”¹⁵⁾ census data,¹⁶⁾ and population estimates for intercensal years.^{17, 18)} The register is based on death certificates issued by doctors. PHD was diagnosed for decedents with the International Classification of Diseases, Ninth Revision (ICD-9) code 416.0 (primary pulmonary hypertension), 416.8 (other chronic pulmonary heart diseases), or 416.9 (chronic pulmonary heart disease unspecified) during 1979–1994 or ICD-10 code I27.0 (primary pulmonary hypertension), I27.8 (other specified pulmonary heart diseases), or I27.9 (pulmonary heart disease, unspecified) during 1995–2006, according to a previous report.¹¹⁾ The annual age-adjusted deaths and mortality rates by gender, using the 1985 Japan population as a standard, which is a common method in Japanese epidemiology, were obtained for each year from 1979 through 2006. For these calculations, we used 5 year step populations up to 85 years old and those 85 or older as the population data in each year. The number of PHD patients (ICD-9 code 416.0, 416.8, or 416.9 or ICD-10 code I27.0, I27.8, or I27.9) was reported separately from that of kyphoscoliotic heart disease (ICD-9 code 416.1 or ICD-10 code I27.1) in total, but not by age. In order from 1979 to 2006, the number of cases of kyphoscoliotic heart disease in males was 2, 1, 1, 1, 2, 0, 0, 0, 0, 1, 0, 0, 0, 1, 1, 2, 2, 1, 1, 0, 1, 0, 1, 3, 1, 0, 2 and 2,

respectively; and in females, 0, 0, 3, 6, 1, 1, 1, 2, 2, 2, 2, 0, 0, 1, 1, 2, 0, 2, 1, 3, 2, 2, 2, 1, 1, 0, 1 and 0. Therefore, the annual age-adjusted deaths and mortality rates from PHD included those from kyphoscoliotic heart disease.

The annual age-specific mortality in Japan by gender was generated using “Vital statistics of Japan,”¹⁵⁾ census data,¹⁶⁾ and population estimates for intercensal years.^{17, 18)}

The number of patients who received the subsidy for “Intractable Diseases,” which is decided by the Ministry of Health, Labour and Welfare, Japan has been reported annually during 1996–2006 by the Japan Intractable Diseases Information Center.¹⁹⁾ IPAH is one of the “Intractable Diseases.” The numbers of annual new cases with IPAH/HPAH were estimated as the sum of the annual increment of cases and annual deaths. Annual mortality was defined as 100 times the annual deaths divided by the numbers of annual new cases.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, IL, USA). The results of Poisson regression analysis²⁰⁾ are presented as estimated relative risks with 95% confidence intervals. Non-ordinal categorical data were analyzed by chi-square statistics.

RESULTS

PHD

Annual deaths from pulmonary hypertension due to kyphoscoliotic heart disease ranged from 0 to 6. Most causes of death from PHD were pulmonary hypertension associated with lung diseases, hypoxemia and/or IPAH/HPAH.

The number of crude deaths and age-adjusted deaths from PHD continue to decrease both in males and in

Fig. 2 Crude deaths in 5 year-age steps (upper panels) and annual age-specific mortality (lower panels) from PHD by gender. PHD: pulmonary heart disease without pulmonary embolism

females in Japan (**Fig. 1**). The numbers of age-adjusted deaths from PHD were higher in males than in females before the 1990s, and similar from the 1990s to 2006.

Crude deaths and age-specific mortality from PHD in Japan are shown in **Fig. 2**; generally, these indexes increased throughout the life span except below 1 year old and decreased in recent years. Male mortality was greater than that of females at most ages. In Poisson regression analysis, the relative risk of mortality from PHD was elevated in males, and the aged except below 1 year old, and decreased in recent years (**Table 1**).

IPAH/HPAH

Numbers of cases with IPAH/HPAH and annual deaths continue to increase (**Fig. 3**). Annual mortality in 2006 was 2.5 per 1,000,000 persons. The prevalence and incidence in 2006 were estimated to be 961 cases (7.5 per 1,000,000 persons) and 433 cases (3.4 per 1,000,000 persons), respectively. Annual mortality among cases with IPAH/HPAH continues to decrease (**Fig. 3**). The estimated number of IPAH/HPAH was 1.11 times (95% con-

fidence interval, 1.03–1.20; $P = 0.007$) higher in 2003–2006 than that in 1996–1998. The relative risk of mortality from IPAH/HPAH was low in males, and increased in recent years (**Table 2**).

The ratio of deaths from IPAH/HPAH to that from pulmonary heart disease increased from 10.9% in the period between 1979 and 1982 to 69.8% in the period between 2003 and 2006 ($P < 0.0001$; see **Fig. 3**).

DISCUSSION

PHD

Age-specific mortality from PHD in Japan showed a high rate among infants <1 year old, and was elevating over 40 years old. In 2003–2006, about 70% of deaths from PHD were IPAH/HPAH. Therefore, the age-distribution in **Fig. 2** is thought to reflect that of IPAH/HPAH. This distribution pattern resembles that from IPAH/HPAH in the United States.¹⁴⁾

The numbers of deaths from PHD have been declining both in males and in females in Japan. The numbers

Table 1 Relative risk of mortality from PHD

	Relative Risk	95% Confidence Interval	P-value
Gender			
Female	1.00	—	—
Male	1.57	1.51–1.61	<0.0001
Year			
1979–1982	2.75	2.59–2.90	<0.0001
1983–1986	2.21	2.09–2.34	<0.0001
1987–1990	1.60	1.50–1.69	<0.0001
1991–1994	1.21	1.14–1.29	<0.0001
1995–1998	1.00	—	—
1999–2002	0.84	0.79–0.90	<0.0001
2003–2006	0.79	0.74–0.84	<0.0001
Age group (y.o.)			
0	6.10	5.58–6.64	<0.0001
1–9	0.29	0.26–0.32	<0.0001
10–19	0.24	0.21–0.27	<0.0001
20–29	0.25	0.22–0.27	<0.0001
30–39	0.31	0.28–0.34	<0.0001
40–49	0.49	0.45–0.53	<0.0001
50–59	1.00	—	—
60–69	2.68	2.52–2.85	<0.0001
70–79	7.35	6.93–7.79	<0.0001
80–	16.28	15.33–17.27	<0.0001

PHD: pulmonary heart disease

of deaths from IPAH/HPAH have been increasing. Therefore, the main reason for the decrease is the decrease in the number of deaths from PHD secondary to chronic obstructive pulmonary disease, fibrosing lung disease or destroyed lung from pulmonary tuberculosis. Another possible reason is that many patients with IPAH/HPAH were not diagnosed as IPAH/HPAH and were diagnosed as only pulmonary hypertension in previous years.

IPAH/HPAH

New therapeutic agents are being developed and the prognosis of IPAH/HPAH is gradually ameliorating in specialized hospitals.^{5–8)} When the number of diagnosed cases is unchanged and management is improved, the number of deaths should decrease at least temporally, and not increase. However, the number of deaths from IPAH/HPAH in the present data shows an unexpected increase.

The number of deaths diagnosed as a certain disease is regulated both by diagnostic power and by the results of treatment. A subtle increment of the estimated diagnostic number after 1996 may be one of the reasons for the change in the number of deaths from IPAH/HPAH.

The number of deaths increases as a result of unsuccessful therapy, but also as a result of good or unchanged therapy with continuously changing the diagnosed number and/or time dependent effect of managements. Therefore, we cannot determine all the effects of new therapeutic agents in nationwide hospitals from the present study. Individual data on the duration from diagnosis to death are needed to estimate the efficacy of managements. However, the data and mortality by age have not been announced officially in Japan. The effect of newer managements on population-based mortality remains to be determined.

Recently, guidelines for the treatment of pulmonary hypertension^{9, 10)} have been published in Japan, and concern about pulmonary hypertension is increasing. The increment of recognition for the disease may contribute to the number of patients diagnosed as having the disease. Pulmonary hypertension associated with human immunodeficiency virus or appetite suppressants seem not to affect the present results, because these types of pulmonary hypertension are very rare in Japan.

The ratio of deaths from IPAH/HPAH to that from pulmonary heart disease was increasing and reached about 70%. Therefore, the age distribution of deaths from

Fig. 3 Changes in the number of cases and deaths with IPAH/HPAH. Annual mortality is that among patients with IPAH/HPAH, that is, population in annual mortality is prevalence of IPAH/HPAH. IPAH: idiopathic pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; PHD: pulmonary heart disease without pulmonary embolism

Table 2 Relative risk of mortality from IPAH

	Relative Risk	95% Confidence Interval	P-value
Gender			
Female	1.00	—	—
Male	0.65	0.62–0.69	<0.0001
Year			
1979–1982	0.34	0.30–0.38	<0.0001
1983–1986	0.51	0.47–0.57	<0.0001
1987–1990	0.62	0.56–0.68	<0.0001
1991–1994	0.75	0.69–0.82	<0.0001
1995–1998	1.00	—	—
1999–2002	1.05	0.97–1.14	0.24
2003–2006	1.15	1.07–1.25	0.0004

IPAH: idiopathic pulmonary arterial hypertension

pulmonary hypertension partly reflects that from IPAH/HPAH, which is considered, based on clinical studies, to appear more commonly in the young and middle-aged. However, the present results show that the crude the number of deaths from pulmonary heart disease were not higher in teens, twenties, or thirties than in other ages. The results from the U.S.A. clearly demonstrate that age-specific mortality from IPAH/HPAH is at a high rate among infants <1 year old, a low rate in childhood, and ascending rate through the remainder of life.¹⁴⁾

The incidence from IPAH/HPAH was 1–2 per million people in the NIH registry,¹²⁾ and 1.7 per million population (95% coincidence interval, 1.0–2.4) in a collaborative study from France, Belgium, United Kingdom, and Netherlands.²¹⁾ The prevalence and incidence from recent reports ranged between 6.5 and 25 per million people and between 1.0 and 3.3 per million people, respectively.^{22–24)} The prevalence (7.5 per million people) and incidence (3.4 per million people) in the present study resembled to the findings of previous reports.

CONCLUSIONS

The annual number of deaths from PHD decreased, and those from IPAH/HPAH increased significantly during 1979–2006 in Japan.

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