# Causes of Death among Persons Affected by Leprosy in Korea, 2010–2013

Young-Hwan Ahn,[1] Hyungcheol Park,[2] and Sun-Seog Kweon[3*]

[1]*Department of Gastroenterology, Ajou University School of Medicine, Suwon, Korea;* [2]*Department of Preventive Medicine, Sorokdo National Hospital, Goheung-gun, Korea;* [3]*Department of Preventive Medicine, Chonnam National University, Hwasun-gun, Korea*

*Abstract.* In addition to the complications of leprosy, people affected by leprosy (PALs) can suffer from chronic diseases. We evaluated the recent pattern of deaths among Korean PALs and compared it with that in the general population. We analyzed the death certificate data of 1,359 PALs from 2010 through 2013. The all-cause and cause-specific standardized mortality ratio (SMR) and standardized mortality with 95% CI were calculated. Malignancy had the highest standardized mortality, with 130.9 deaths per 100,000 persons, followed by cardiovascular diseases (CVDs; 85.5 deaths) and respiratory diseases (38.2 deaths). Of malignancies, liver cancer caused the greatest number of cancer deaths (40.0 deaths). The all-cause mortality of PALs was significantly lower than that in the general population, corresponding to an SMR of 0.84 (95% CI 0.79–0.88). Deaths from malignancy and CVDs were significantly lower, corresponding to SMRs (95% CIs) of 0.88 (0.79–0.98) and 0.75 (0.67–0.84), respectively. The death rates for lung and stomach cancers were lower, whereas mortality due to liver cancer was higher, with an SMR of 1.79 (95% CI 1.43–2.22). Except for liver cancer and infection, the causes of mortality of PALs tend to be lower than that in the general population. The most common underlying cause of death in PALs was stroke, followed by ischemic heart disease, liver cancer, and pneumonia.

## INTRODUCTION

About 200,000 new cases of leprosy were reported worldwide in 2018, but the incidence of leprosy is continuously decreasing in most countries, including Korea.[1,2] Accordingly, strategies for managing people affected by leprosy (PALs) have been revised. Rather than emphasizing acute-phase treatment, the emphasis is now on the quality of life (QOL),[3] oral hygiene,[4] preventing disabilities, and eradicating the stigma and discrimination experienced by elderly PALs.[5–7] In addition, some studies have examined diabetes and hepatitis in PALs.[8–10]

In this context, it is important to know the pattern of deaths among PALs to manage these patients effectively. Suicide, cardiovascular disease (CVD), and organ failure are major causes of death in active leprosy patients.[11] In Brazil, which has the second highest incidence of leprosy worldwide,[2] leprosy is considered a neglected cause of death. The proportion of leprosy-related deaths is less than 0.1% of all deaths, and mortality due to leprosy decreased by 2.8% annually between 2000 and 2011.[12] However, there have been few reports on the causes of death of PALs other than active leprosy patients.

Therefore, this study evaluated the circumstances of death among Korean PALs from 2010 to 2013 with the aim of identifying the major underlying causes of death and comparing mortality among PALs with that among the Korean population.

## MATERIALS AND METHODS

In 2010, 13,316 PALs (7,152 males and 6,164 females) were registered with the Korean Hansen Welfare Association (KHWA). Of these, 7,530 lived in their own homes, 4,067 lived in 87 settlements for PALs, and 1,179 lived in seven residential facilities for PALs. All domestic PALs in South Korea are registered in the KHWA database.[13] The status of deaths of total 13,316 PALs was followed from 2010 to 2013 and the underlying causes of death of the identified deaths were investigated. During those 4 years, 1,359 deaths were identified. Death and the underlying causes of death were confirmed by linkage with the death certification database of the Korean National Statistics Office (NSO). Information available on NSO death certificates include age, gender, disease activity, disease duration and subtype, marital status, occupation, and date, place, and cause of death.

The underlying causes of death were categorized as CVD (ICD-10 codes, I00–I99), malignancy (C00–C97), respiratory diseases (J00–J98), infectious diseases (A00–B99), diabetes (E10–E14), suicide (X60–X84), and unidentified (R00–R99). In detail, CVD was categorized as hypertensive disease (I10–I13), ischemic heart disease (IHD; I20–I25), and stroke (I60–I69). The malignancy category includes lung (C34), liver (C22), stomach (C16), colon and rectal (C18–C21), and pancreatic (C25) cancers and leukemia (C91–C95). Infectious diseases include leprosy (A30–A49), and respiratory diseases comprise pneumonia (J12–J18) and chronic obstructive pulmonary diseases (J40–J47).

The demographic data for the total Korean population, used as the standard population, obtained from the NSO database, included population by age categories, age-specific mortality, and cause-specific mortality in the same calendar years. The age used in the standardization was classified into 14 categories at 5-year intervals and ranged from 15 years to 80 years and older. Standardized mortality ratios (SMRs) and their 95% CIs were calculated using an indirect standardization method to compare the mortality with that of the Korean population. We also calculated the all-cause and cause-specific mortality with their 95% CIs to compare the magnitude of mortality among underlying causes of death in PALs.

**Ethics statement.** This study was approved by the Institutional Review Board of Masan National Tuberculosis Hospital, Republic of Korea (approval No. IRB-398837-2019-E07). The requirement for informed consent was waived because of the retrospective nature of the study and the use of de-identified data.

## RESULTS

During the study period (2010–2013), 1,359 deaths occurred among PALs. The mean age of the subjects was

*Address correspondence to Sun-Seog Kweon, Department of Preventive Medicine, Chonnam National University Medical School, 264 Seoyang-ro, Hwasun-gun 58128, Korea. E-mail: ujingogo@paran.com

79.6 ± 8.4 years (males 78.5 ± 8.4 years, females 81.1 ± 8.2 years), and 58.6% of the subjects were male. Fifty-four percent of the study subjects were older than 80 years, and only 1.7% was aged less than 60 years. Table 1 summarizes the frequencies of leprosy subtypes, place of death, occupation, marital status, age of leprosy diagnosis, and age of death (Table 1).

Of the deaths, 26% were caused by malignancies, including liver (6.3%), lung (5.2%), stomach (3.6%), and colorectal (3.6%) cancers. Cardiovascular disease caused 23% of deaths, including stroke (8.2%), IHD (6.7%), and other hypertensive diseases (2.7%). The proportionate mortality ratios among PALs were similar to those in the general population, except for the relatively higher rates of respiratory diseases and lower rates of malignancy and suicide in the general population (Figure 1).

Malignancy had the highest standardized mortality among PALs, with 130.9 deaths per 100,000 persons, followed by CVDs (85.5 deaths), respiratory diseases (38.2 deaths), suicide (22.2 deaths), infectious diseases (17.3 deaths), and diabetes (16.8 deaths). In the subcategories of malignancies, liver cancer was the leading cause of cancer death (40.0 deaths), followed by lung (23.2 deaths), stomach (13.3 deaths), and colorectal (12.2 deaths) cancer. In the CVD subcategories, stroke (30.8 deaths) was the leading cause of death, followed by IHD (25.9 deaths) and hypertensive disease (8.5 deaths).

The all-cause mortality of PALs was lower than that of the general population, corresponding to an age-standardized mortality of 436.8 persons per 100,000 and SMR of 0.84 (95% CI 0.79–0.88)). The SMRs were lower in both genders: 0.75 (95% CI 0.70–0.80) in males and 0.87 (95% CI 0.80–0.95) in females.

Mortality due to malignancy was significantly lower in PALs than in the general population, with an SMR of 0.88 (95% CI 0.79–0.98). The difference was significant in males, with an SMR of 0.75 (95% CI 0.66–0.85) but not in females with an SMR of 0.89 (95% CI 0.73–1.07). By cancer sites, lower mortality was observed for lung and stomach cancer, with SMRs of 0.98 (95% CI 0.56–0.90) and 0.70 (95% CI 0.49–0.96), respectively, but higher for liver cancer, with an SMR of 1.79 (95% CI 1.43–2.22). No significant difference was found for colorectal cancer, pancreatic cancer, or leukemia.

The mortality rate for CVDs was lower in PALs than in the general population, with SMRs of 0.75 (95% CI 0.67–0.84), 0.71 (95% CI 0.61–0.83), and 0.78 (95% CI 0.66–0.92) in all, male, and female PALs, respectively. Of these, the SMRs for IHD, hypertensive disease, and all stroke were 0.95 (95% CI 0.76–1.16), 0.86 (95% CI 0.60–1.18), and 0.60 (95% CI 0.49–0.72), respectively.

Mortalities due to respiratory disease (SMR 0.73; 95% CI 0.59–0.89), chronic obstructive pulmonary disease (SMR 0.63; 95% CI 0.43–0.89), and suicide (SMR 0.63; 95% CI 0.38–0.99) were lower in male subjects than in males in the total population (Table 2).

## DISCUSSION

In this study, we found that mortality rates for PALs were significantly lower than that of the general population for most underlying causes of death, with the exceptions of liver cancer and infectious diseases. Ranking by the main underlying cause of death among PALs differed from that of the general population. To our knowledge, few studies have reviewed the epidemiological characteristics of deaths among PALs and compared these with the general population. The baseline characteristics of the two populations seem to differ greatly, including the male-to-female ratio (116.0 and 98.7 in the general population and PALs, respectively), mean age (37.0 years and 69.9 years, respectively), proportion of jobless among the 15 years and older age-group (45.8% and 72.3%, respectively), and proportion of national basic livelihood recipients (72.2% and 3.2%, respectively).[14] Therefore, we compared the death levels between the two populations using the age-standardized mortality rate.

**The reason for lower total mortality in PALs than the general population.** Few reports have compared the death pattern of PALs with that of the general population. In 2010, Cho et al.[15] reported that the survival of PALs was higher than that of the general population, and postulated that side effects of dapsone caused the higher survival rate in PALs because dapsone enhances an individual's antioxidant ability, increases the survival of *Caenorhabditis elegans*, and inhibits the production of free radicals. However, they focused on the effects of dapsone without mentioning what percentage of PALs was still taking dapsone after disease resolution. These results are controversial because dapsone has adverse side effects, such as hemolytic anemia, methemoglobinemia, agranulocytosis, and hepatitis.[16,17] Anti-sarcopenic effects of dapsone were also reported in elderly female leprosy survivors who have recent dapsone

TABLE 1
Baseline characteristics of study subjects identified their death during 2010–2014 (*n* = 1,359)

| | Number (%), or means ± SD |
|---|---|
| Male | 796 (58.6) |
| Active disease | 12 (0.9) |
| Leprosy subtype | |
|   Lepromatous leprosy | 909 (66.9) |
|   Tuberculoid leprosy | 450 (33.1) |
| Place of death | |
|   Home | 200 (14.7) |
|   Hospital | 1,055 (77.6) |
|   Nursing home | 65 (4.8) |
|   Road | 33 (2.4) |
|   Others | 6 (0.5) |
| Occupation | |
|   Joblessness | 1,076 (79.2) |
|   Housekeeper | 51 (3.8) |
|   Service | 5 (0.4) |
|   Agriculture and fishing | 167 (12.3) |
|   Skilled worker | 34 (2.5) |
|   Others | 26 (1.9) |
| Marital status | |
|   Single | 69 (5.1) |
|   Married | 1,232 (90.6) |
|   Divorce | 54 (4.0) |
|   Unknown | 4 (0.3) |
| Mean age of disease onset (years) | 24.1 ± 11.9 |
| Mean age of death (years) | 79.6 ± 8.4 |
| Age of death (years) | |
|   40–49 | 2 (0.1) |
|   50–59 | 22 (1.6) |
|   60–69 | 129 (9.5) |
|   70–79 | 472 (34.7) |
|   80–89 | 575 (42.3) |
|   90–99 | 157 (11.6) |
|   100–109 | 2 (0.1) |

## Proportionate mortality ratio (%)
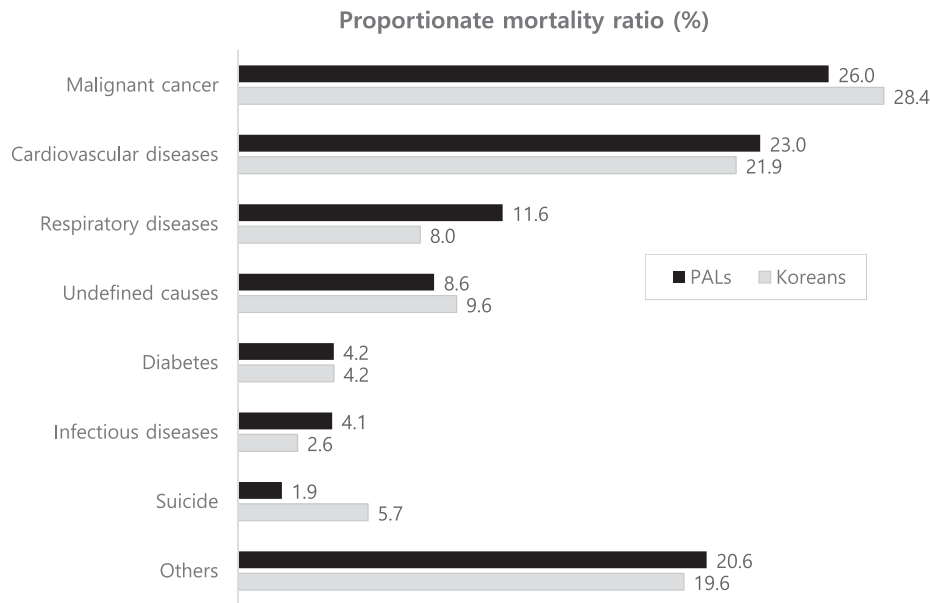


FIGURE 1.    Proportionate mortality ratio among the 1,359 persons affected by leprosy.

medication.[18] Sarcopenia is associated with drastic reduction in the QOL in elderly people and may be directly associated with a wide range of health outcomes from functional dependency to higher mortality rates.[19]

In our study, the survival of PALs was also higher than that of the general population. Why do PALs have lower mortality than the general population? One possible explanation is that PALs in Korea may have better access to medical services than groups of similar age in the general population because of the health care program provided to all registered PALs. According to the KHWA, more than one-third of all PALs (3,856/9,632 as of 2018) live in facilities or dedicated settlements for PALs, where medical care services are provided free

of charge. Even those living in their own homes receive medical care services through government-provided mobile or home visit medical services. The KHWA reported that it provided 51,187 medical services for PALs in 2016.[13] The better access to health care services is presumed to have contributed to the longer survival of PALs than the general population for the same age groups. In addition, a comprehensive national leprosy control program, including case finding, treatment, rehabilitation, and welfare services, is being provided to all registered PALs in Korea. In 2018, a total of 129 active prevalent cases, six new cases, and one relapsed case were reported in Korea.[2] It is a quite different situation from that in countries with a high incidence of leprosy. So,

TABLE 2
Mortality of persons affected by leprosy according to cause of death, 2010–2013

| Causes of death | Deaths (person) | | | Standardized mortality ratio (95% CI) | | | Age-standardized mortality (per 100,000 people) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Male | Female | Total | Male | Female | Total | Male | Female |
| Total mortality | 1,359 | 796 | 563 | 0.84 (0.79–0.88) | 0.75 (0.70–0.80) | 0.87 (0.80–0.95) | 436.8 | 432.6 | 406.6 |
| Infection (A00–B99) | 56 | 19 | 37 | 1.27 (0.96–1.65) | 0.66 (0.40–1.04) | 2.09 (1.47–2.88) | 17.3 | 9.9 | 25.5 |
| Leprosy (A30) | 7 | 3 | 4 | – | – | – | 1.5 | 0.9 | 2.2 |
| Leprosy and others (A30–A49) | 29 | 10 | 19 | 1.88 (1.26–2.70) | 1.20 (0.57–2.21) | 2.66 (1.60–4.16) | 7.5 | 4.2 | 12.1 |
| Cancer (C00–D48) | 353 | 244 | 109 | 0.88 (0.79–0.98) | 0.75 (0.66–0.85) | 0.89 (0.73–1.07) | 130.9 | 139.1 | 98.4 |
| Lung (C43) | 70 | 50 | 20 | 0.98 (0.56–0.90) | 0.53 (0.39–0.70) | 0.91 (0.56–1.41) | 23.2 | 25.1 | 16.1 |
| Liver (C22) | 85 | 59 | 26 | 1.79 (1.43–2.22) | 1.45 (1.10–1.87) | 2.05 (1.33–3.00) | 40.0 | 48.2 | 23.2 |
| Stomach (C16) | 36 | 29 | 7 | 0.70 (0.49–0.96) | 0.67 (0.45–0.96) | 0.46 (0.18–0.95) | 13.3 | 16.6 | 6.1 |
| Colorectal (C18–C21) | 36 | 27 | 9 | 0.77 (0.54–1.07) | 0.80 (0.53–1.17) | 0.53 (0.24–1.01) | 12.2 | 14.5 | 7.3 |
| Pancreas (C25) | 17 | 9 | 8 | 0.67 (0.39–1.08) | 0.56 (0.25–1.06) | 0.79 (0.34–1.56) | 6.1 | 5.5 | 6.6 |
| Leukemia (C91–C95) | 8 | 5 | 3 | 1.28 (0.55–2.53) | 1.09 (0.34–2.55) | 1.36 (0.26–4.01) | 4.1 | 4.0 | 3.7 |
| Diabetes (E10–E14) | 57 | 35 | 22 | 0.78 (0.59–1.01) | 0.80 (0.56–1.11) | 0.70 (0.44–1.06) | 16.8 | 17.5 | 15.0 |
| Cardiovascular diseases (I00–I90) | 312 | 166 | 146 | 0.75 (0.67–0.84) | 0.71 (0.61–0.83) | 0.78 (0.66–0.92) | 85.5 | 76.7 | 93.9 |
| Hypertensive disease (I10–I13) | 37 | 18 | 19 | 0.86 (0.60–1.18) | 1.06 (0.62–1.67) | 0.82 (0.50–1.29) | 8.5 | 6.6 | 11.6 |
| Ischemic heart disease (I20–I25) | 91 | 52 | 39 | 0.95 (0.76–1.16) | 0.90 (0.67–1.18) | 0.95 (0.68–1.30) | 25.9 | 26.0 | 24.7 |
| Stroke (I60–I69) | 112 | 56 | 56 | 0.60 (0.49–0.72) | 0.50 (0.380.-66) | 0.70 (0.53–0.90) | 30.8 | 24.8 | 37.1 |
| Respiratory diseases (J00–J96, U04) | 158 | 96 | 62 | 0.92 (0.78–1.07) | 0.73 (0.59–0.89) | 1.03 (0.79–1.32) | 38.2 | 34.3 | 37.5 |
| Pneumonia (J12–J18) | 78 | 43 | 35 | 0.99 (0.78–1.23) | 0.80 (0.58–1.07) | 1.13 (0.79–1.57) | 18.3 | 14.9 | 20.7 |
| COPD (J40–J47) | 48 | 33 | 15 | 0.80 (0.59–1.06) | 0.63 (0.43–0.89) | 0.84 (0.47–1.38) | 11.5 | 11.4 | 9 |
| Suicide (X60–X84) | 26 | 19 | 7 | 0.74 (0.48–1.08) | 0.63 (0.38–0.99) | 0.72 (0.28–1.48) | 22.1 | 25.8 | 13.7 |
| Undefined (R00–R99) | 117 | 68 | 49 | 0.59 (0.49–0.71) | 0.67 (0.52–0.85) | 0.94 (0.39–0.69) | 29.7 | 29.9 | 29.2 |

better access to medical services of PALs may not be applicable to all countries.

Another possible reason is the positive effect of PALs' community lifestyle. One-third of PALs live in various settlements or hospitals reserved exclusively for PALs. The community members may have relatively stronger interrelationships. Social support can enhance a healthy lifestyle and reduce mortality, especially in elderly individuals.[20] In addition, PALs living in a leprosarium in Korea had better cognitive functions than did a control population living in rural areas.[21] Higher cognitive functioning in elderly persons is associated with longer mortality.[22] Poor survival of colon cancer was reported among patients living alone, which is also a strong independent predictor of deaths from colorectal cancer.[23] It is well known that PALs have a poor QOL because of physical and psychosocial disabilities.[3] However, active social support and national control policies could prevent the deterioration of QOL and reduce mortality of PALs. Therefore, better access to medical services, a cohabiting lifestyle in their own settlements or facilities, and healthier behaviors such as exercise and regular screening might be related to lower mortality in PALs.

**Characteristics of cancer deaths in PALs.** Because lepromatous leprosy, a subtype of Hansen's disease, depresses cellular immunity,[24] studies have examined whether the risk of cancer increases in PALs; most studies have found no significant difference between PALs and the general public.[25–27] However, now that most of the leprosy patients have been cured, no data have been reported on cancer deaths for PALs. In 2013, the top four causes of cancer death in the Korea population were lung (34.0 deaths per 100,000 people), liver (22.6 deaths), stomach (18.2 deaths), and colorectal (16.4 deaths) cancer.[28] In our study, the top four causes of cancer death among PALs were the same as in the Korean population, although the ranking and rates by cancer sites differed. The most common cause of cancer death in PALs was liver cancer (40.2 deaths per 100,000 people), followed by lung (23.2 deaths), stomach (13.3 deaths), and colorectal (12.2 deaths) cancer.

The mortality of lung and stomach cancers was lower in PALs, whereas that of liver cancer was significantly higher in PALs than in the general population. No differences were observed in colon or pancreatic cancer or in leukemia.

Although we assume that healthy behaviors, such as low smoking rates, that result from cohabiting in their own communities may have contributed to the decrease in mortality from lung cancer in men, it is not clear whether PALs have lower smoking rates than the general population.[29] Indeed, one report indicated high smoking rates in PALs. In 2013, Kwon et al.[30] reported that of 153 PALs, 50.6% of males and 6.1% of females were smokers. This was higher than the smoking rates (41.4% in males and 5.7% in females) in the general population of South Korea for the same period.[28] However, the sample size was too small to determine the smoking rate among the PALs and generalize the findings.

Stomach cancer is the most common cancer in Japanese autopsy cases with leprosy,[31] similar to the pattern of cancer incidence and cancer-related deaths in a Japanese population.[32] In our study, death from stomach cancer was lower in PALs than in the general population, with an SMR of 0.70 (95% CI 0.49–0.96). This is assumed to be related to the higher rate of participation in endoscopic gastric cancer screening,

which is provided to almost all PALs at no cost. In Korea, the participation in gastric cancer screening via the National Cancer Screening Program (NCSP) was less than 40% before 2010.[33] In an environment with relatively better medical accessibility, the effectiveness of endoscopic screening appears to have been maximized. In this context, it is assumed that colorectal and pancreatic cancer and leukemia had patterns similar to the general public, as there are no effective screening tools, and many patients refused screening due to the discomfort. In Korea, colorectal cancer is screened using the fecal occult blood test, and the screening rate in the NCSP was less than 30% before 2010.[34] In conclusion, mortality from all cancers and the major types of cancer was significantly lower in PALs than in the general population. Various medical services and managed care organized by the KHWA seem to have contributed to early detection and treatment, reducing mortality. However, details of the cancer deaths and explanation by cancer sites have uncertainties that need to be explained in further large-scale prospective studies.

**Death from liver cancer was extremely high.** In this study, death from liver cancer was extremely high in PALs compared with that in the general population, with an SMR of 1.79 (95% CI 1.43–2.22). This seems to be due to the higher prevalence of viral hepatitis and liver cirrhosis among PALs. The global prevalence of hepatitis C virus (HCV) infection is 1.0%,[35] whereas it is 1.8–5.5% in the Korean population.[36] However, Kim et al.[37] reported that the prevalence of anti-HCV antibody was 28.5% in PALs. A higher prevalence of HCV infection in PALs has been reported in several countries.[38,39] Hepatitis B virus (HBV) infection may have similar prevalence rates in the general population and in PALs,[40] although some studies have reported a high prevalence of HBV in PALs compared with that in the general public.[41,42] Furuta et al.[31] reported that the prevalence of cirrhosis at autopsy in PALs was 10.9%. It seems that proper treatment and management of liver diseases, such as viral hepatitis and liver cirrhosis, will likely reduce the number of deaths of PALs.

**Study strengths.** People afflicted with leprosy constitute the leading underprivileged group of this era. They still suffer from complications and chronic diseases and need proper management strategies. Much information is required to establish such management strategies. However, studies of neglected diseases attract little public attention, and there are only a few reports on this topic. Ours is a unique, original study of PALs. The results help to identify the characteristics of deaths among PALs. Comparing the mortality patterns with the general population helps to identify the chronic diseases to which PALs are vulnerable. We showed that mortality from liver cancer in PALs is far higher than that in the general population. We think this finding has implications for establishing a management plan for PALs.

**Study limitations.** Although hypertensive disease, IHD, and stroke have similar pathophysiology, only mortality from stroke was lower in PALs. This discrepancy in the results is thought to be due to a lack of statistical power caused by the small sample size. Some of the gender differences in the results are also thought to have been caused by a lack of statistical power rather than any biological differences between men and women. In this study, we were unable to explain what caused the differences in mortality between PALs and the general population, the gender differences, and the discrepancy by causes of death. Basic data on the status of health

habits or risk factors among PALs are lacking. In addition, it was impossible to compare mortality according to epidemiological or clinical factors, such as leprosy subtype, socioeconomic factors, and leprosy treatment type, because of issues related to protection of personal information. Larger scale prospective studies are required to clarify the mechanism underlying the lower mortality in PALs and to identify the causes of gender differences. Last, we did not include contributory causes of death but only analyzed the underlying causes of death. So, the attribution of leprosy to death may be underestimated because leprosy tends to be considered by health professionals as an associated cause of death.

In conclusion, mortality of PALs tends to be lower than that of the general population. In PALs, deaths caused by lung and stomach cancers and by stroke were lower than that in the general Korean population, whereas deaths due to liver cancer were higher. The most common cause of death in PALs was stroke, followed by IHD, liver cancer, and pneumonia.

Authors' addresses: Young-Hwan Ahn, Department of Gastroenterology, Ajou University School of Medicine, Suwon, Korea, E-mail: ntop0329@naver.com. Hyungcheol Park, Department of Preventive Medicine, Sorokdo National Hospital, Goheung-gun, Korea, E-mail: kjdhc@hanmail.net. Sun-Seog Kweon, Department of Preventive Medicine, Chonnam National University, Hwasun-gun, Korea, E-mail: ujingogo@paran.com.

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