Epidemiological characteristics of nontuberculous mycobacteriosis and bronchiectasis: comparative study using national mortality statistics from 1970 to 2015 in Japan

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Shareable abstract (@ERSpublications)
The epidemiological trends in NTM-related and bronchiectasis (BE)-related mortality are interrelated. Female BE-related deaths increased in the mid-1990s due to the prominent increase in NTMosis. NTMosis might be the leading cause of BE. https://bit.ly/3DTChdL

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Abstract

Background This study assessed longitudinal national data on mortality due to nontuberculous mycobacteriosis (NTMosis) and bronchiectasis and the association between the two diseases.

Methods We analysed the national death statistics of Japan from 1970 to 2015. The International Classification of Disease (ICD) codes were used to extract the relevant data. Crude mortality, age-adjusted mortality and standardised mortality rates were calculated using vital statistics and the population in 2000. We also identified domestic publications related to NTMosis and bronchiectasis with an internet-based search system.

Results The total number of bronchiectasis-related deaths remained at the same level, which was approximately 1000, for 45 years, although the number of deaths has consistently decreased in males but increased in females since the mid-1990s. A substantial increasing trend in females was also observed for NTMosis in the same period. The age-adjusted mortality data showed an increase in mortality in women due to NTMosis and confirmed the trend in bronchiectasis in women. The patterns in the number of domestic reports showed a recent slight increase in bronchiectasis and a marked increase in NTMosis.

Conclusions The trends in bronchiectasis-related mortality differed by sex. The epidemiological trends in the two diseases were associated, especially in elderly females since the mid-1990s. It is suggested that pulmonary NTMosis without pre-existing bronchiectasis might be a leading cause of postinfectious bronchiectasis in Japan.

Introduction

The incidence and prevalence of nontuberculous mycobacteriosis (NTMosis), a pulmonary disease, have been increasing worldwide [1]. Moreover, an increase in the mortality rate of >25% has been reported in several countries, including Japan [2, 3]. Because mortality data indicate the accumulation of severe cases, examining these statistics is useful for determining the burden of the disease. Meanwhile, in recent decades, bronchiectasis, which is regarded as an orphan and complicated disease, has drawn considerable attention, leading to a significant increase in the number of studies in European and North American

countries [4–6]. Although epidemiological data, including mortality data, were reported from these countries [7–10], population-based data have rarely been reported from Asian countries [11].

The nodular bronchiectasis type, which is the most prevalent type of pulmonary NTMosis, mainly affects elderly females who do not have apparent underlying lung disease [12–15]. This disease type can start as small nodular lesions in the peripheral lung field and ultimately progress to cystic bronchiectasis. On the other hand, nontuberculous mycobacteria (NTM) can exacerbate pre-existing bronchiectasis. Because both lesions share common radiographic findings, it is often difficult to determine whether the patients have underlying bronchiectasis [14].

Furthermore, FUJITA *et al.* [16] reported that approximately 45% of *Mycobacterium avium-intracellulare* complex (MAC) patients had chronic co-infection with pathogenic microorganisms, such as methicillin-sensitive *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Aspergillus* spp., among which 85.1% of patients had bronchiectasis. Interestingly, they found that *P. aeruginosa was* isolated more frequently after MAC negative conversion. MAC disease is an important cause of bronchiectasis [17], and in the US Bronchiectasis Registry, 63% of the patients had a history of pulmonary NTMosis or NTM isolated at baseline. Japanese Registry data, which were reported at the American Thoracic Society International Conference in 2020, also showed that as many as 74% of cases had pulmonary NTMosis [5]. Hence, the epidemiology of the two diseases is likely to be interrelated, and the discrimination of the cause of death between the two diseases is difficult. Therefore, it is important to analyse the epidemiological data regarding the two diseases simultaneously. In a previous study, NTM mortality data showed that the number of deaths increased substantially in females, with 1121 deaths in 2010 [2, 18]. However, the data lacked information on the influence of bronchiectasis and vice versa.

Accordingly, in the present study, we investigated longitudinal national data on mortality due to NTMosis and bronchiectasis and the relationship between the diseases, focusing on age-, sex- and region-related differences during the preceding 45 years in Japan. In addition, we analysed the change in the number of domestic publications related to both diseases.

Study design and methods

This was a retrospective review of death certificates and record review to clarify the overall epidemiological characteristics of NTMosis and bronchiectasis using publicly available mortality data and the published domestic medical literature.

Mortality data from vital statistics

The government collects death certificates authorised by physicians, which report the main cause of death and any comorbid diseases. The International Classification of Disease (ICD) death code is used to describe the cause of death on the death certificate, and only the main cause of death is registered in the official death statistics every year. We obtained the annual total number of deaths caused by NTMosis and bronchiectasis from the Vital Statistics of Japan from 1970 to 2015 [19], which is published annually by the Ministry of Health, Labor and Welfare Japan. The International Classification of Disease versions 8 to 10 (ICD-8–10) death codes were used to describe the cause of death on death certificates summarised in the official death statistics. The codes for death due to NTMosis in ICD-8–10 were extracted according to the method described in a previous study [2]. The codes for death due to bronchiectasis were 518 in ICD-8, 494 in ICD-9 and J47 in ICD-10. To focus on pulmonary disease as much as possible, disseminated types of NTMosis with acquired immunodeficiency syndrome (AIDS) classified as B20.0 were not included in this analysis. This study used “nontuberculous mycobacteriosis” because extrapulmonary data could have been included. However, considering the rarity and mortality rate, the influence of extrapulmonary NTM on death statistics would be minimal. As mentioned above, disseminated NTM cases complicated with AIDS were excluded from this study. When the sentences clearly describe the pulmonary disease, “pulmonary” is added. The cause of death was bronchiectasis, which does not include the death cases due to NTMosis and aspergillosis registered on the ICD code. In this instance, bronchiectasis could be a sequela of pulmonary NTMosis, and mild pulmonary NTMosis might also coexist.

Analytical method

The rates of mortality due to NTMosis and bronchiectasis were calculated as the number of deaths obtained from Vital Statistics divided by the population size reported in the Census of Japan, which is published every 5 years by the Ministry of Internal Affairs and Communications [20]. The mortality rate was stratified by age group and sex. The statistical analyses were divided into two periods, from 1970 to 1994 and from 1995 to 2015, in accordance with a previous study [2]. The death rate was adjusted for the age distribution of the population in 2000.

The number of reported paper analyses

Previous studies suggested that enhanced awareness of NTMosis among medical staff could have contributed to the increase in the diagnosis and reporting of NTMosis [21]. Therefore, we conducted a domestic medical literature survey to determine the annual number of reports until 2015 in Japan as a proxy for the awareness of NTMosis and bronchiectasis among medical staff. We searched for relevant publications in an internet-based search system provided by the Japan Medical Abstract Society (Ichushi Web) with the key words "nontuberculous mycobacteriosis" or "bronchiectasis".

This study was approved by the Institutional Review Board for Human Research at Fukujuji Hospital (#14046). The review board approved the informed consent waivers.

Results

Numbers of deaths due to pulmonary NTMosis and bronchiectasis from 1970 to 2015

The number of NTMosis-related deaths markedly increased from 1970 to 2015 (supplementary figure S1). The increasing trend in deaths due to NTMosis accelerated after 1995 (y=11x–58 (1970–1994) and y=52.9x+276 (1995–2015)). In contrast, the number of deaths caused by bronchiectasis remained roughly the same (1076 in 1970 and 1021 in 2015), although it slightly decreased up to 1994 and then plateaued (y=−7.3x+1063 (1970–1994) and y=0.4x+891 (1995–2015)). The number of NTMosis-related deaths surpassed the number of bronchiectasis-related deaths in 2006.

Trend in the number of deaths due to NTMosis and bronchiectasis stratified by sex from 1970 to 2015

The increasing trend in NTMosis-related deaths accelerated. A female predominance developed in the 1990s, and the sex difference was the largest in 2015 (male: 480; female: 917) (male: y=5.5x−26, female: y=5.6x−32 (1970–1994); male: y=15.2x+172, female: y=37.7x+104 (1995–2015)) (supplementary figure S2). The number of bronchiectasis-related deaths decreased from 663 to 304 among males, and the trends were similar before and after 1995 (y=−8.7x+680 (1970–1994) and y=−8.9x+436 (1995–2015)). However, among females, the number of deaths increased from 413 to 717 over the study period, and the increase accelerated in the 1990s (y=1.4x+382 (1970–1994) and y=9.4x+455 (1995–2015)). The number of bronchiectasis-related deaths among females exceeded that in males in the mid-1990s, when the number of deaths due to NTMosis among females started to markedly increase.

Trends in the crude rates of death attributed to NTMosis and bronchiectasis stratified by sex from 1970 to 2015

The trend in crude death was similar to the trend in the number of deaths (figure 1). The crude rate of death due to bronchiectasis decreased until 1995 and then plateaued until 2015. The rates of death due to bronchiectasis and NTMosis in females increased after 1990 (figure 2).

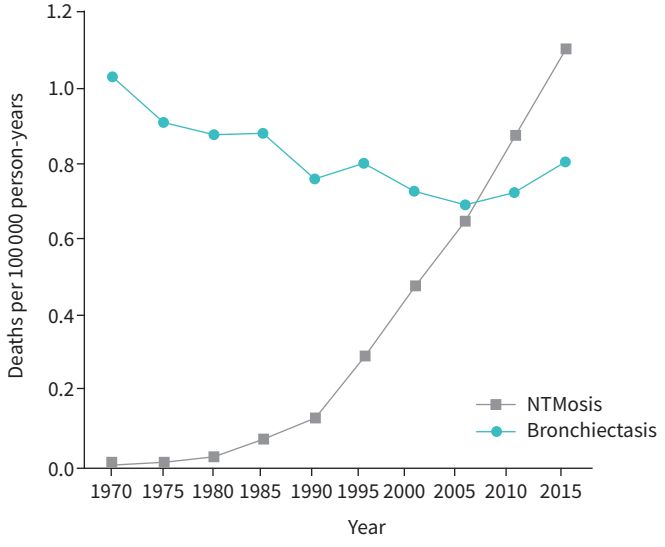

FIGURE 1 Crude death rate due to nontuberculous mycobacteriosis (NTMosis) and bronchiectasis, 1970–2015.

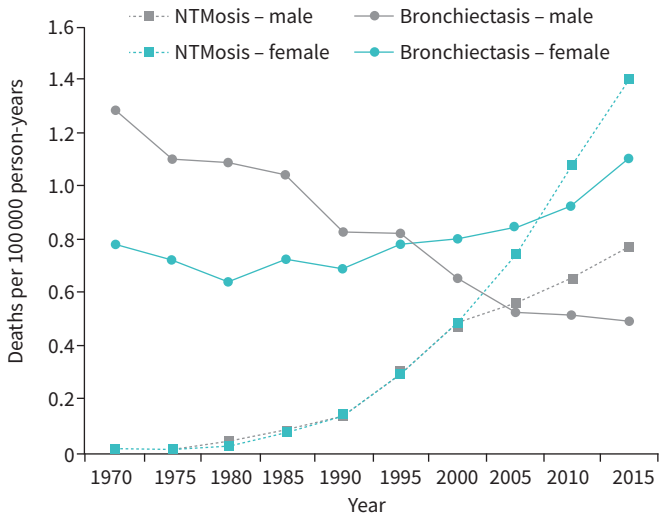

FIGURE 2 Crude death rate due to nontuberculous mycobacteriosis (NTMosis) and bronchiectasis by sex, 1970–2015.

Age-specific rates of death due to NTMosis and bronchiectasis in 1975 and 2015

The rates of death due to NTMosis and bronchiectasis increased with age, peaking in the group older than 85 years in 2015. The rate of death due to NTMosis was slightly higher than that due to bronchiectasis (figure 3).

The age-specific death rates were compared between 1975 and 2015. Although the death rate was consistently relatively higher in the elderly population over the last 40 years, there was a change from male to female predominance for both NTMosis and bronchiectasis (supplementary figure S3).

Trends in age-adjusted rates of death due to NTMosis and bronchiectasis from 1970 to 2015

The age-adjusted rate of mortality due to bronchiectasis decreased in both sexes, but the mortality rate in females started to plateau after 2010 (0.67 per 100 000 population in 2010 and 0.68 per 100 000

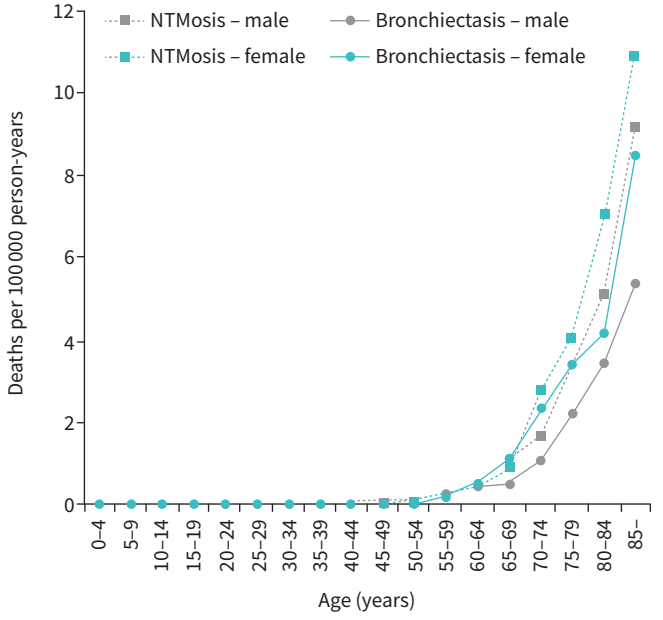

FIGURE 3 Age-specific rates of death due to nontuberculous mycobacteriosis (NTMosis) and bronchiectasis in 2015.

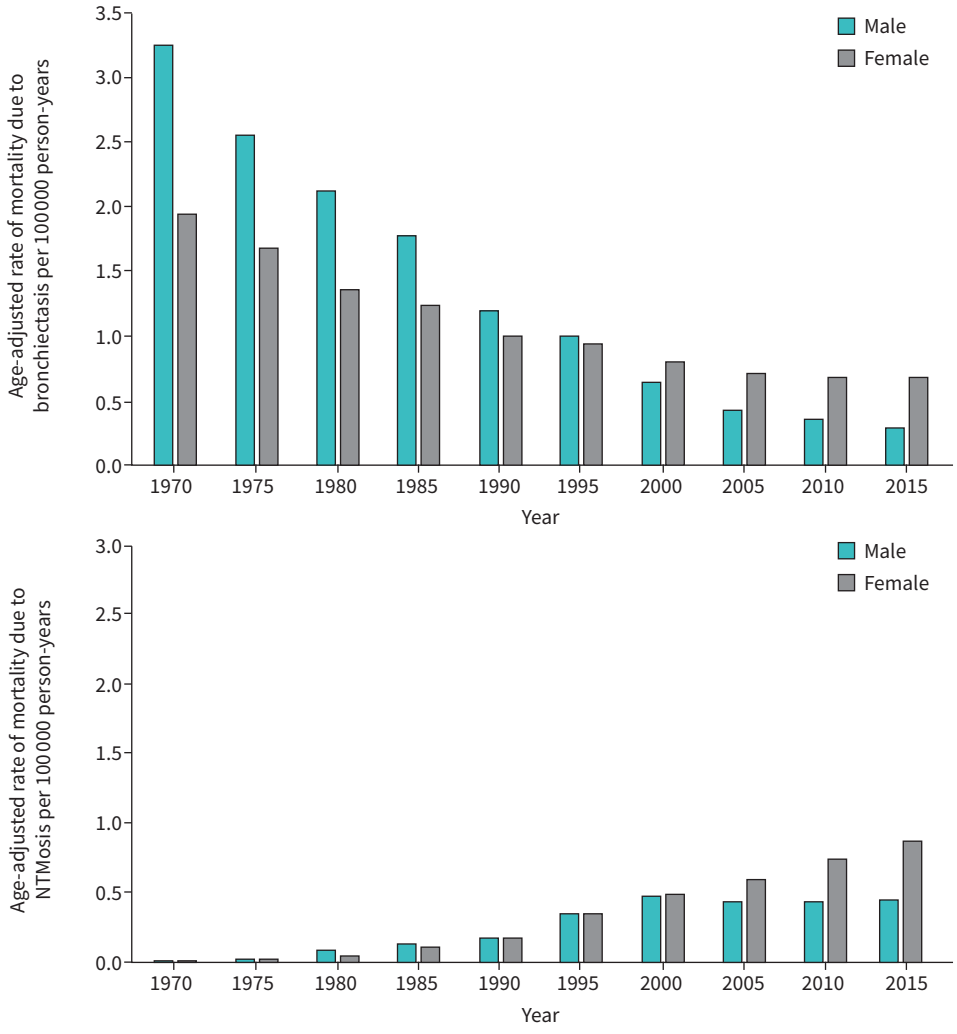

FIGURE 4 Age-adjusted rates of mortality due to nontuberculous mycobacteriosis (NTMosis) and bronchiectasis, 1970–2015.

population in 2015) (figure 4). The age-adjusted rate of mortality due to NTMosis consistently increased in females, but in males, it plateaued after 2000. The rate of mortality due to NTMosis exceeded that due to bronchiectasis in both males and females in 2010 (males: 0.45 per 100 000 population; females: 0.85 per 100 000 population in 2015).

Numbers of reported studies on NTMosis and bronchiectasis in Japan

The number of reported studies on bronchiectasis showed a peculiar trend. The first peak occurred between 1986 and 1990 (n=485), but the number of publications subsequently decreased. However, there was a slight increase after the period from 1996 to 2000, and the second peak occurred between 2011 and 2015 (n=568). The number of publications about NTMosis consistently increased, especially after the period from 1991 to 1995 (n=352) and from 2011 to 2015 (n=3009) (supplementary figure S4).

Discussion

This study is the first to analyse the epidemiology of NTMosis and bronchiectasis concurrently using national mortality data. Notably, the total number of bronchiectasis-related deaths remained at the same level, approximately 1000, over the last 45 years. However, the number consistently decreased in males, but started to increase in females in the mid-1990s. The increasing trend in females occurred at the same time as the more marked increase in the number of deaths due to NTMosis in females. The age-adjusted mortality data showed a marked decrease in bronchiectasis-related deaths in both sexes since 1970 but

confirmed the changes in the trend in bronchiectasis-related deaths in females, while NTMosis-related deaths in females showed a consistent increase. The epidemiological trends in the two diseases were interrelated, especially in elderly females.

Several factors are potentially responsible for the observed fluctuation in bronchiectasis-related mortality. The decrease in the number of bronchiectasis-related deaths is mainly due to improvements in treatment strategies for infectious diseases such as TB and pneumonia [22]. Advancements in the treatment of bronchiectasis with antibiotics and macrolides as immunomodulators could also have contributed [23, 24]. In the present study, a consistent decrease in the number of deaths was observed in males, while that in females started to increase in the 1990s. Surprisingly, the increase in the number of deaths in females was large enough to surpass the decrease in the number of deaths in males. Therefore, it seems likely that the classic postinfectious type of bronchiectasis has become less common in both sexes, and the underlying cause of postinfectious bronchiectasis has changed to NTMosis over the last 40 years, especially in females.

A marked increase in NTMosis-related deaths in females is likely to be due to the accumulated severe cases. This, in turn, could have caused the observed increase in bronchiectasis-related deaths in females. Indeed, an increasing trend in both NTMosis- and bronchiectasis-related deaths in females has been observed since the 1990s. Although the number of NTMosis-related deaths also slightly increased in males in the same period, the increase was not large enough to surpass the decrease in bronchiectasis-related deaths. A higher proportion of male NTMosis-treated cases were complicated with underlying pulmonary diseases such as chronic obstructive lung disease, TB sequelae and interstitial pneumonia, which showed a sharp increase with age [25]. These cases might not be shown to be bronchiectasis. We confirmed that these findings were consistent even after adjustment for the age distribution in the population in 2000.

We speculated that the age-specific rate of death due to bronchiectasis might have changed during the study period and compared it between 1975 and 2015. Although a higher death rate was consistently observed in the elderly population, there was a change from a male to a female predominance [26]. These data emphasise the importance of future investigations regarding female NTMosis and bronchiectasis independently as well as collectively.

It has been widely reported that the increased awareness of NTMosis among medical staff might have, in part, contributed to the increase in NTMosis prevalence. Interestingly, the number of domestic reports on bronchiectasis somewhat reflects the epidemiological trends in mortality. The first peak in publications on bronchiectasis in the 1980s occurred when diffuse panbronchiolitis was recognised and low-dose macrolide therapy was invented in Japan [23]. Despite the substantial number of deaths, especially in males, the relative rarity of published reports prior to the 1980s indicates that the level of interest in the disease was limited in the majority of medical staff. It is expected that the slight increase observed in recent years in publications on bronchiectasis in other countries will also occur in Japan [6, 27, 28].

The present study had several limitations. First and most importantly, the medical records of the dead patients in the mortality statistics were not available; therefore, we could not obtain any additional information. Second, the increased awareness of NTMosis among medical staff could have driven a progressive bias towards the selection of NTMosis as a cause of death. Third, although we focused on the substantial increase in NTMosis-related deaths in females after 1995, an increasing trend was observed from the 1970s. The influence of NTMosis on bronchiectasis-related deaths in this period might have already existed but was not recognised. Last, we could not analyse the microbiological data; thus, the species of causative NTMs and their distribution were unknown. Information on *P. aeruginosa* and *Aspergillus* species is also essential to analyse bronchiectasis mortality. Similarly, other underlying diseases, such as rheumatoid arthritis and sequelae of TB, could not be analysed. Therefore, a multicenter prospective study is needed to clarify the natural histories of NTMosis and bronchiectasis, and their mutual relationship.

In summary, the epidemiology of bronchiectasis in Japan might have been influenced by NTMosis, especially among females starting in the 1990s. Although the number of bronchiectasis-related deaths decreased in males over the 45 years of the study period, in contrast, it increased in females after the mid-1990s, which seemed to be in line with the trend in NTMosis-related deaths. Accordingly, the interrelatedness of the two diseases seems clear, and the influence of NTMosis on bronchiectasis may become more important in Japan. In Japan, where cystic fibrosis is rare, further study is urgently needed to clarify the data regarding NTMosis and bronchiectasis and the association between the two diseases.

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Author contributions: K. Morimoto designed and conducted the study, and was responsible for data collection, data analysis and writing the manuscript. K. Iwai supervised the study and contributed to the data analysis. All other authors analysed the results and critically reviewed the manuscript

Conflict of interest: K. Morimoto reports grants from AMED during the study, JSPS KAKENHI and lecture fees from INSMED outside the submitted work. T. Asakura reports grants from JSPS KAKENHI and AMED outside the submitted work. Y. Tanaka reports personal fees from Nippon Boehringer Ingelheim Co, Ltd, outside the submitted work. M. Ato reports grants from AMED outside the submitted work. N. Hasegawa reports grants from AMED and JSPS KAKENHI, and lecture fees from INSMED outside the submitted work. K. Iwai, T. Yoshiyama, M. Ito, F. Uesugi, T. Osawa, K. Furuuchi, A. Kurahsima, K. Fujiwara, K. Shoji, Y. Shiraishi, S. Mitarai, and K. Ohta declare that they have no competing interests.

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