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Title

Pollinosis and all-cause mortality among middle-aged and elderly Japanese: a population-based cohort study

Running head

Pollinosis and mortality in Japan

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Summary

Background Having an allergic disease may have health implications beyond those more commonly associated with allergy given that previous epidemiological studies have suggested that both atopy and allergy are linked to mortality. More viable immune functioning among the elderly, as indicated by the presence of an allergic disease might therefore be associated with differences in all-cause mortality.

Objective Using data from a Japanese cohort, this study examined whether having pollinosis (a form of allergic rhinitis) in a follow-up survey could predict all-cause and cause-specific mortality.

Methods Data came from the Komo-Ise cohort, which at its 1993 baseline recruited residents aged 40–69 years old from two areas in Gunma prefecture, Japan. The current study used information on pollinosis that was obtained from the follow-up survey in 2000. Mortality and migration data were obtained throughout the follow-up period up to December 2008. Proportional hazard models were used to examine the relation between pollinosis and mortality.

Results At the 2000 follow-up survey, 12% (1 088 out of 8 796) of respondents reported that

they had pollinosis symptoms in the past 12 months. During the 76 186 person-years of follow-up, 748 died from all-causes. Among these there were 37 external, 208 cardiovascular, 74 respiratory, and 329 neoplasm deaths. After adjusting for potential confounders, pollinosis was associated with significantly lower all-cause (hazard ratio 0.57 [95% confidence interval = 0.38 to 0.87]) and neoplasms mortality (hazard ratio 0.48 [95% confidence interval = 0.26 to 0.92]).

Conclusions and clinical relevance Having an allergic disease (pollinosis) at an older age may be indicative of more viable immune functioning and be protective against certain causes of death. Further research is needed to determine the possible mechanisms underlying the association between pollinosis and mortality.

Keywords

all-cause mortality, cohort study, elderly, pollinosis

Introduction

A rise has been observed in the prevalence of allergic diseases in both developed and developing countries in the past several decades [1, 2]. Although it is uncertain what underpins this increase it has been suggested that increasingly infrequent exposure to

infectious diseases, or a “cleaner environment”, during childhood may be contributing to the rising prevalence of these diseases, i.e. the hygiene hypothesis [3].

Having an allergic disease may have health implications beyond those more commonly associated with allergy given that previous epidemiological studies have suggested that atopy and allergy are both linked to mortality. In particular, a number of cross-sectional and prospective studies, using subjective and objective measures [4, 5], have highlighted both protective and harmful effects of atopy and allergy on cancer mortality across different sites. In terms of the former, the “immune surveillance” hypothesis has been mooted to explain reduced mortality risk [5]. This states that persons with more active immune reactions are more likely to be allergic/atopic and that increased immune-activation reduces the chance of cancer cells multiplying [5]. In contrast, the “antigenic stimulation” hypothesis, suggests that the positive association between allergy/atopy and cancer mortality is due to the increased stimulation of cell growth in allergic diseases and chronic inflammation which increases the risk of developing cancer [5]. While the possible role of immune suppression in the promotion of cancer has been studied extensively in both animals and humans, the exact mechanisms underlying these associations are not yet clear [6].

Earlier research has raised the possibility that immune functioning among the elderly, as measured by either immunological biomarkers or hypersensitivity tests, might be associated with differences in all-cause mortality. For example, prospective studies targeting

elderly people have shown that individuals who failed to exhibit a positive response in tests for delayed hypersensitivity have higher mortality [7], even after adjusting for health status at baseline [8]. Immunological phenotypes such as a decreased number of CD4⁺ T cells [9], decreased naïve T cells [10], poor proliferative T cell responses, and expanded numbers of natural killer cells [9], have all been associated with higher morbidity and mortality in the elderly.

Considering that allergy is a form of hypersensitivity that involves T cell proliferation, it can be hypothesised that having an allergy may be indicative of a more active immune response to pathogens and thus could possibly be associated with reduced mortality. Two previous studies have examined the association between atopy, i.e. the tendency to produce allergen-specific Immunoglobulin E (IgE) and all-cause mortality in younger and older adults. A Danish population-based cohort study (mean age at baseline ranged from 38 to 50 years old) found no statistically significant association between atopy, i.e. IgE positivity against inhalant allergens, and all-cause mortality [11]. Similarly, a US-based study targeting 30- to 75-year-old individuals at baseline found no association between atopy, i.e. allergen skin test reactivity, and all-cause mortality [12].

While several earlier studies have focused on the association between asthma and mortality among all-age adults [13, 14], to the best of our knowledge, no research has explored the possible association between allergy and all-cause mortality specifically among

older adults. This is an important research gap. As evidence suggests that the prevalence of allergic rhinitis is higher in younger than older adults [15], it is possible that its presence among the latter might serve as a marker of immunological viability, as manifest possibly, in differences in mortality.

To test this supposition, the current study used data from Japan. The Japanese population has one of the longest life expectancies in the world [16] and the prevalence of allergic diseases is high in this setting; Japanese cedar pollinosis is especially widespread with 26.5% of the adult population estimated to have this allergy in 2008 [15]. Against this background we used data from a large cohort study that targeted middle-aged and elderly men and women in Japan, to examine whether having pollinosis during a follow-up survey could predict all-cause and cause-specific mortality across an 8 year period.

Methods

Study population

Data came from the Komo-Ise cohort in Gunma prefecture, Japan [17, 18]. The baseline for the cohort was established in 1993 when self-administered questionnaires were sent to all registered residents aged 40–69 years old in Komochi village ($n = 4\,875$) and Isesaki city ($n = 7\,755$). The response rate was 91.6%. In 2000, a follow-up survey was conducted to update lifestyle and health status information, where information was also collected on the presence of allergic disease (pollinosis). A total of 9 650 participants responded (88.5%) in the follow-up survey [19]. Among these, 9 533 (mean age 61.7 years, range 47–77 years) were still living in the study areas as of 1 January 2000 and their responses were regarded as the beginning of the observation period for the current study. Cohort death and migration data were ascertained through the municipal resident registration file, *Jumin Kihon Daicho*, from 2000 to 2008. Participants who had migrated out of the study area were contacted via mail and non-responders were censored.

Pollinosis status and mortality

A participant's pollinosis disease status was determined by his/her response to the question "Have you ever had pollinosis?" and a follow-up question "Did you have the disease at any time during the past year?" Participants who were missing information for at least one

of the two questions were excluded ($n = 737$ or 7.7% of the cohort in the year 2000). Data from the remaining 8 796 participants were analysed. A comparison was made between those who self-reported having pollinosis during the past year (i.e., the current pollinosis group) and those currently without the disease (i.e., the control group). More restrictive definitions of pollinosis were also examined to check the stability of the results (sensitivity analysis). Specifically, in addition to the previous questions, the analysis was repeated for those who also reported (i) having consulted doctors, and (ii) taken prescription medication for their condition, in addition to (i). Participants who had pollinosis but no medical consultation and prescription were excluded from the sensitivity analysis. In addition, besides those with a “current pollinosis” status, we also examined participants who reported having had the disease in the past but not within the previous year.

There were 748 deaths (8.5%) as of 31 December 2008. These were classified according to the International Classification of Diseases 10th Revision (ICD-10). Information was extracted from the death certificates, *Shibo-Kohyo*, available at the local public health centre. All-cause mortality, neoplasm (C00–D48), cardiovascular disease (I00–I99), respiratory disease (J00–J99), digestive organ cancer (C15–C26), and stomach cancer (C16) deaths were examined. Subgroup analyses were also carried out for external (S-Z), non-external, non-neoplastic, non-cardiovascular and non-neoplastic deaths (excluding external deaths) for comparison. More than 97% of the death cases were assigned ICD-10

codes; those with an unknown cause ($n = 21$) were included in the all-cause mortality analysis, but excluded from the cause-specific analysis. The study was approved by the ethical institutional review board of Gunma University Graduate School of Medicine, Maebashi, Japan.

Data categorization and analyses

Cox proportional hazards regression models were used to determine the associations between pollinosis (i.e., self-reported pollinosis disease status during the past year) and all-cause and cause-specific mortality. The follow-up time from 1 January 2000 was used as the time axis. Participants who migrated out of the study areas ($n = 43$) were followed up until their last known activity. Survival times of participants who were alive at the end of the follow-up were censored. Information on known risk factors for all-cause and cause-specific mortality was extracted from the survey and included in the multivariable models to account for potential confounding. In the first model, we adjusted for demographic characteristics, e.g., age (in years), area of residence (urban or rural) and sex. We termed this the minimally adjusted model. In the second model, further adjustment was made for lifestyle and other known risk factors such as body mass index (BMI, <18.5 ; 18.5 – 22.9 ; ≥ 23.0 kg/m²), smoking (never; former; current), alcohol consumption (none; occasional; frequent), frequency of exercise (never; sometimes; often), education level (primary/junior high; high

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school/vocational; college and higher), marital status (never; married; separated/widowed), and self-reported doctor-diagnosed hypertension, hyperlipidaemia, and diabetes during the past year (yes; no). This was termed the fully adjusted model. All models included only participants with complete information for all variables. We also reanalysed the minimally adjusted model using the identical sample from the fully adjusted model so that the effect of additional adjustments could be compared on a like-for-like basis with the participants included in the initial model. Schoenfeld's tests were performed to evaluate the proportional hazard assumption. Results are presented as hazard ratios (HR) and the corresponding 95% confidence intervals (CI). All analyses were performed in R version 3.0.3 (R Project for Statistical Computing, Vienna, Austria).

Results

At the 2000 follow-up survey, 12% of respondents (1 088 out of 8 796) reported that they had pollinosis symptoms during the past 12 months. On average, participants with pollinosis were more likely to be younger, never-smokers, and live in urban areas (Table 1).

During the 76 186 person-years of follow-up, 748 people died from all-causes. Among these, there were 37 external, 329 neoplasm, 208 cardiovascular, 62 stomach cancer, and 181 digestive organ cancer deaths (Table 2).

Pollinosis was associated with significantly lower all-cause mortality. After adjusting

for age, sex, and area of residence, the HR was 0.59 (95% CI: 0.42, 0.83) (Table 2, minimally adjusted model). When further adjusted for other risk factors, it remained statistically significant (HR 0.57, 95% CI: 0.38, 0.87) (Table 2, fully-adjusted model). Pollinosis was associated with a significantly reduced HR for neoplasm deaths in both the minimally adjusted (HR 0.58, 95% CI: 0.35, 0.95) and fully adjusted (HR 0.48, 95% CI: 0.26, 0.92) models. There was no significant association between pollinosis and non-neoplastic death in the fully adjusted model (HR 0.57, 95% CI: 0.30, 1.08) (Table 2). There was also no significant association between pollinosis and mortality due to external causes, cardiovascular disease, stomach cancer, or digestive organ cancer. Because there were no respiratory deaths among the pollinosis group, a HR could not be calculated.

Similar trends were also observed when a more restricted definition of pollinosis was used in the analysis i.e. self-reported doctor-diagnosed and self-reported doctor-diagnosed and prescribed medication use (Table 3). When we undertook additional analyses that compared the group with a past history of the disease ($n = 304$) and those who currently had the disease ($n = 1\,088$) with the group that had never had the disease ($n = 7\,404$), we found that the past pollinosis group were intermediate in terms of their risk for all-cause mortality (HR 0.63, 95% CI 0.32, 1.22) while the current pollinosis group had a significantly reduced risk (HR 0.56, 95% CI 0.37, 0.85) (data not shown).

Discussion

To the best of our knowledge, this is the first study to specifically investigate the association between allergy and all-cause mortality among a middle-aged and elderly population. It showed that having pollinosis at an older age was associated with a significantly reduced hazard ratio for all-cause mortality and death from neoplasms compared to those without the disease.

Having pollinosis at an older age may be indicative of a more viable immune function as a lower prevalence of pollinosis is usually found in older adults compared to their younger counterparts [15]. Similarly, the prevalence of atopy, as determined for example, by a specific IgE test or positive skin prick test, tends to be lower among older adults compared to younger adults [20, 21]. A longitudinal study with a 15-year follow-up showed that a decline in rhinitis symptoms among the elderly was associated with changes in serum total and specific IgE, skin prick tests, and nasal eosinophils [22]. Therefore, an age-related decline in atopy and allergy might, at least in part, be explained by immunological ageing characterized by dysfunctions in T cell proliferation and a decrease in naïve B and T cells [23].

Our finding that allergy (pollinosis) is associated with reduced all-cause mortality, contrasts with the results from two previous studies which found no significant association between atopy and all-cause mortality [11, 12]. This discrepancy might be related to the

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difference between atopy and allergy. While being atopic, i.e. having an elevated IgE level, is a prerequisite for being allergic, only a certain proportion of atopic individuals go on to manifest allergic disease. For example, in a population-based US sample, 37% of individuals with elevated IgE reported no allergic conditions, i.e. hay fever, eczema, rhinitis, itchy rash [24]. Research suggests that among atopic individuals, those with a relatively higher total IgE are more likely to be allergic when compared to those with a lower level of IgE [25].

In this study the proportion of neoplasm deaths was high (48%), while having pollinosis was associated with a significantly reduced hazard ratio for neoplasms mortality.

Previous studies, many of which have focused on specific types of neoplasm such as brain, lymphatic and hematopoietic cancers, have produced mixed findings (negative, positive, and null) concerning the association between allergy and cancer mortality [4, 5]. In the current study, more than a half of all neoplasm-related mortality was attributable to cancer of the digestive organs (181 out of 329 deaths), among which, stomach cancer was the most common form. Although it is uncertain what underlies this association, it can be hypothesised that *Helicobacter pylori* infection might play a role. Specifically, the prevalence of the infection tends to be lower in young Japanese affected with pollinosis compared to those without this allergic disease [26, 27]. This might be important as this infection is a known risk factor for stomach cancer [28, 29]. However, although the hazard ratio was less than one, as there was no significant association between pollinosis and stomach cancer mortality in

this study, this supposition remains at best speculative. Future research that uses a larger sample followed-up over a longer period of time will help to further elucidate the associations observed in this study.

It is noteworthy that no respiratory deaths occurred among the pollinosis group, especially as pollinosis patients are more likely to have asthma. In fact, only 1 out of 74 respiratory deaths was due to asthma (ICD-10 code J45). We suspect this is because the majority of respiratory death (45 out of 74) were due to pneumonia from unspecified organisms (ICD-10 code J18.9), which is not necessarily linked to allergic status. Rather, it can be related to aspiration pneumonitis and/or aspiration pneumonia, which are both common among the elderly [30].

The present study has several limitations. The sample size was too small to permit a more detailed division of causes of death which might have permitted us to gain a better understanding of the observed associations. Also, we lacked information on possible confounding factors such as childhood living conditions and the type and duration of allergy medication used by the participants. Moreover, since our results were derived from only two communities in a single prefecture, these results might not be readily generalised to the whole of Japan. In addition, pollinosis status was self-reported and not corroborated by either medical records or biomarker data. Despite these limitations, the current study presents the possibility that pollinosis could be an indicator of immunological functioning and future

mortality among the elderly. Further prospective studies that employ biochemical measurements are now needed to test this hypothesis.

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Conflict of Interest

The authors declare no conflict of interest.

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Table 1. Characteristics of the Komo-Ise Cohort Participants at the Time of the 2000 Follow-up Survey

Characteristic	Participants with current pollinosis (<i>n</i> = 1 088)		Participants without current pollinosis (<i>n</i> = 7 708)	
	No.	%	No.	%
Area of residence				
Rural	372	34.2	3 183	41.3
Urban	716	65.8	4 525	58.7
Sex				
Male	469	43.1	3 686	47.8
Female	619	56.9	4 022	52.2
Age (y)				
45-54	484	44.5	1 743	22.6
55-64	396	36.4	2 584	33.5
65-74	199	18.3	2 874	37.3
≥75	9	0.8	507	6.6
Marital status				
Never	42	3.9	379	5.1
Married	917	86.0	6 069	80.9
Separated	107	10.0	1 055	14.1
BMI (kg/m ²)				
<18.5	44	4.1	424	5.6
18.5-22.9	520	48.8	3 417	45.5
23.0+	501	47.0	3 664	48.8
Smoking status				
Never	627	60.3	3 571	50.0
Former	228	21.9	1 385	19.4
Current	185	17.8	2 189	30.6
Alcohol consumption				
None	415	38.6	3 468	46.1
Occasional	279	26.0	1 476	19.6
Frequent	380	35.4	2 579	34.3
Exercise				
Never	561	55.1	3 864	55.8
Sometimes	158	15.5	1 064	15.4

Often	300	29.4	2 000	28.9
Education				
Primary/junior high	295	27.9	3 304	44.2
High school/vocational	579	54.8	3 355	44.9
College and higher	182	17.2	817	10.9
Hypertension ^a	202	19.6	1 809	25.6
Hyperlipidemia ^a	153	15.0	895	12.6
Diabetes ^a	41	3.9	577	7.7

BMI, body mass index; y, years.

^a Presence of doctor-diagnosed diseases in the past 12 months.

Table 2. Adjusted Hazard Ratios for All-cause and Cause-specific Mortality for Komo-Ise Cohort Participants With Current Pollinosis vs. Participants Without Current Pollinosis.

Cause of death	Minimally adjusted model ^b		Fully adjusted model ^c		Minimally adjusted model with restricted samples ^d	
	Number of deaths	Adjusted hazard ratio (95%CI)	Number of deaths	Adjusted hazard ratio (95%CI)	Number of deaths	Adjusted hazard ratio (95%CI)
All-cause	748	0.59 (0.42, 0.83)	488	0.57 (0.38, 0.87)	488	0.52 (0.35, 0.79)
External	37	0.74 (0.22, 2.44)	31	0.93 (0.28, 3.15)	31	0.89 (0.27, 2.96)
Non-external	690	0.58 (0.41, 0.83)	444	0.52 (0.33, 0.83)	444	0.48 (0.31, 0.76)
Neoplasms	329	0.58 (0.35, 0.95)	222	0.48 (0.26, 0.92)	222	0.45 (0.24, 0.86)
Non-neoplastic ^a	361	0.58 (0.35, 0.96)	222	0.57 (0.30, 1.08)	222	0.52 (0.27, 0.98)
Cardiovascular	208	0.82 (0.47, 1.45)	128	0.80 (0.39, 1.67)	128	0.71 (0.34, 1.46)
Non-cardiovascular, non-neoplastic ^a	153	0.26 (0.08, 0.81)	94	0.24 (0.06, 1.00)	94	0.25 (0.06, 1.01)
Stomach cancer	62	0.37 (0.09, 1.51)	42	0.52 (0.12, 2.21)	42	0.48 (0.12, 1.91)

		1.52)		2.18)		2.02)
Digestive organ cancer	181	0.64 (0.33, 1.22)	122	0.47 (0.19, 1.17)	122	0.42 (0.17, 1.04)

Abbreviations: CI, confidence interval

^a Deaths due to external-causes were excluded.

^b Adjusted for age (as a continuous variable), area of residence (rural or urban), and sex. $n = 76\ 186$ person-years for all-cause and $n = 76\ 088$ person-years for the other causes of death.

^c Adjusted for age, area of residence, sex, BMI category, smoking, alcohol consumption, exercise, education level, marital status, and doctor-diagnosed hypertension, hyperlipidemia, and diabetes in the past 12 months. $n = 53\ 530$ person-years for all-cause and $n = 53\ 470$ person-years for the other causes of death.

^d Adjusted for age (as a continuous variable), area of residence (rural or urban), and sex. The same participants were included as in the fully adjusted model. $n = 53\ 530$ person-years for all-cause and $n = 53\ 470$ person-years for the other causes of death.

Table 3. Adjusted Hazard Ratios for All-cause and Cause-specific Mortality for Komo-Ise Cohort Participants With Current Pollinosis vs. Participants Without Current Pollinosis of the Komo-Ise Cohort Participants. Pollinosis was Restricted to Those with Doctor-diagnosed and Prescription Medicine.

Cause of death	Self-reported doctor-diagnosed				Self-reported doctor-diagnosed and prescription medicine			
	Minimally adjusted model ^{bd}		Fully adjusted model ^{ce}		Minimally adjusted model ^{bf}		Fully adjusted model ^{cg}	
	Number of deaths	Adjusted hazard ratio (95%CI)	Number of deaths	Adjusted hazard ratio (95%CI)	Number of deaths	Adjusted hazard ratio (95%CI)	Number of deaths	Adjusted hazard ratio (95%CI)
All-cause	736	0.54 (0.36, 0.80)	479	0.49 (0.29, 0.83)	729	0.43 (0.27, 0.69)	475	0.40 (0.22, 0.73)
External	36	0.66 (0.16, 2.79)	30	0.83 (0.19, 3.57)	36	0.74 (0.17, 3.11)	30	0.91 (0.21, 3.91)
Non-external	679	0.52 (0.34, 0.80)	436	0.43 (0.24, 0.77)	673	0.42 (0.26, 0.70)	433	0.36 (0.18, 0.69)
Neoplasms	322	0.46 (0.24, 0.87)	217	0.33 (0.14, 0.82)	320	0.41 (0.20, 0.83)	216	0.29 (0.11, 0.80)
Non-neoplastic ^a	357	0.58 (0.33, 1.04)	219	0.55 (0.26, 1.18)	353	0.44 (0.22, 0.89)	217	0.43 (0.18, 1.06)
Cardiovascular	204	0.76 (0.39, 1.49)	125	0.69 (0.28, 1.71)	201	0.56 (0.25, 1.28)	123	0.45 (0.14, 1.44)
Non-cardiovascular, non-neoplastic ^a	153	0.35 (0.11, 1.09)	94	0.33 (0.08, 1.36)	152	0.26 (0.06, 1.06)	94	0.36 (0.09, 1.49)
Stomach cancer	61	0.25 (0.03, 1.80)	41	0.34 (0.05, 2.54)	61	0.28 (0.04, 2.01)	41	0.38 (0.05, 2.80)
Digestive organ cancer	177	0.51 (0.22, 1.15)	120	0.38 (0.12, 1.21)	175	0.38 (0.14, 1.02)	119	0.28 (0.07, 1.15)

Abbreviations: CI, confidence interval

^a Deaths due to external-causes were excluded.

^b Adjusted for age (as a continuous variable), area of residence (rural or urban), and sex.

^c Adjusted for age, area of residence, sex, BMI category, smoking, alcohol consumption, exercise, education level, marital status, and doctor-diagnosed hypertension, hyperlipidemia, and diabetes in the past 12 months.

^d $n = 73\,858$ person-years for all-cause and $n = 73\,760$ person-years for the other causes of death.

^e $n = 51\,700$ person-years for all-cause and $n = 51\,640$ person-years for the other causes of death.

^f $n = 73\,133$ person-years for all-cause and $n = 73\,038$ person-years for the other causes of death.

^g $n = 51\,187$ person-years for all-cause and $n = 51\,130$ person-years for the other causes of death.