

Original Article

Development of Many So-Called Autoimmune Diseases Including Various Vasculitis Syndromes May be Commonly Triggered by Pollen Exposure

Akira Awaya^{1,2}¹Dermatology & Epidemiology Research Institute (DERI), 4978 Totsuka-cho, Totsuka-ku, Yokohama, Kanagawa 244-0003, Japan²Department of Genome System Science, Yokohama City University, Seto 22-2, Kanazawa-ku, Yokohama, Kanagawa 236-0027, Japan**Corresponding author:* Akira Awaya, Dermatology & Epidemiology Research Institute (DERI) 4978 Totsuka-cho, Totsuka-ku, Yokohama 244-0003, Japan. E-mail: awaya@home.email.ne.jp*Received Date:* 11-25-2018*Accepted Date:* 11-28-2018*Published Date:* 12-10-2018*Copyright:* © 2018 Akira Awaya**Abstract**

Background: Takayasu arteritis (TAK) and Kawasaki disease (KD) are systemic vasculitides first reported in Japan. A report in 2003 suggested that KD is a pollen-induced disease with delayed-type hypersensitivity.

Methods: The author analyzed the transition of the number of TAK and other vasculitis syndrome patients, and autoimmune disease patients who have been reported by the Japan Intractable Diseases Research Foundation, comparing with the change of the number of pollen release in Tokyo and Kanagawa.

Results: Seeing the graph of cumulatively registered numbers of TAK patients, a new line graph of TAK incidence from 1975 to 2014, which differed from the authorized conventional bar graph, was created that demonstrated a previously unrecognized, distinct, sharp peak of newly registered 590 patients in 1984. Similarly, graphing of data of 10 diseases including Behcet's disease, Buerger's disease, Aplastic anemia, Systemic lupus erythematoses, Rheumatoid vasculitis, Scleroderma, Sarcoidosis, Granulomatosis with polyangiitis, Periarteritis nodosa, Pemphigus, showed all at once the same peaks simultaneously around 1984. In 1982, Japan recorded the largest ever release of Japanese cedar and other pollen. The largest number of new KD patients (i.e., 15,519) and outpatients with pollinosis also presented for care in 1982.

Conclusions: Circumstantial evidence suggests that the increased incidence of many autoimmune diseases is commonly associated with peak pollen release in 1982. The concept is reasonably proposed that development of these 11 of systemic inflammatory diseases whose lesional organs and tissues are different from each other may be commonly triggered and induced by exposure to pollen substances which are released from major species of plant kingdom in each country.

Keywords: 1982; cumulatively registered number; delayed-type hypersensitivity (DTH); increment; intractable diseases; Kawasaki disease; lymphocyte stimulation test (LST); pollen exposure, pollen-induced diseases (PID); Takayasu arteritis.

Abbreviations

KD: Kawasaki Disease; DTH: Delayed-Type Hypersensitivity; TAK: Takayasu Arteritis; JIDRF: Japan Intractable Diseases Research Foundation; TAO: Thromboangiitis Obliterans; SLE: Systemic Lupus Erythematoses; GPA: Granulomatosis With Polyangiitis; PAN: Periarteritis Nodosa

Introduction

Widespread cedar planting after 1945 and increased environmental pollution due to rapid urbanization in the 1950s to 1960s may have created a type of Japanese endemic disease characterized by allergic rhinitis/conjunctivitis as an immediate-type allergic response and KD as a DTH response[1-5].

Pollen release monitoring was initiated in Kanagawa Prefecture in 1965 [1, 2]. A significant increase in Japanese cedar and other pollen release was first observed in 1978-1979, and reached to maximum in 1982 before 1995 in each district of Japan [1, 2]. Three peaks of KD incidence were observed in 1979, 1982, and 1985-1986, coinciding with 3 peaks of massive pollen release [1, 2, 5].

The authors also noted an increase in allergy-related disorders in 1982, 1985-1986, and 1995.

The most voluminous pollen release across these years has been reported to occur in both 1982 and 1995[1,2]. So, I have always pointed out the 1982, successive 1985-1986, and 1995 problems in the field of allergic diseases in conference brochures, too [4]. The former 1982 and 1985-1986 periods were years when many patients with KD experienced a very sudden onset, and further many patients experienced hand, foot, and mouth diseases and aseptic meningitis. In contrast, a 1993 report by the Otorhinolaryngology Department of Osaka University Hospital showed an increased rate of outpatient visits for allergic rhinitis, with 3 peaks between 1979 and 1986 [6].

The latter period of 1995 was a year when only one increase peak appeared in a graph that showed a long-term gradual downward trend in the number of deaths in patients with asthma due to the increased use of inhalation steroid therapies during the 1980s to 1990s[7].

We first proposed in 2003 that infants with allergy might develop KD triggered by pollen exposure [1, 2]. A report in 2014 presented that a combination of cross-correlation (CC) and trend analyses of monthly KD patients (total of 6,000 cases) and monthly pollen release numbers in Kanagawa reveals that KD is a pollen-induced DTH disease [3,4]. Another report in 2016 showed that the onset of KD had been suppressed during seasonal influenza epidemics for 30 years in Japan [5]. Influenza infection-induced interferon- β levels might suppress the development of KD, and

inapparent influenza infections might ameliorate the symptoms of patients with KD during flu season [5].

Although the inflammatory lesions of TAK and KD differ in pathophysiologic appearance, both are classified as systemic vasculitides [8, 9]. Because both diseases were first reported in Japan, the author's speculation has led him to this study that these diseases may be triggered by the same antigenic agents. Since 1970, nationwide surveys on KD have been performed every 2 years in Japan. The number of patients has re-increased steadily from 6,107 in 1995 to 16,323 in 2015[10]. On the other hand, JIDRF began the registration of TAK patients in 1975[8]. However, epidemiological analyses of TAK incidences have seemed not to be fully performed, and the causes of TAK have been unknown and never been investigated in association with pollen release.

A bar graph that showed the change in the registered numbers of TAK patients in a chapter of JIDRF public information brochure [8] happened to draw the author's attention. In the row of bars from 1975 to 2011, a large and rapid increase in the 1984 bar was noticed. Therefore, we created a merged polygonal line graph of the number of patients who were newly and cumulatively registered each year, extending to 2014[11]. According to distinct results not ever known then, I moved to make graphs for other systemic inflammatory diseases including vasculitis, Behçet's disease, Thromboangiitis Obliterans (Buerger's disease), systemic lupus erythematoses, rheumatoid vasculitis and further other so-called autoimmune diseases one by one and then all together, and in this article I report also about other 10 intractable diseases[10, 11].

Materials and Methods

In the tables found in the JIDRF brochure [11], numbers of recipient certificates issued for specific disease treatment were reported from the registration beginning year 1974 or 1975, 1983, and so on until 2014. Major specific diseases (intractable diseases) are listed in it. The data shown are those of both cumulatively registered numbers in each year and increment from the previous year. The increments are occasionally negative numbers because the cumulatively registered numbers after reregistration decreased from the previous year, and so the decrements happened to the newly registered numbers. The numbers

of 11 diseases were copied and pasted into Excel tables. Moreover, as opposed to the bar graph of numbers of cumulatively registered TAK patients until 2011, which had been created by the JIDRF, we created and drew a merged polygonal line graph of the number of patients for a total of 11 diseases, i.e., increment and cumulatively registered number of each year, extending to 2014. The breakdown of the list of diseases is as follows: 3 vasculitis syndromes and vasculitis-related disease and 8 so-called autoimmune diseases categorized in hematopoietic system and connective tissues. TAK, Behçet's disease, Buerger's disease (Thromboangiitis Obliterans, TAO), aplastic anemia, systemic lupus erythematosus (SLE), rheumatoid vasculitis, scleroderma, sarcoidosis, granulomatosis with polyangiitis (GPA), periarteritis nodosa (PAN) and pemphigus were selected and examined. For comparing reference, the figure that contains the annual number of KD patients in Tokyo, Kanagawa, and

all of Japan from 1970 to 2014 and the pattern of pollen scattering at Bunkyo in Tokyo, in Tokyo and at Sagami-hara in Kanagawa from 1982 to 2015 is shown in (Figure 12), which was already published and is modified at present [5].

Results

As a result of drawing a line graph (Figure 1), an outstanding peak pattern of change in increment in the number of TAK patients in the year 1984 appeared which has never been recognized and publicly reported before in the authorized conventional graph of the cumulative numbers until 2011.

Moreover (Figure 2, Figure 3) show graphs of the disease that the name of the discoverer is included in reported abroad, Behçet's disease and Buerger's disease (TAO).

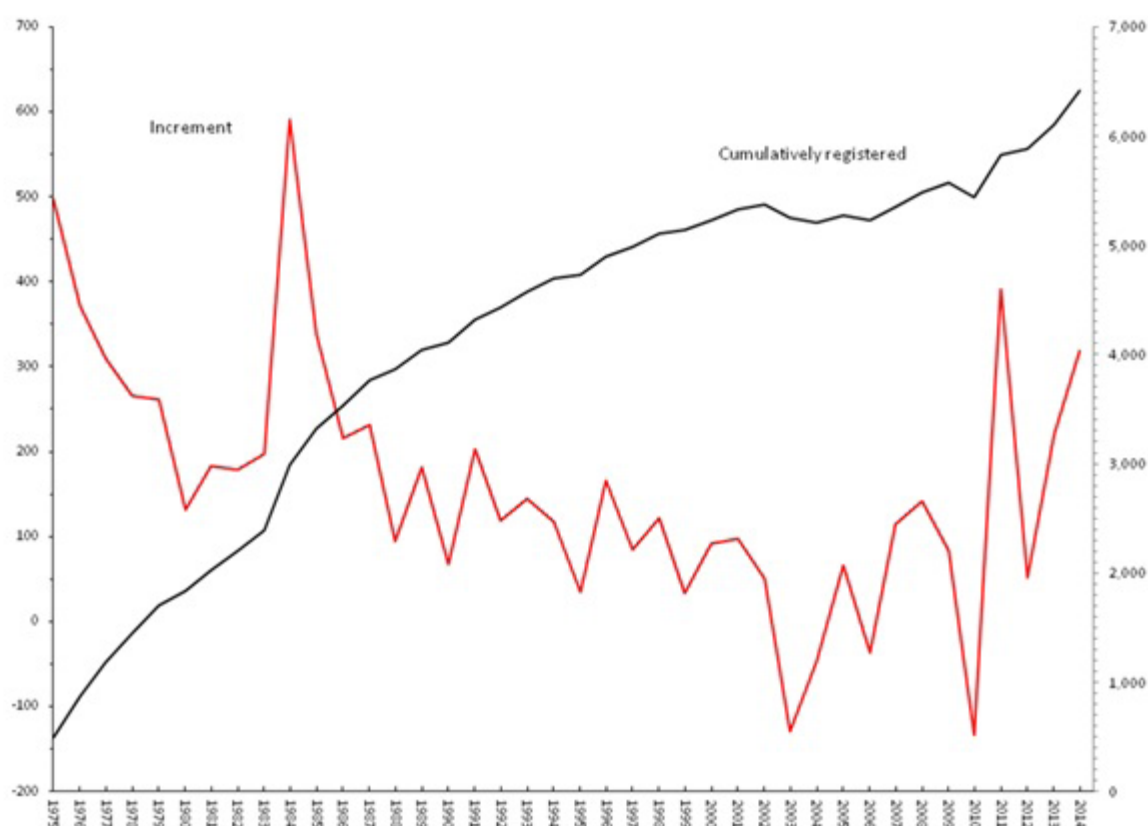


Figure 1: Change of enrollment of patients with Takayasu's arteritis from 1975 to 2014. Increment (red line) and cumulatively registered (black line) number in each year are shown.

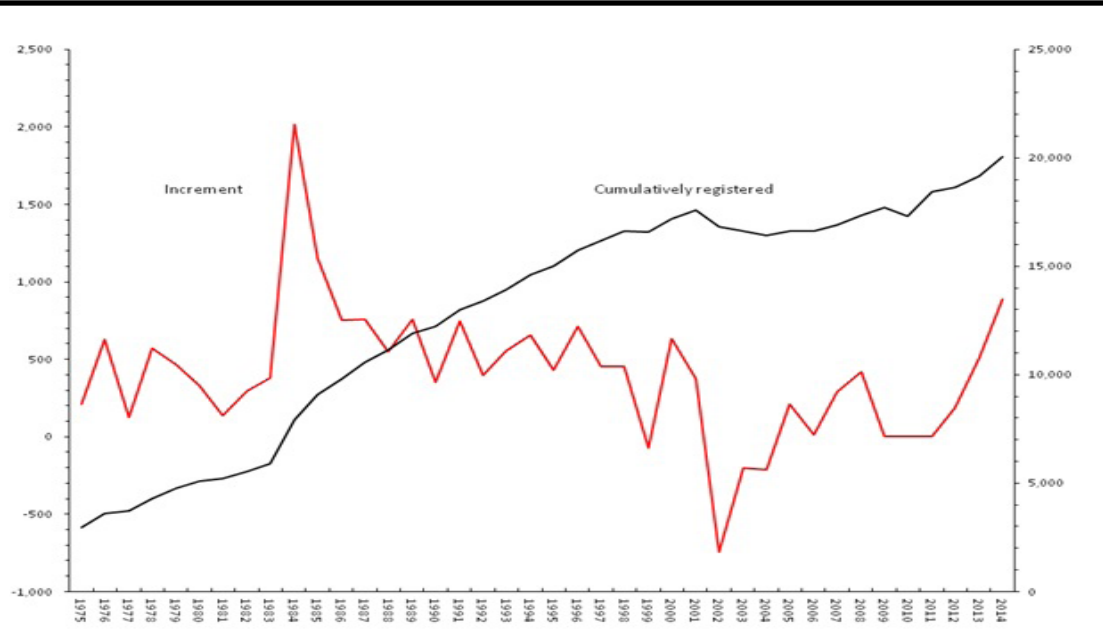


Figure 2: Change of enrollment of patients with Behcet's arteritis from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

Increment and cumulatively registered number in each year are shown.

The same pattern of line graphs having a peak of increment in 1984 is shown. As for TAK and Behçet's disease, there was a period when the cumulative number de-

creased to a small extent, but recently there is a tendency of a minimal increase. On the other hand, regarding TAO the decreasing trend did not stop after 1998. (Figure 4) shows a graph for aplastic anemia. Compared to previous findings, there were more increase in 1984 and a peak in 1985.

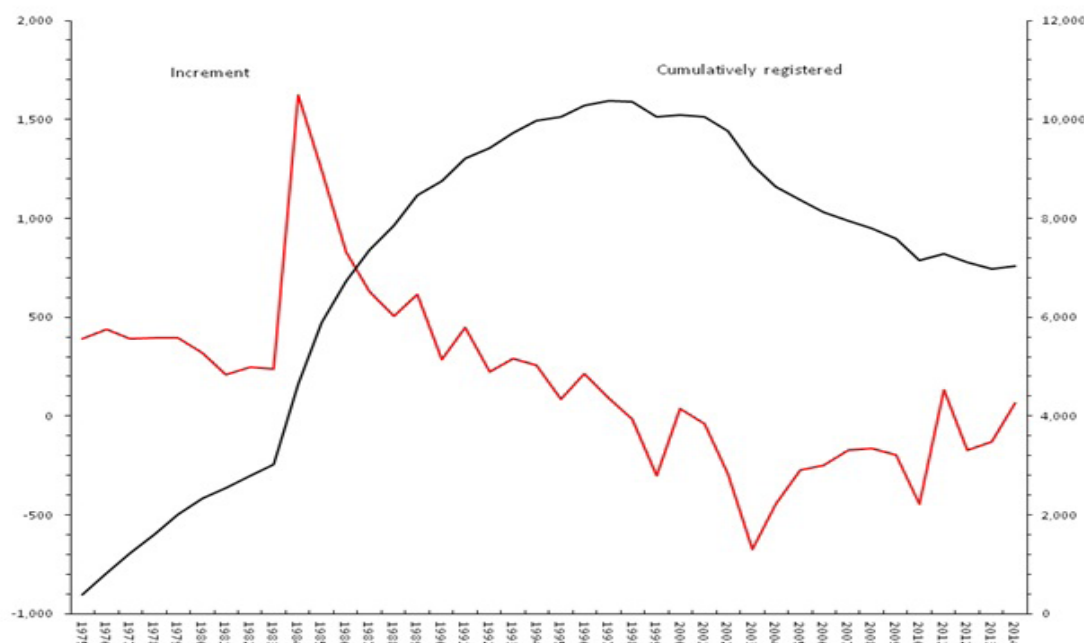


Figure 3: Change of enrollment of patients with Thromboangiitis Obliterans (Buerger's disease), from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

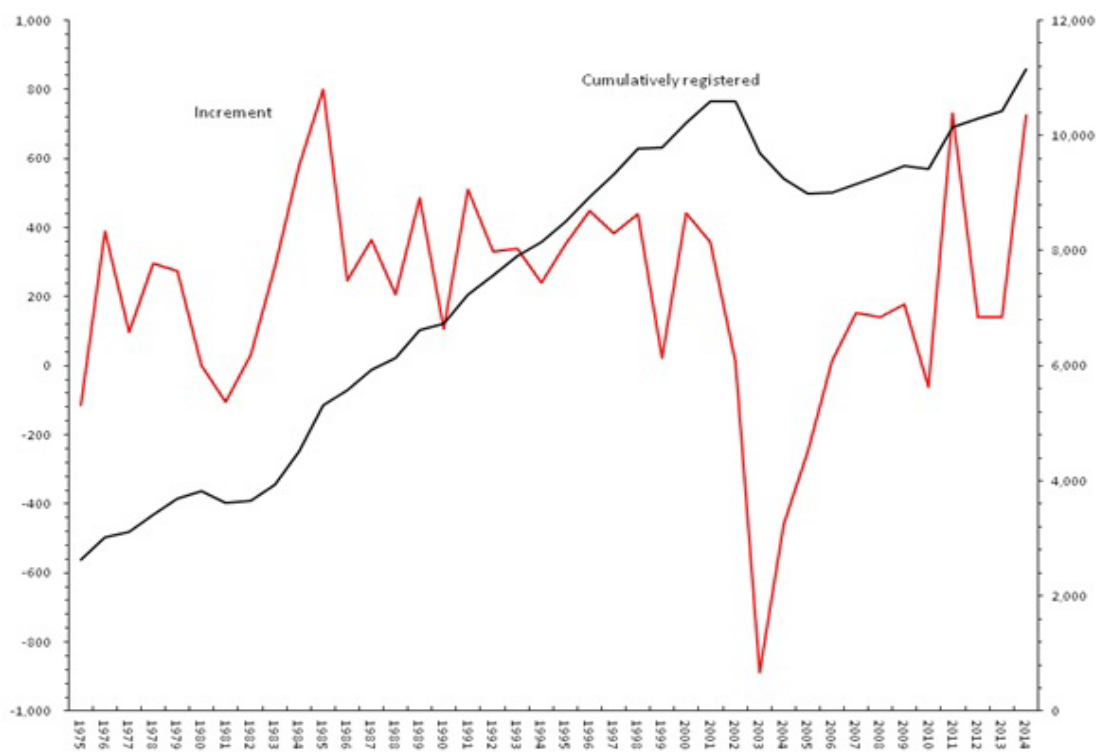


Figure 4: Change of enrollment of patients with Aplastic anemia from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

A movement corresponding to KD onset and pollen release shown in (Figure 12) was seen. (Figure 5) shows a graph for SLE. There is a peak of increment in 1984, and cumulative numbers continue to increase, which is the highest among these 11 diseases reported in 2014. It can be said that there are similarities in the increase pattern in 1984 or 1985 between these 5 diseases.

(Figure 6) shows graph of rheumatoid vasculitis in which a peak of increment in 1984-1986 and a top at 1985 were seen.

Further movement pattern of increment of patients was found that may correspond to the pattern of KD development and pollen release in Tokyo and at Sagami-hara in Kanagawa from 1970 to 2015 shown in (Figure 12). (Figure 7) shows a graph for scleroderma, in which a peak of increment in 1984-1987 and a top at 1984 were seen.

Pollen scattering in both 1982 and 1984-1986 may affect this peak of consecutive increment of patients. (Figure 8) shows a graph for sarcoidosis, in which a peak of in-

crement in 1984 and following increase in 1985 were seen.

(Figure 9) shows a graph for GPA in which two peaks of increment in 1984 and 1986 were seen. The increase in the number of GPA patients is distinct in recent years.

(Figure 10) shows a graph for PAN, in which 2 peaks of increment in 1982 and 1985 were found. PAN may be a disease that reacts to pollen exposure immediately in patients at predilection ages.

In (Figure 11), pemphigus cases are shown, wherein an increase began in 1984 and reached peak in 1985 and continued to 1987.

The author observed first the phenomenon that patient wannabees of each of these 11 diseases developed on a large scale for all-at-onceness for the first time in history during the period before registration in 1984. It is supposed that rapid distinct peaks of registered patients of each disease in around 1984 might correspond to large peak of newly developed patients with KD in 1982 shown in (Figure 12).



Figure 5: Change of enrollment of patients with Systemic lupus erythematoses from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

There seems to be a similarity among transition patterns of increment of each disease after around 1984 to 2014 shown in such as (Figure1-7).

Discussion

In these studies, firstly, I noticed a large increase in the number of TAK patients in 1984, and I understood that the sudden and sharp increase in the number of patients implied that an allergic pathology was present in the patient population that was caused by voluminous pollen exposure that occurred in 1982 as shown in graph on KD versus pollen release of (Figure 1) suggests that TAK onset is associated to some degree with pollen exposure, although these patients who developed TAK differed in clinical condition from those with KD and type I hypersensitivity of polli-nosis.

Next, we proceeded to investigation of other 10 intractable diseases including systemic connective tissue diseases and vasculitis such as Behçet's disease, Buerger's disease, SLE and rheumatoid vasculitis, and further other so-called autoimmune diseases. We gained similar results

as in TAK.

The reason elucidating the lag between peaks of registered numbers of patients with intractable diseases in 1984 and pollen exposure in 1982, referring to KD case

The reason elucidating the lag or delay between the increment of TAK patients and patients of other 10 diseases in 1984 or 1985 and above-mentioned phenomena in 1982 is discussed below. The lag between the period of greatest pollen release in 1982 and distinct increment of patients in 1984 can be explained as follows. A characteristic of type I immediate hypersensitivity is that the individual who develops allergic rhinitis or conjunctivitis that is sensitized by pollen develops allergic symptoms promptly at the next pollen scattering time [7].

In contrast, as mentioned in preceding section, in our previous study on the monthly volume of pollen release at Sagamihara in Kanagawa and change in KD incidence (total of 6,000 cases) between 1991 and 2002 in Kanagawa, we found a significant positive CC with 9- to 10-month delays following pollen release and a smaller but significant CC

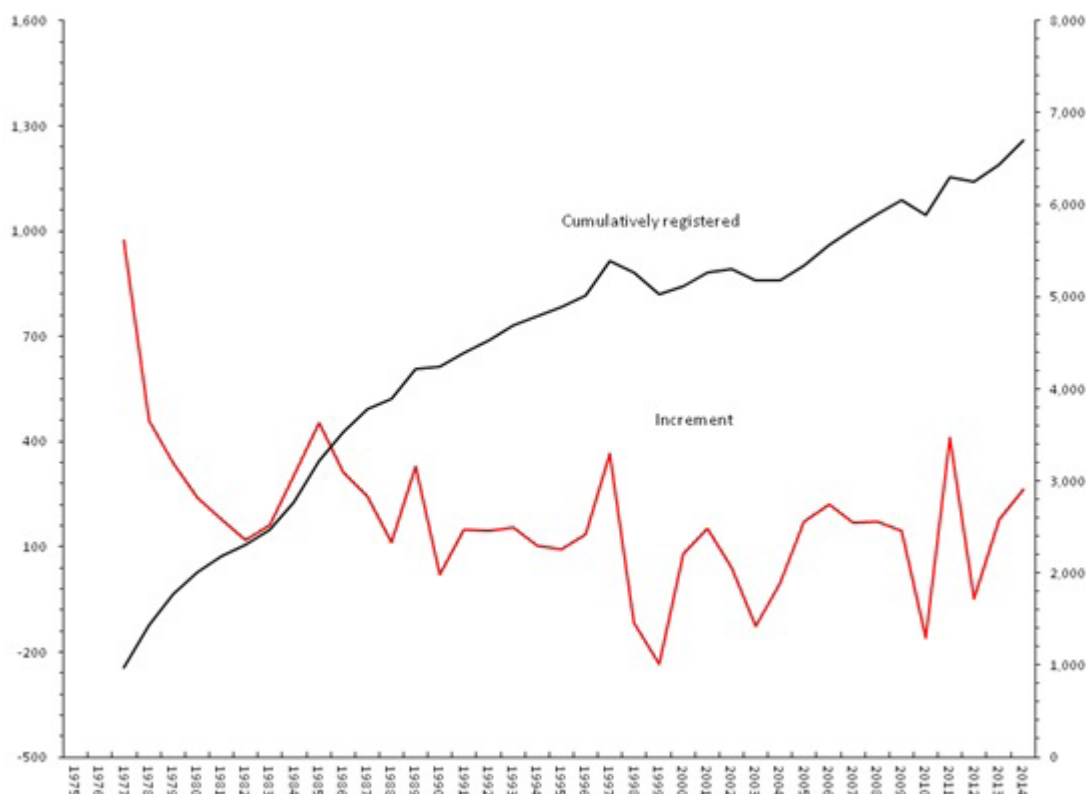


Figure 6: Change of enrollment of patients with Rheumatoid vasculitis from 1975 to 2014., Increment and cumulatively registered number in each year are shown.

with 3- to 4-month delay. The time between pollen exposure and the onset of KD was estimated to be 21.4 months on average by another trend analysis that used an exponential function[4]. This 21.4 months period corresponds to my another analysis. So that, my calculation of the data from a nationwide survey [10] indicated that approximately 90% of patients who developed KD in Japan were aged <4 years. Specifically, 25% were aged <1 year, with 25% aged 12–23 months, 18% aged 2 years, 12% aged 3 years, and 10% aged 4 years[3,4].

It is known that at the time of KD development, inflammation at the Bacillus Calmette-Guérin (BCG) vaccination site (i.e., BCG reactivation such as a skin redness and swelling reaction that is similar to those observed in tuberculin test, ulcerations, and lesions) is observed in these patients [3,4,10]. These phenomena suggest that hyperimmune responses of delayed-type hypersensitivities that are originally triggered by pollen exposure are increased and propagated in parallel with immune response to pollen

[4,5]. In a subacute or chronic manner, KD may develop in infants as a delayed-type hypersensitive reaction that differs from the conventional delayed-type hypersensitivities that are observed in tuberculin reactions during skin tests post BCG vaccination [4,5]. According to these KD data, TAK shows possible similarities with other type of DTH reactions to pollen.

In addition, such a large increase in new registration numbers in 1984 may have resulted from delays in the diagnosis and treatment of TAK, and further administrative affairs may have delayed the authorization of coverage and registration of patients with TAK [11].

Analysis of epidemiological evidence of development of systemic vasculitides and auto-immune diseases due to delayed hypersensitivity to pollen exposure as likely as in KD onset

Evaluation of the epidemiology of TAK incidence requires retrospective examination of medical treatment records and other information sources for 1982-1984. Sea-

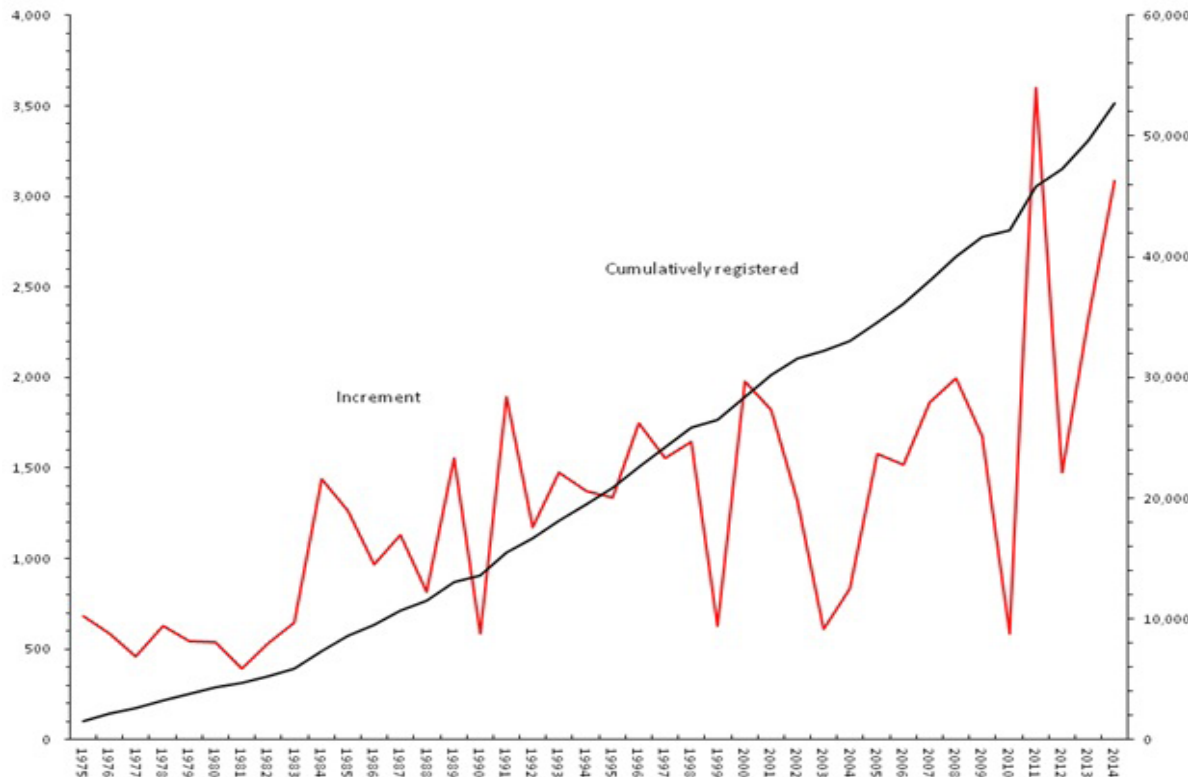


Figure 7: Change of enrollment of patients with Scleroderma from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

sonality of TAK onset and laboratory data in allergy were expected from review of such records. Although the primarily female TAK patients aged mainly 10-30 years [8] presumably had a long history of pollen exposure, they did not experience KD onset during infancy and childhood. The reactivity to pollen may have weakened over time, but upon massive reexposure in 1982, these TAK candidate patients gradually had delayed hypersensitivity reactions, with progression through 1983 and 1984, ultimately developing vasculitis. Based on circumstantial evidence regarding KD epidemiology, I concluded that the significant and sharp increase in TAK incidence and registration in 1984 was due to the onset of systemic vasculitis triggered by hypersensitivity to massive pollen exposure, as likely as in KD onset, after such average 21.4 months delay from first pollen exposure, as above mentioned [4].

It is assumed that the ongoing steady increase in KD, SLE, scleroderma, and other cases is partly due to the annual increase in pollen release between 1995 and 2005 and the recent repetition in considerable amounts of pollen

release that has occurred every several years since 2005 shown in [Figure 12] as a result of global warming [5]. Moreover, observing atmosphere of conferences it is possible that health care providers who treat patients with KD have failed to promote pollen avoidance in infants of parents with allergy, in spite of the consequence that the incidence of KD and TAK and other various autoimmune diseases affected with pollen exposure distinctly in the first half of 1980s as described above. The epidemiological evidence presented in this study to which an attention should be paid among professional clinicians of each intractable disease that pollen exposure may have triggered and induced development of not only systemic vasculitides but also connective tissue diseases of so-called autoimmune diseases.

The need for careful attention to rapid increase of all-at-oneness of registered numbers of intractable diseases in 1984 and forthcoming analysis of transition of increase of patients during latest era

The correlation between yearly KD incidence in 8 prefectures, including Tokyo Megalopolis and neighboring

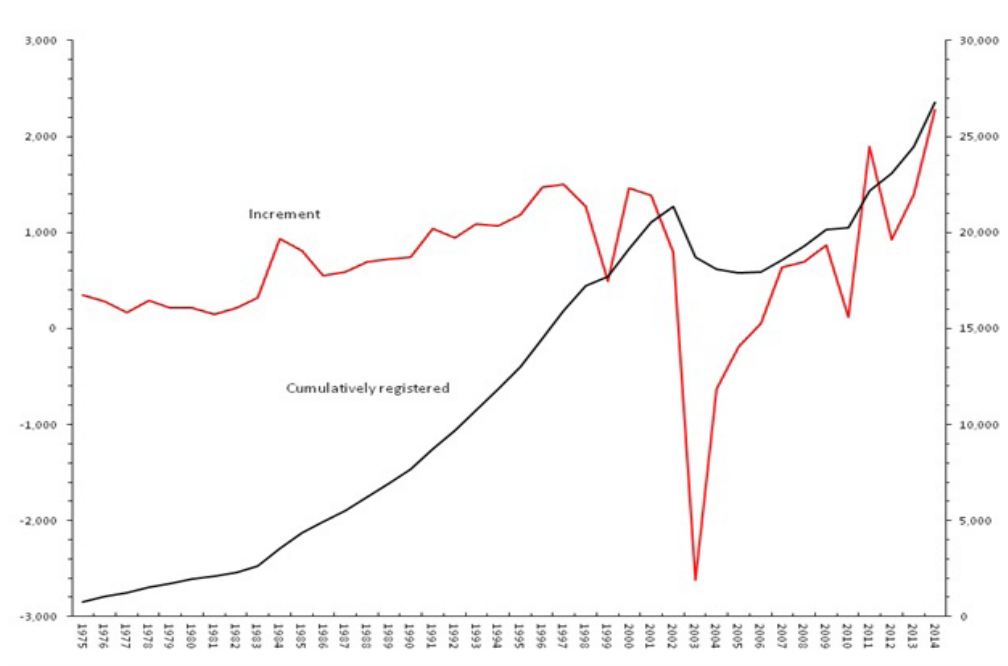


Figure 8: Change of enrollment of patients with Sarcoidosis from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

Kanagawa Prefecture, and yearly pollen releases observed at 8 cities in each of the 8 prefectures between 1975 and 2002 was also first examined [1,2]. My review of these studies suggests that 1982 was characterized by the greatest volume of pollen release nationwide in response to weather conditions in that year [1, 2, 5]. On the other hand, Tokyo region and Kanagawa among 47 prefectures in Japan would be expected to have the highest number of each intractable disease case, because the number of cases is population dependent, as in the case of KD. But, as compared with KD case in which onsets occur in sensitive infants, it may be difficult to conduct cross correlation analysis [4] between a few numbers of patients with these intractable diseases and numbers of pollen release. As a matter of fact, numbers of newly registered patients have not been announced, but only increments have been reported in the brochure. Therefore careful attention by professionals should be focused on the first distinct, rapid increase of numbers of patients with each intractable disease around 1984.

In my preliminary study showing the relation between pollen release and onsets of patients with intractable diseases in the same graph, it seems at a glance that peaks of

patient numbers accord with those of pollen numbers to a considerable degree when a line graph of patient numbers is moved to the left for two years on a line graph of pollen numbers, as likely as in KD case shown in [Figure 12].

Concluding Remarks

The origin of the autoimmune disease has been explained in connection with virus infection conventionally [12]. From now on, clinicians and professional researchers in each intractable disease will investigate actively the truth of each intractable disease using this information. As I reported in studies on KD [3-5], it is essential to demonstrate that pollen exposure or pollen immunization in animals can cause vasculitis, such as KD and TAK, and other autoimmune diseases in humans. Furthermore, 11 diseases in this study as well as PID will require a study on blastoid transformation of lymphocytes sensitized to specific antigenic constituents of pollens, such as Cryj1 and Cryj2 [13], in patients with vasculitis syndromes and other autoimmune diseases. A lymphocyte stimulation test [14,15] in adult patients should be performed both in the acute phase and during a recurrence. Clinically, it is interesting to study whether infection of influenza would suppress recurrence

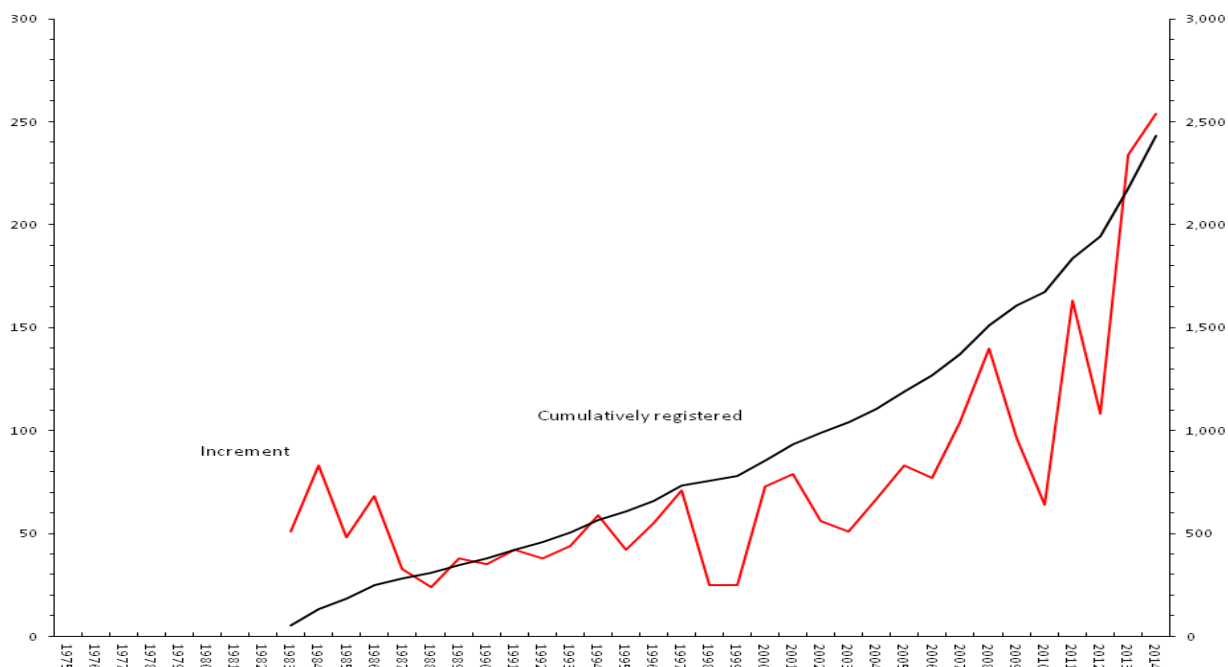


Figure 9: Change of enrollment of patients with Granulomatosis with polyangiitis from 1983 to 2014. Increment and cumulatively registered number in each year are shown.

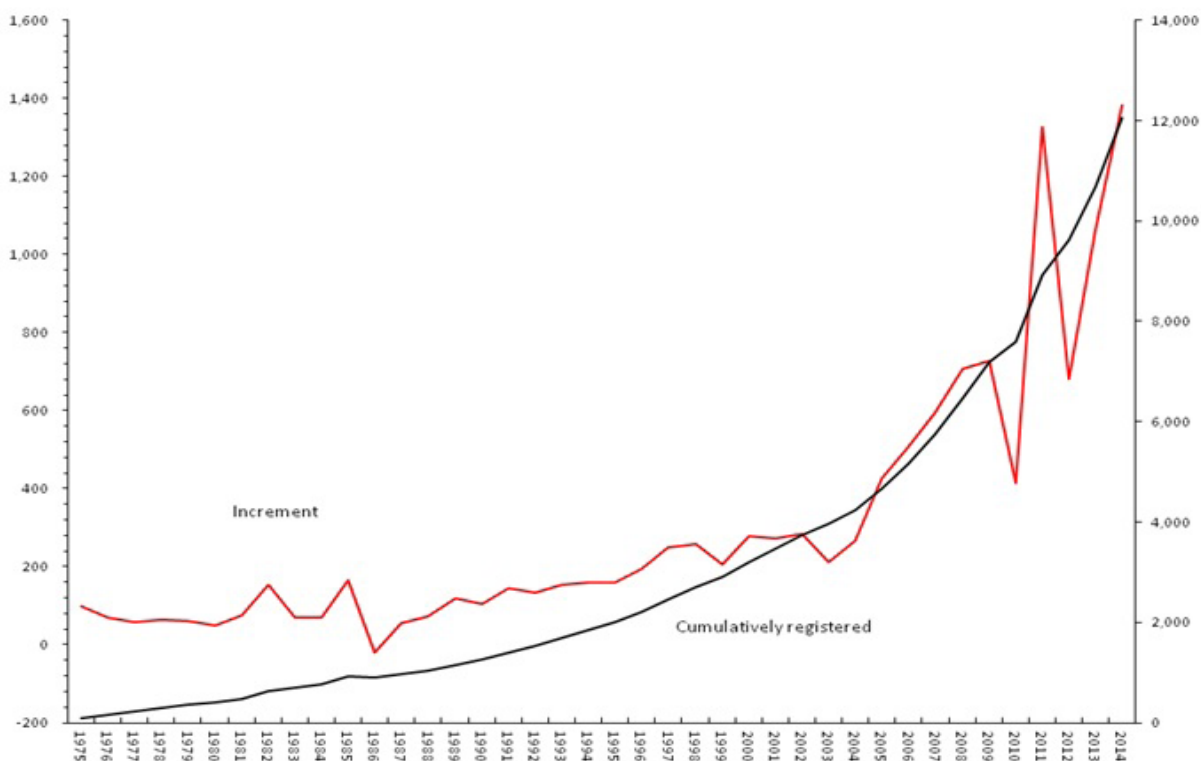


Figure 10: Change of enrollment of patients with Periarthritis nodosa from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

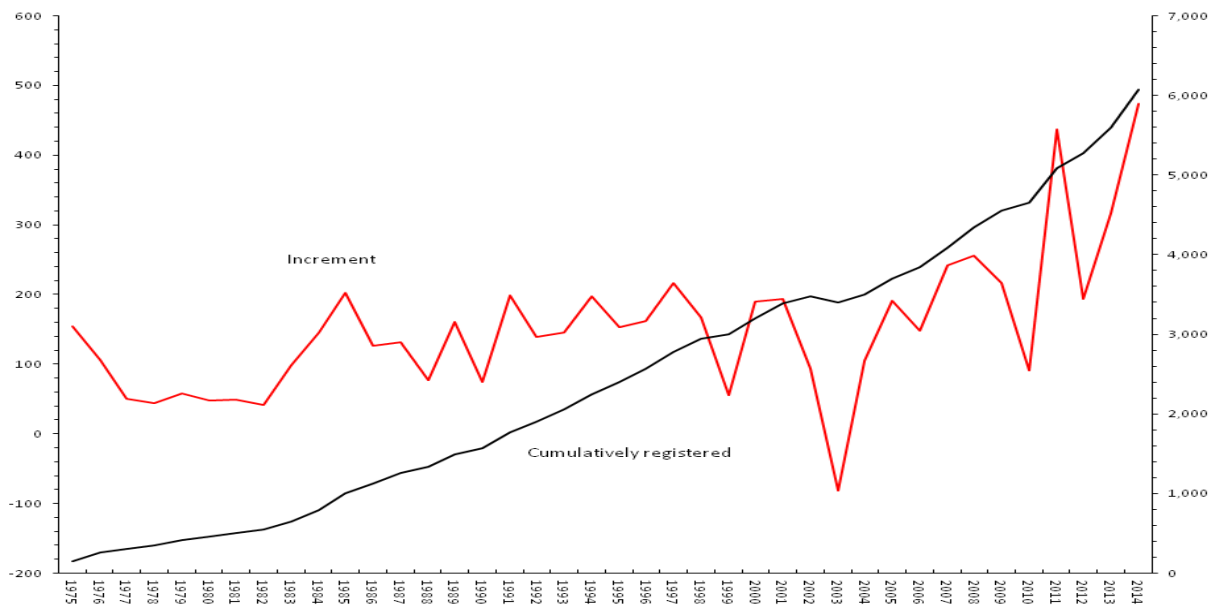


Figure 11: Change of enrollment of patients with Pemphigus from 1975 to 2014. Increment and cumulatively registered number in each year are shown.

of intractable diseases as likely as the suppression of KD development around February. Finally, it may be more proper to think that many intractable diseases have been commonly triggered by pollen substances released from major species of plant kingdom in each country than to suppose that each intractable disease has been caused by each unknown agent different from each other. And it is important for patients with each of these 11 diseases to avoid pollen exposure to prevent recurrences or ameliorate symptoms.

Acknowledgement

Akira Awaya expresses gratitude to Mr. Koichi Iwata for valuable minute data processing and design.

Conflicts of Interest

The author declares no conflict of interest.

References

1. Awaya A, Sahashi N. The aetiology of Kawasaki disease: Does intense release of pollen induce pollinosis in constitutionally allergic adults, while constitutionally allergic infants develop Kawasaki disease? *Biomed Pharmacotherapy*. 2004;58:136-140.
2. Awaya A. Urgent effort of the start of the study to demonstrate many existence of pollen-induced diseases (PID). *Clinics in allergy*. 2004;24, 376-379. Japanese.
3. Awaya A, Murayama K. Positive correlation between Japanese cedar pollen numbers and the development of Kawasaki Disease. *Open Allergy J*. 2012; 5:1-10.
4. Awaya A, Nishimura C. A combination of cross correlation and trend analyses reveals that Kawasaki disease is a pollen-induced delayed-type hyper-sensitivity disease. *Int J Environ Res Public Health*. 2014; 11:2628-2641.
5. Awaya A. Suppressive influence of seasonal influenza epidemic on Kawasaki disease onset. *Jpn. J. Clin. Immunol*. 2016;39:535-544.
6. Ogino S. Clinical statistics of allergic rhinitis. *Iyaku No Mon*. 1993;33:185-190. Japanese.
7. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol*. 2003;91(3):288-96.
8. Brochure downloaded from HP of Japan Intractable Diseases Research Foundation, <http://www.nanbyou.or.jp/entry/141>. Japanese.
9. Kawasaki T. Non-scarlet fever desquamative syndrome. *Chiba Med J*. 1962;38, 279. Japanese.
10. The data downloaded from <http://www.jichi.ac.jp/dph/kawasakibyout/20170928/mcls24report.pdf>. Japanese.
11. The data downloaded from <http://www.nanbyou.or.jp/entry/1356> in <http://www.nanbyou.or.jp/entry/141>. Japanese.

12. Pender MP. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. Trends Immunol. 2003;24(11):584-8.

13. Sugimura K, Hashiguchi S, Takahashi Y, Hino K, Taniguchi Y, Kurimoto M et al. Th1/Th2 response profiles to the major allergens Cry j 1 and Cry j 2 of Japanese cedar pollen. Allergy. 1996; 51(10):732-40.

14. Awaya A, Sugane K, Yamauchi J and Kimura M. Stimula-

tion of lymphocytes of patients administered with a trypsin inhibitor, Trasylol (basic pancreatic trypsin inhibitor pharmaceutical), *in vitro* with BPTI and other several stimulants. Jpn J Exp Med 1975; 45:541-549.

15. Awaya A, Takeuchi T, Saito T, et al. Studies on a patient whose lymphocytes were stimulated *in vitro* with aprotinin in spite of having no history of therapy with aprotinin preparation. Rinshomeneki. 1979;10:1093-1100. Japanese.

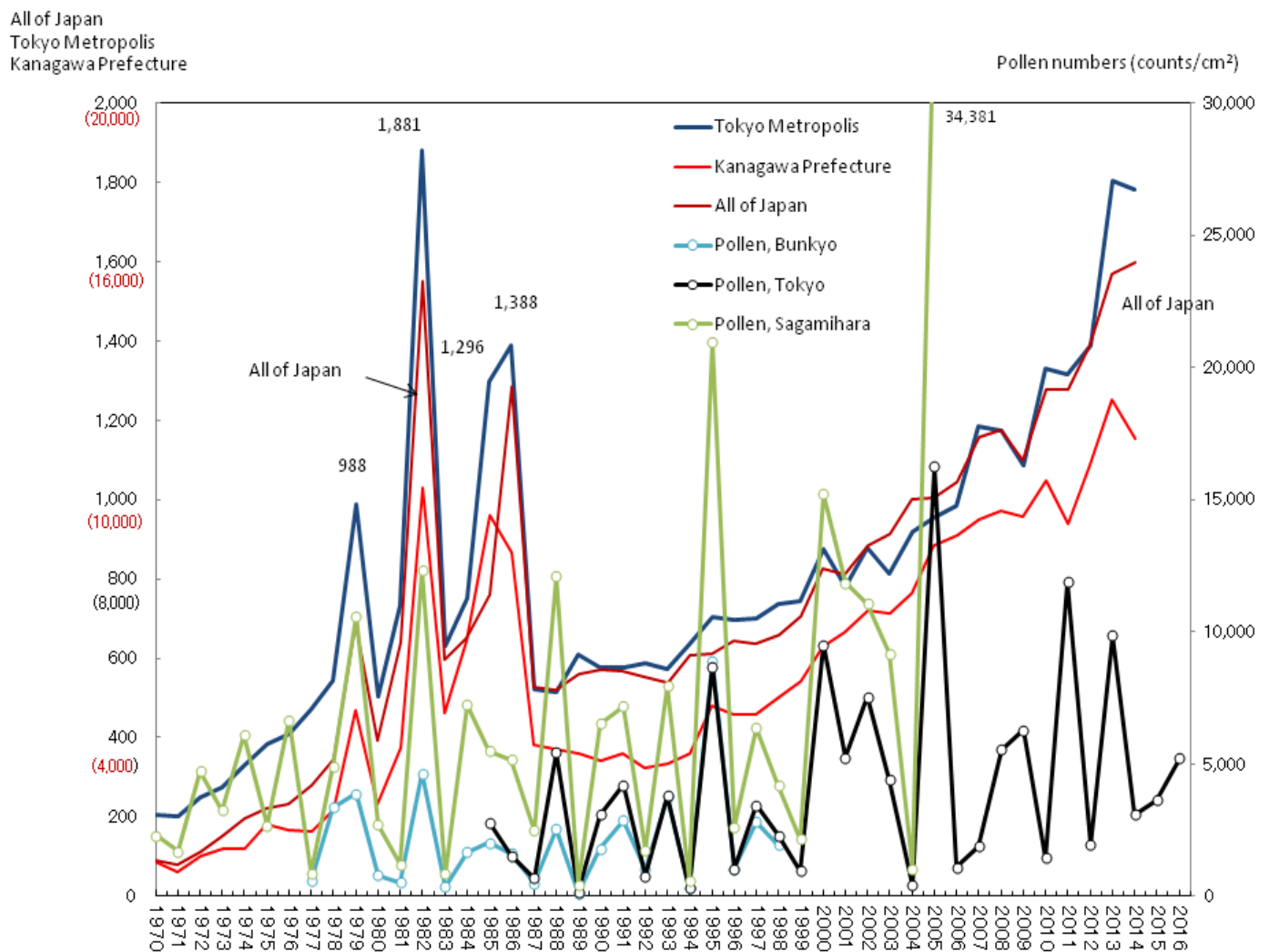


Figure 12: Annual numbers of Kawasaki disease patients in Tokyo Metropolis, Kanagawa Prefecture and all of Japan from 1970 to 2014, and the pattern of scattering pollen numbers at Bunkyo in Tokyo, in Tokyo and at Sagami-hara in Kanagawa from 1982 to 2015.