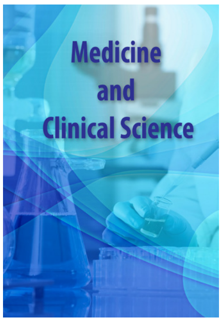
Medicine & Clinical Science

Original Article



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Keywordst

uterine cancer, cervical cancer, corpus uteri cancer, prostate cancer, bladder cancer, stomach cancer, cancer of gallbladder and bile ducts, malignant lymphoma, oral and pharyngeal cancer (o-phar. cancers), laryngeal cancer, Kawasaki disease, airborne pollen, pollen exposure, pollen levels, pollen-induced diseases, pollen diseases, patient-registry year, newly registered patients,Tokyo Metropolitan, Sagamihara City.

Abbreviations

AP: airborne pollen, PE: pollen exposure, PID: pollen-induced diseases, nRPs: newly registered patients

The Relationship Between Annual Airborne Pollen Levels and the Occurrence of Uterine Cancer, Cervical Cancer, Corpus Uteri Cancer, Prostate Cancer, Bladder Cancer, Stomach Cancer, Cancer of the Gallbladder and Bile Ducts, Malignant Lymphoma, and Cancer of Oral and Pharyngeal, and Laryngeal Cancer: A Retrospective Study Based on The National Registry Database of Cancer Incidence In Japan, 1975–2015

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Abstract

Background: *In Japan, pollen counts increased between 1977 and 1987, including three peaks (1978-1980, 1982, 1984-1986) coinciding with triphasic Kawasaki disease (KD) outbreaks. Epidemiological findings have been extensively accumulated that KD since 2003 and, from 2018 related specific intractable diseases such as systemic vasculitis, collagen diseases, inflammatory bowel diseases, idiopathic dilated cardiomyopathy and further from 2019 various cancers such as lung, breast, pancreatic, skin and kidney cancers may be correlated to pollen exposure (PE).*

Methods and results: *To elucidate the effects of PE on occurrence of other cancers, we evaluated the annual occurrence of disorders in relation to pollen counts using data from a national database. Specifically, we evaluated the occurrence of uterine cancer, cervical cancer, corpus uteri cancer, prostate cancer, bladder cancer, stomach cancer, cancer of gallbladder and bile ducts (GBB), malignant lymphoma (ML), oral and pharyngeal cancer (o-phar. cancers), laryngeal cancer. During 1975–2015, the 1978-80 and 1984-1986 peaks of pollen scatter was the earliest big peaks with which simultaneous increase in occurrence of uterine, cervical, bladder, stomach, GBB, o-phar. cancers and laryngeal cancers. Furthermore, simultaneous outbreaks of each cancer coincided with subsequent ten peaks of pollen scatter till 2015. Our results showed statistically significant correlations for o-phar cancers, laryngeal, prostate and stomach cancers between the annual number of newly registered patients (nRPs) in the patient-registry year and annual pollen levels in the same patient-registry year.*

Significant correlations were also shown between the number of nRPs in the patient-registry year and annual pollen levels measured 1 year (GBB), 2 years (prostate), 3 years (corpus uteri, stomach, ML), 5 years (uterine), 6 years (uterine, corpus uteri, prostate, bladder, GBB), 7 years (o-phar, laryngeal) and, 9 and 16 years (cervical) before the patient-registry year.

Conclusion: *We assume that cumulative effects of PE in many cases within about 6 years and more before the diagnosis of cancers might possibly trigger onset of cancers when cumulative effects of PE as environmental stress overwhelmed immunoreactive threshold. The authors would like to discuss the triggering effect of PE (the action of PE to induce a carcinogenic state in humans) on humans as a compromised host, in the preliminary stages of cancer development, in which human papillomavirus is thought to be involved in the pathogenesis.*

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Introduction

The National Cancer Center's new 12 Articles on Cancer Prevention states that prevention and control of heavy drinking, smoking, and obesity are recommended [1]. Some cancers and malignancies have been determined or assumed to be caused by smoking or viruses, but some cancers are described in the paper as having no clear cause [2-13]. On the other hand, the authors initially focused on Kawasaki disease (KD) and found the epidemiological fact that "pollen may be the triggering factor for KD" in 2003, and since then, a total of four papers were reported until 2016 [14-18]. Then, the correlation between the number of patients and fluctuations in pollen counts over a 40-year period was analyzed for 40 designated intractable diseases, including collagen diseases, inflammatory bowel diseases (ulcerative colitis and Crohn's disease), interstitial pneumonia, and vasculitis syndromes other than KD, such as Takayasu disease, starting at June in 2018. As a result, we were able to present a correlation between the two, and we started reporting papers, etc at the end of 2018 and have already reported four papers [19-24]. These findings on the relationship between pollen exposure (PE) and disease led the authors to develop a discussion from the perspective of the commonality of life phenomena. The authors then began a similar analysis and study of 24 cancer and malignancy types in the summer of 2019. As a result, finally in June 2 2020, the first paper on the correlation between cancer and PE was published for all types of cancer and lung, breast, and pancreatic cancer [25]. Then, in December 2020, as the second paper on the correlation between cancer and PE, we published a general and preliminary short report of the correlation analysis which was performed for the three areas of KD, designated incurable diseases and cancer/malignant tumors together, shifting the number of years between the year of disease onset and the year of pollen dispersal [26].

We reported three papers [27-29] in 2021, when the city was under the COVID-19 pandemic situation, pointing out that why SARS-CoV-2 was mutated and newborn in Wuhan City in November 2019 is related to the background that Wuhan City used to be the city with the highest pollen dispersal by far in China. Next, our one paper described that the seasonal influenza epidemic in Tokyo and Kanagawa Prefecture began 10 months after the pollen dispersal every year since 1980 [30]. This ten months lag of epidemic after pollen scatter is the same as months lag of onset of KD after pollen dispersal. In 2022, we reported the third [21] and fourth [22] papers on the correlation between designated incurable diseases and PE, as well as the third [31] paper on the correlation between cancer and PE for thyroid, skin, esophagus, kidney and ovary cancers, leukemia, multiple myeloma, and all cancers. This is the fourth article on the correlation between cancer PE and reports in detail on uterine cancer, cervical cancer, corpus uteri cancer, prostate cancer, bladder cancer, stomach cancer, cancer of the gallbladder and bile ducts (GBB), malignant lymphoma (ML), oral and pharyngeal cancer (o-phar.cancer), and laryngeal cancer.

Materials and methods

Since 1958, the governmental authority in Japan, the NCC, has been gathering cancer incidence data by registering patients and releasing the data to the public [32,33]. The data shows the number of presently registered patients (RPs) in each present calendar year. In this study, we initially imported the number of presently RPs into the Excel tables. We then calculated the number of newly RPs in each year based on the annual number of presently RPs in some year and that in its previous year for all cancers and for each of 23 types of cancers or malignant tumors. The work was performed in accordance with the ethical principles for medical research outlined in the Declaration of Helsinki in 1964 and its subsequent revisions (https://www.wms.net/). Data on airborne pollen (AP) release was provided by Dr. Yozo Saito, Dr. Hiroshi Yasueda and Professor Norio Sahashi [14]. Dr. Saito gathered AP data based on the research unit in the Tokyo Medical and Dental University Graduate School of Medicine, Bunkyo-City, Tokyo [14], while Dr. Yasueda surveyed AP data based on the research unit in the National Hospital Organization, Sagamihara National Hospital, Sagamihara, Kanagawa [14-26,31]. As he ended his service of information transfer in 2006, no data has been obtained since then. The AP data in the Tokyo Metropolis collected from 12 research sites was donated by Mr. Hiroshi Kaneko. The AP data was downloaded after administrative information disclosures from the Tokyo Metropolitan Institute of Public Health website [34].

In the present study, data of numbers of patients with cancers and malignancies in all the Japan were imported into tables in Microsoft Excel. This data was used to create figures of line graphs for each cancer. These figures represent annual numbers of presently RPs as well as newly RPs, and the scattered pollen counts in three areas in Japan (the Bunkyo-City area of Tokyo, the whole area of Tokyo Metropolitan, and Sagamihara City in Kanagawa).

A correlation analysis was performed for each cancer and malignancy, to evaluate the association between the annual number of newly RPs in each patient-registry year “x” during 1975–2015, and the annual amount of AP levels in Tokyo and Sagamihara, measured in the same year as the patient-registry data. A correlation shift analysis was also performed between the annual number of newly RPs in each patient-registry year “x” between 1975 and 2015 and the annual AP levels in both cities measured “α” years prior to the patient-registry year “x” (“α”=1~20). Correlation coefficients and p values were calculated using the Excel function PEARSON via the method described in the brochure http://imnstir.blogspot.com/2014/04/p.htm. A statistically significant positive correlation was defined as $p<0.05$. Marginally significant associations that indicated a possible positive tendency ($0.05 \le p \le 0.10$) were also reported for reference.

Results

Occurrence of upward peaks in the line graphs of the annual number of newly RPs for ten cancers and malignant tumors in relation to the annual levels of AP scatter

Graphs were created simultaneously plotting the number of patient (both presently and newly RPs) cases of cancers and malignant tumors, and the number of pollen dispersal for the period 1985–2015 (Figures 1–10). The five line graphs in our figures for ten diseases consist of two line graphs visualizing the annual patient-registry data for presently RPs and nRPs, and three line graphs visualizing the annual amount of AP scatter measured in three geographical areas. As shown in our line graphs, the amount of cedar and cypress pollen scatters in both Sagamihara City and Bunkyo-City started to increase during 1977–87, showing three distinct peaks (1978–80, 1982, 1984–86). Fundamentally, steady phasic increases in annual numbers of both presently and nRPs concurrent with a consecutive series of 13 upward AP peaks (1978–80, 1982, 1984–86, 1988, 1990–91, 1993, 1995, 1997–98, 2000–03, 2005, 2008–09, 2011 and 2013) were observed for ten cancers (Table1), in the same way as already reported in our previous articles on cancers [25,26,31]. Below described findings also suggest that the occurrence of each cancer appeared to start simultaneously and to increase

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***Table 1.** Peaks of occurrence of cancers and malignant tumors in Japan between 1975 to 2015*

Figure. No	**Figure 1**	**Figure 2**	**Figure 3**	**Figure 4**	**Figure 5**	**Figure 6**	**Figure 7**	**Figure 8**	**Figure 9**	**Figure 10**
Years of pollen peaks and next years	Uterine cancer	Cervical cancer	Corpus uteri	Prostate cancer	Bladder cancer	Stomach cancer	GBB	ML	O-phar. cancers	Laryngeal cancer
1978-79, 1980	○	○	○	○	○	○	○	○	○	○
1982, 1983	○		○	○	○	○	○	○	○	○
1984~86, 1987	○	○	○	○	○	○	○	○	○	○
1988, 1989	○	○	○	○	○	○	○		○	○
1990-91, 1992	○	○	○	○	○	○	○	○	○	○
1993, 1994	○	○	○	○	○	○	○	○		○
1995, 1996	○	○	○1994	○	○	○1994	○	○1994	○	○
1997-98, 1999	○	○	○	○	○	○	○	○	○	○
2000~03, 2004	○	○	○	○	○	○	○	○	○	○
2005, 2006	○	○2004	○	○	○	○	○	○	○	○
2008~09	○	○	○	○	○	○	○	○	○2007	○
2011, 2012	○	○	○	○	○	○	○	○	○	○
2013, 2014	○	○	○	○	○		○	○	○	○

Cancer of gallbladder and bile ducts is abbreviated as GBB. Malignant lymphoma is abbreviated as ML. Cancer of oral and pharyngeal cancer is abbreviated as O-phar. cancers. The peaks of 1994, 2004 and 2007 are to be considered as the contribution of not so little patients numbers based on forerunning pollen scatter after hot summer in Sep. to Dec.

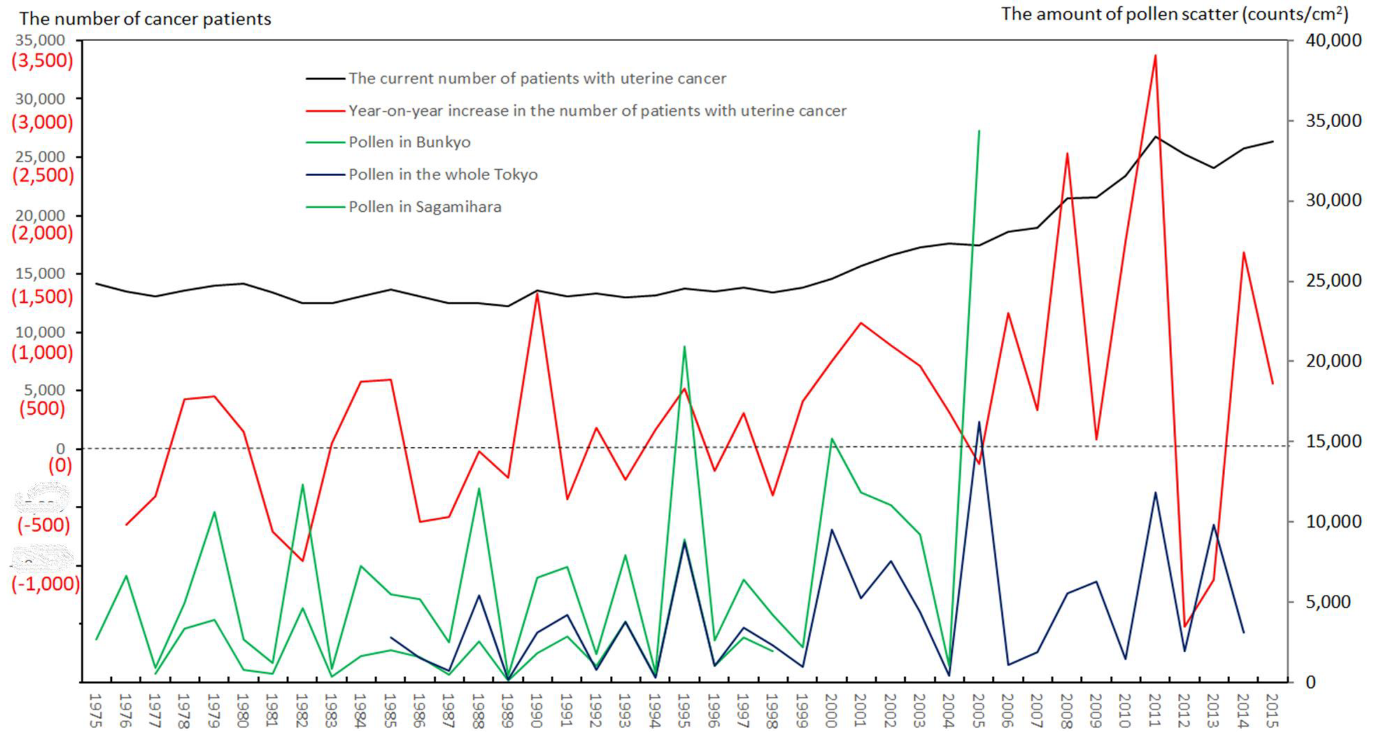

Figure 1. Total number of Japanese males and females for uterin cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. The line graphs for all cancers representing numbers of presently and newly registered patients in each year, as well as the amount of pollen scattered in Bunkyo-City area of Tokyo, the whole Tokyo Metropolitan area and Sagamihara City during the period from 1975 to 2015. Numbers of patients are shown on the left axis whose scales consist of red numbers for newly registered patients and black numbers for presently registered patients. Pollen numbers in counts/cm2 are shown on the right axis.

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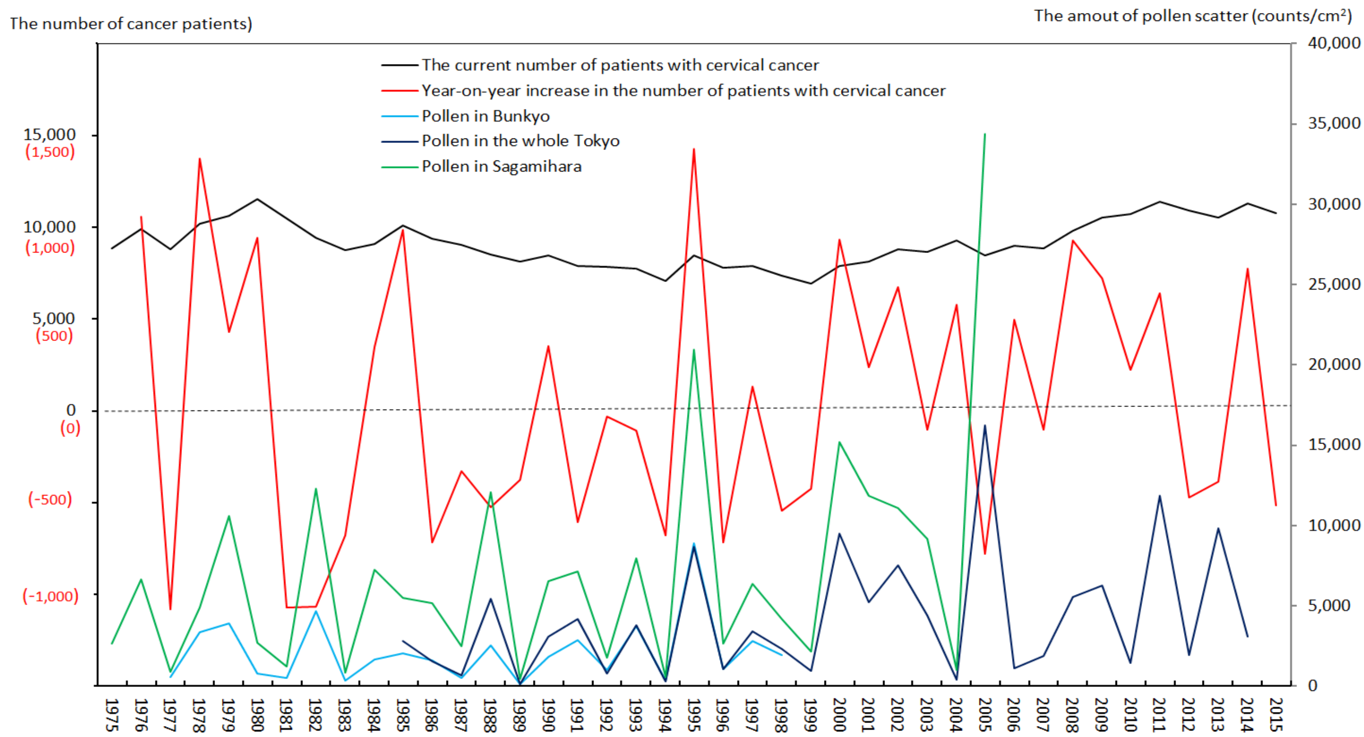

Figure 2. Total number of Japanese males and females for cervical cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

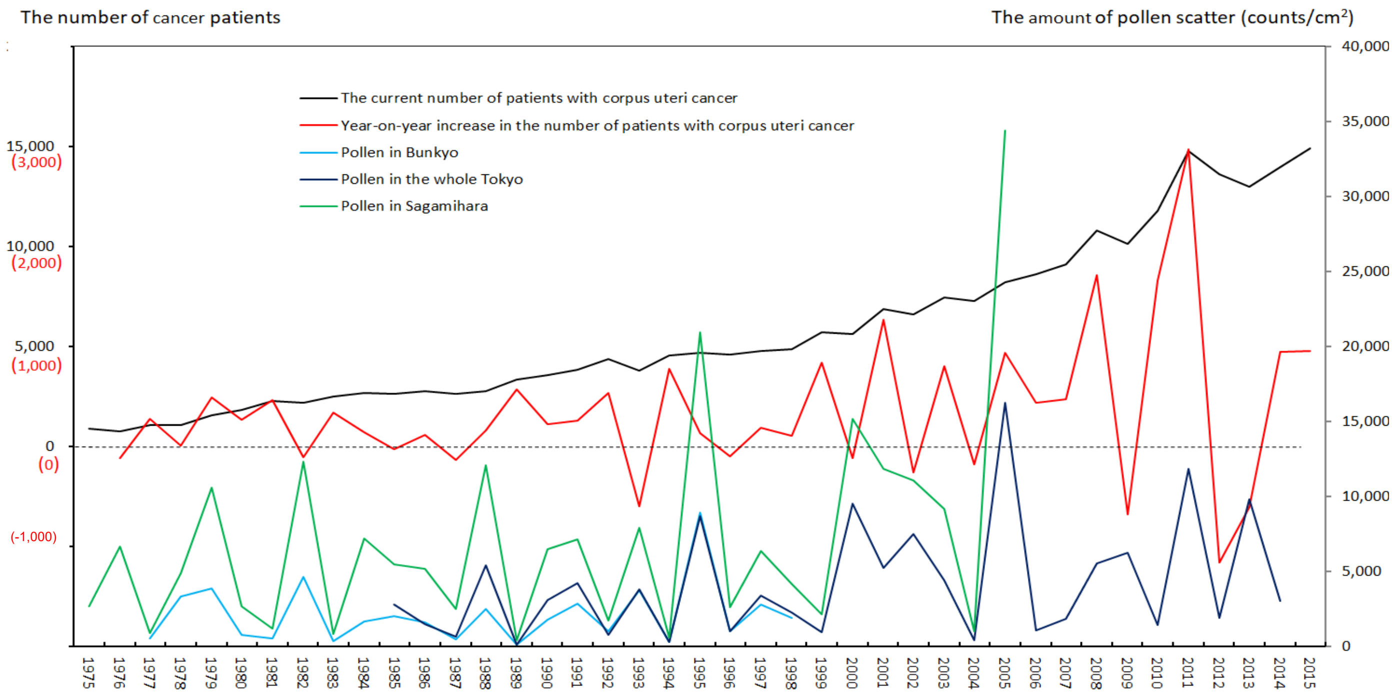

Figure 3. Total number of Japanese males and females for corpus uteri cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

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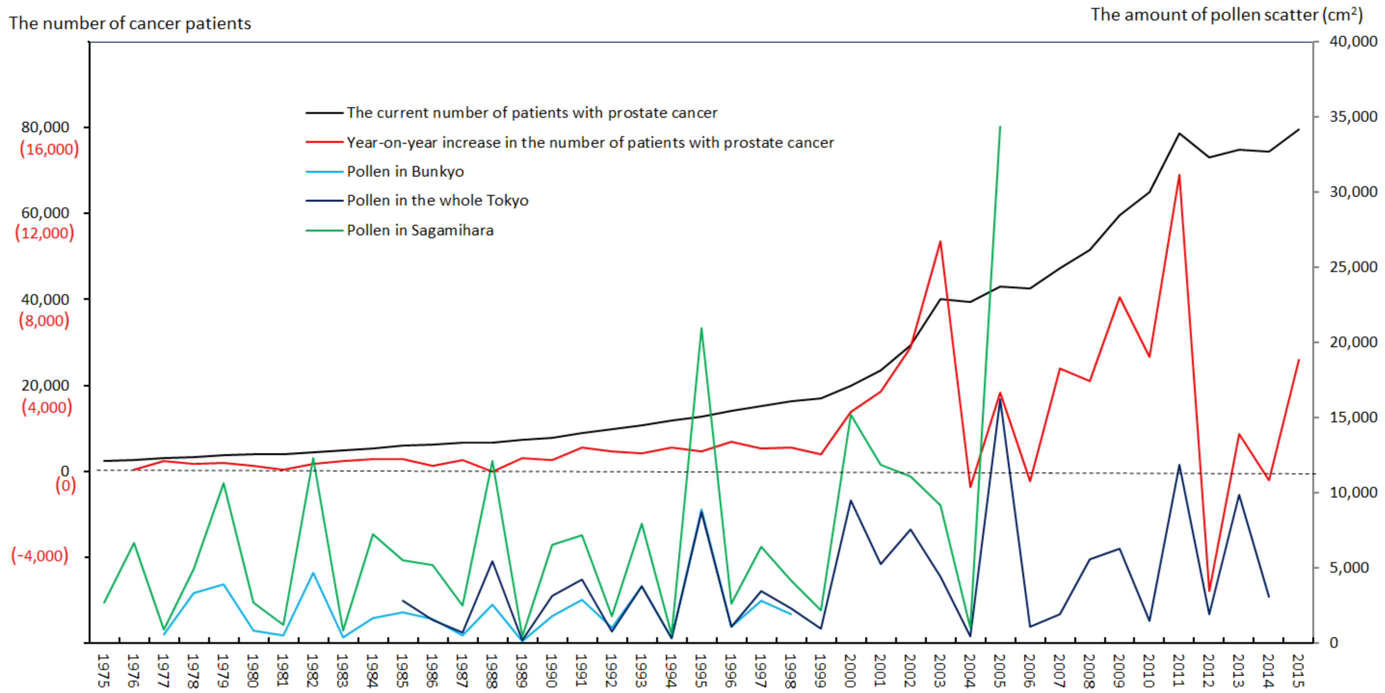

Figure 4. Total number of Japanese males and females for prostate cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

concurrently with pollen scatter in Japan from the latter half of the 1970s until the early 2010s.

Graphs showing the current number of patients registered for uterine cancer, cervical cancer and corpus uteri cancer, and the increase or decrease in the number of patients compared to the number registered in the previous year, compared to the number of pollen are shown in Figures 1-3, respectively. For uterine cancer, cervical cancer and corpus uteri cancer, the current patient registries were 14,176, 8,832, 892 and 26,345, 10,776, 14,909 in 1975 and 2015, respectively. It is noteworthy that the current patient enrollment has increased over the 40 years from 1975 to 2015, especially for corpus uteri cancer. The nRPs cases of cervical cancer (Figure 2) were observed to increase significantly in conjunction with the increase in the pollen counts, such that a significant peak in nRPs cases was seen in 1978-1980, 1984-85, 1995, 2000-2004, 2006-2011 and 2014. On the other hand, as for corpus uteri cancer (Figure 3), the peak of nRPs cases in 2010-2011 was remarkable, while the peaks in 1994, 1999, 2001-2003, and 2005-2008 were not so remarkable as those of uterin cancer. For nRPs cases of uterine cancer overall (Figure 1), peaks in 1978-1980, 1984-1985, 1990, 1999-2004, 2006-2008, 2010-2011, and 2014 were significant.

For prostate cancer, the number of presently RPs cases were 2,412 and 79,631 in 1975 and 2015, respectively (Figure 4). A sharp increase in the number of nRPs cases of prostate cancer was observed from 2000-2003 and 2005-2011, probably due to the spread of diagnostic methods.

For bladder cancer, the number of presently RPs cases in 1975 and 2015 were 3,672 and 20,640, respectively (Figure 5), and showed a significant increase peak in 1978-1980, 1988-1991, 1995-1998, 1999-2003, 2005-2012, and 2014.

Among them, the increase in presently RPs cases of bladder cancer peaked significantly in 2001, and was small in 1982-1986, while the increase in 1988-1991 was somewhat larger.

For stomach cancer, the number of presently RPs cases were 75,133 and 128,881 in 1975 and 2015, respectively (Figure 6), and showed a significant increase peak linked to increase in pollen counts in 1978-1981, 1982-1986, 2000-2003, 2004-2005, 2007-2008 and 2010-2011.

For cancer of gallbladder and bile ducts, the number of presently RPs cases were 5,340 and 22,281in 1975 and 2015, respectively (Figure 7), and showed a steady increase peak in 1978-1983, 1984-1987, 1990-1993, 1994-1998, 2000-2004, 2005-2006, 2007-2009 and 2010-2011, successively.

For malignant lymphoma, the number of presently RPs cases were 4,013 and 30,103 in 1975 and 2015, respectively (Figure 8), and showed a steady increase peak until the year 2000, associated with a sharp increase peak in 2001-2003, 2004-2006, 2007-2009 and 2010-2012.

For oral and pharyngeal cancer, the number of presently RPs cases were 2,497 and 18,478 in 1975 and 2015, respectively (Figure 9), and showed a steady increase peak linked to increase in pollen counts until the year 1994. The increase in the number of presently RPs cases with oral and pharyngeal cancer over the past 40 years was 1.9 times higher than that of laryngeal cancer.

Four major peaks in the number of cases of nRPs were seen in 1995, 2000-2003, 2005-2009, and 2010-2012, including a sharp increase in the number of nRPs in 1995, when the largest pollen dispersal on record at that time occurred. Of these four peaks, the increase in the latter two peaks was very large.

The largest pollen count to date was observed in 2005, and the second largest pollen count ever was observed in 2011. For laryngeal cancer, the number of presently RPs cases were 1,418 and 5,505, in 1975 and 2015, respectively (Figure 10) , and showed a steady increase peak linked to increase in pollen counts until the year 2000. The number of presently RPs showed a significant increase peak in 1984, 2000-2003, 2005, 2006-2009, 2010-2012 and 2013-2015.

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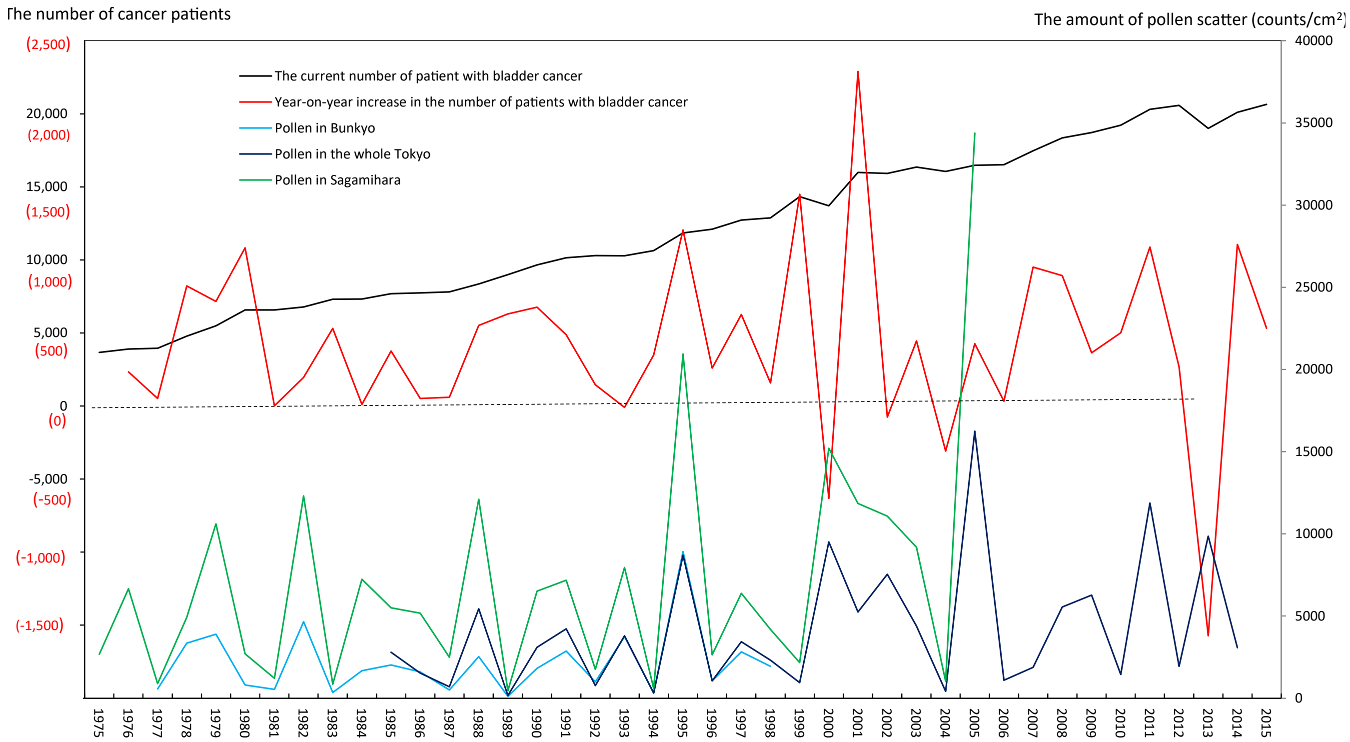

Figure 5. Total number of Japanese males and females for bladder cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

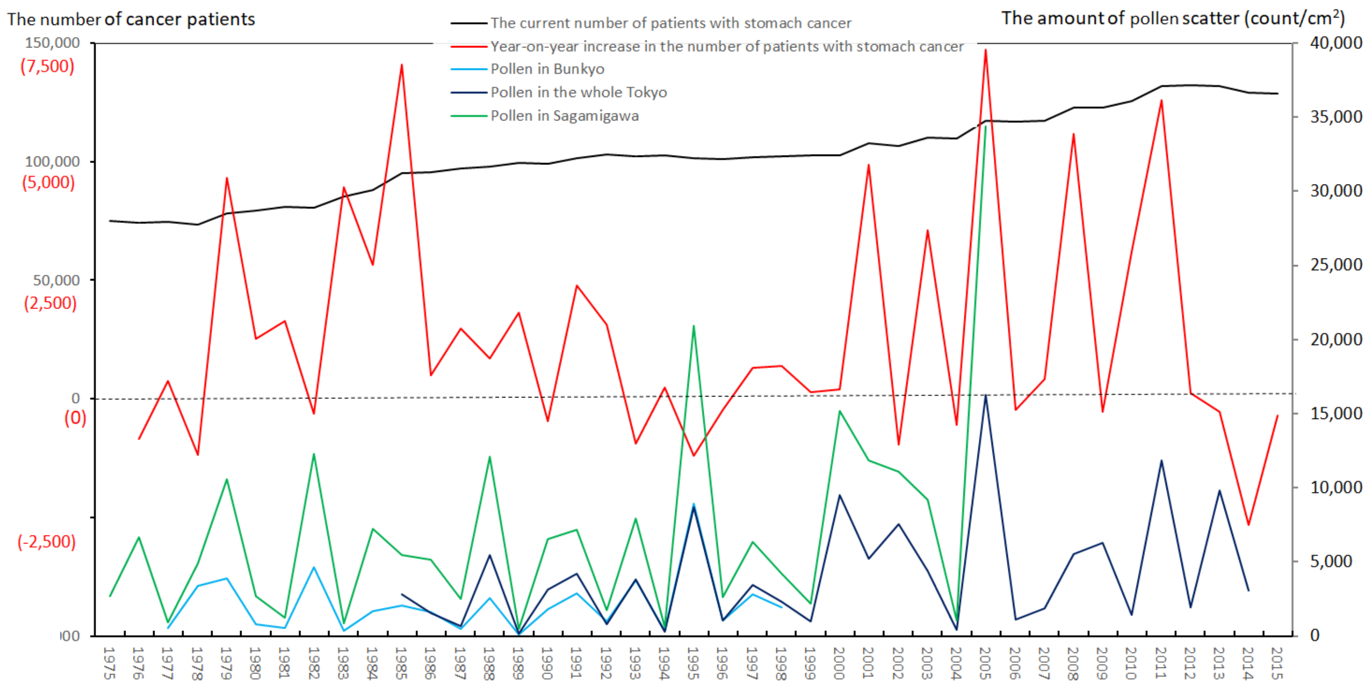

Figure 6. Total number of Japanese males and females for stomach cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

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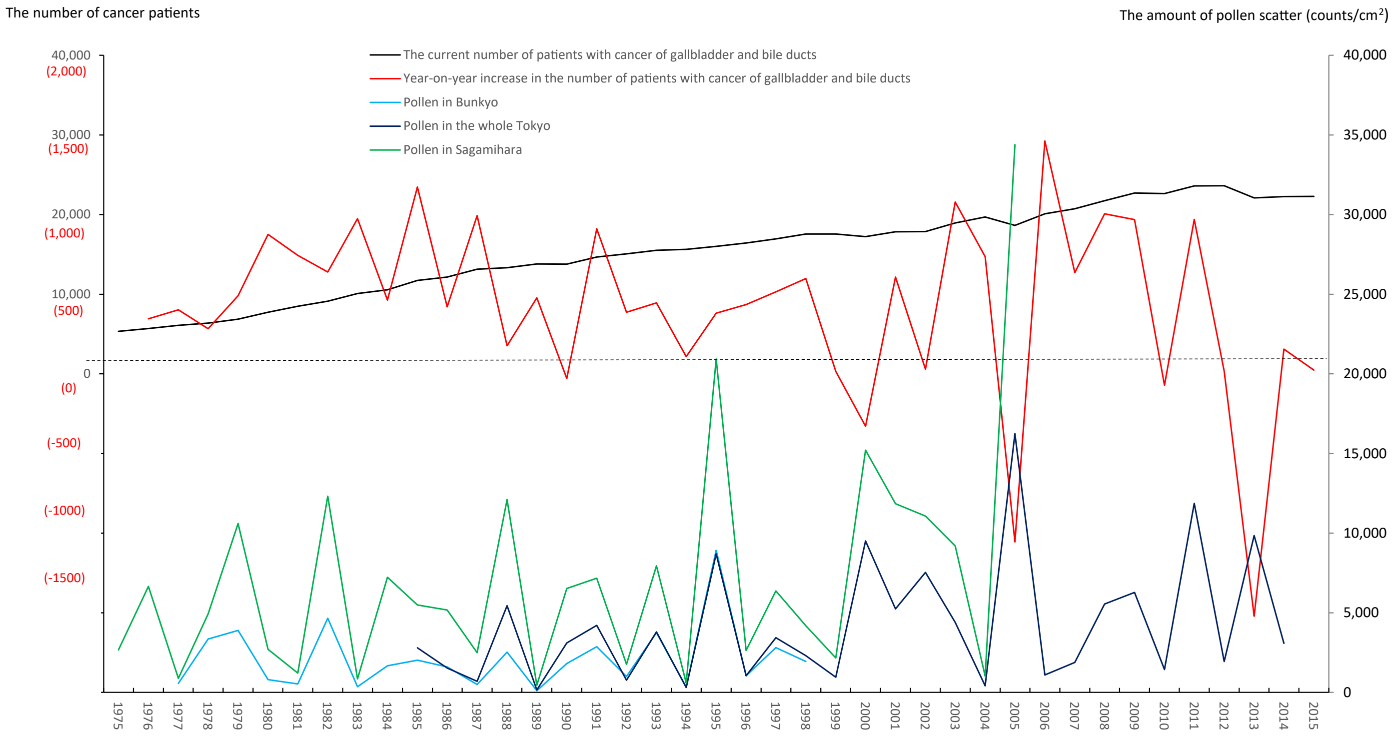

Figure 7. Total number of Japanese males and females for cancer of gallbladder and bile ducts at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

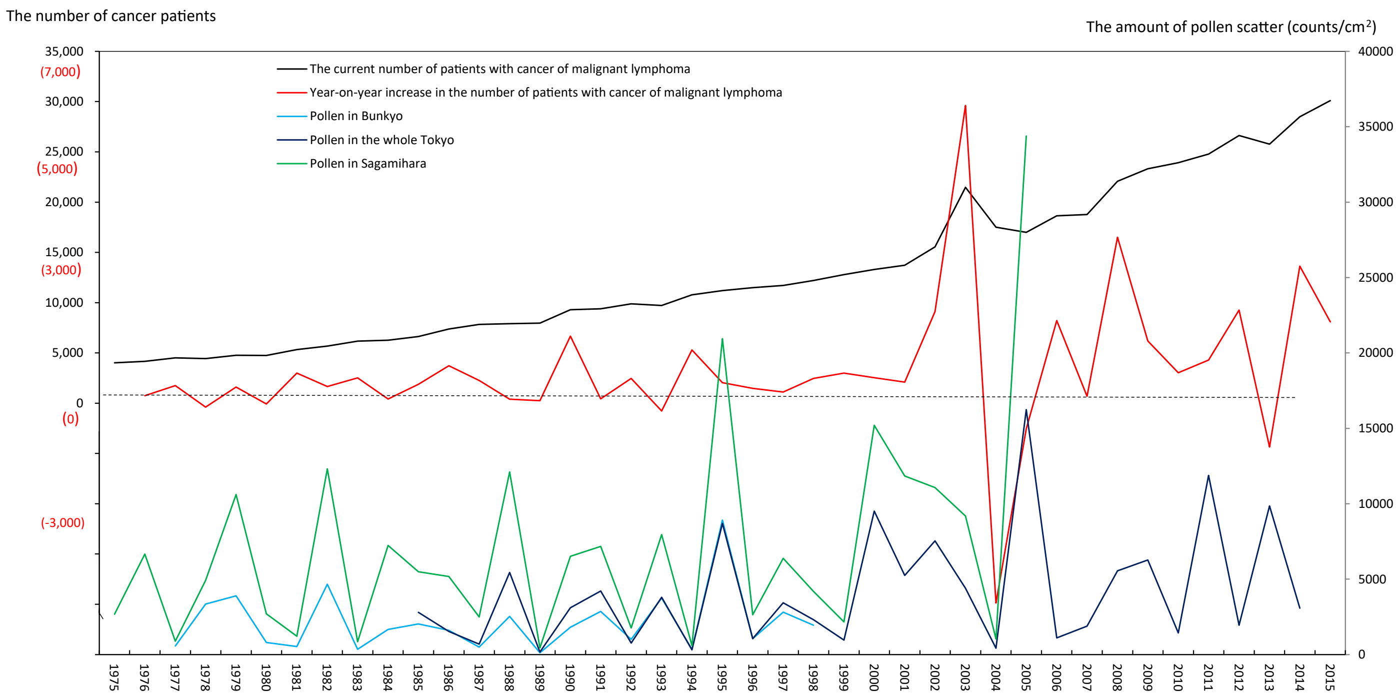

Figure 8. Total number of Japanese males and females for malignant lymphoma at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there..

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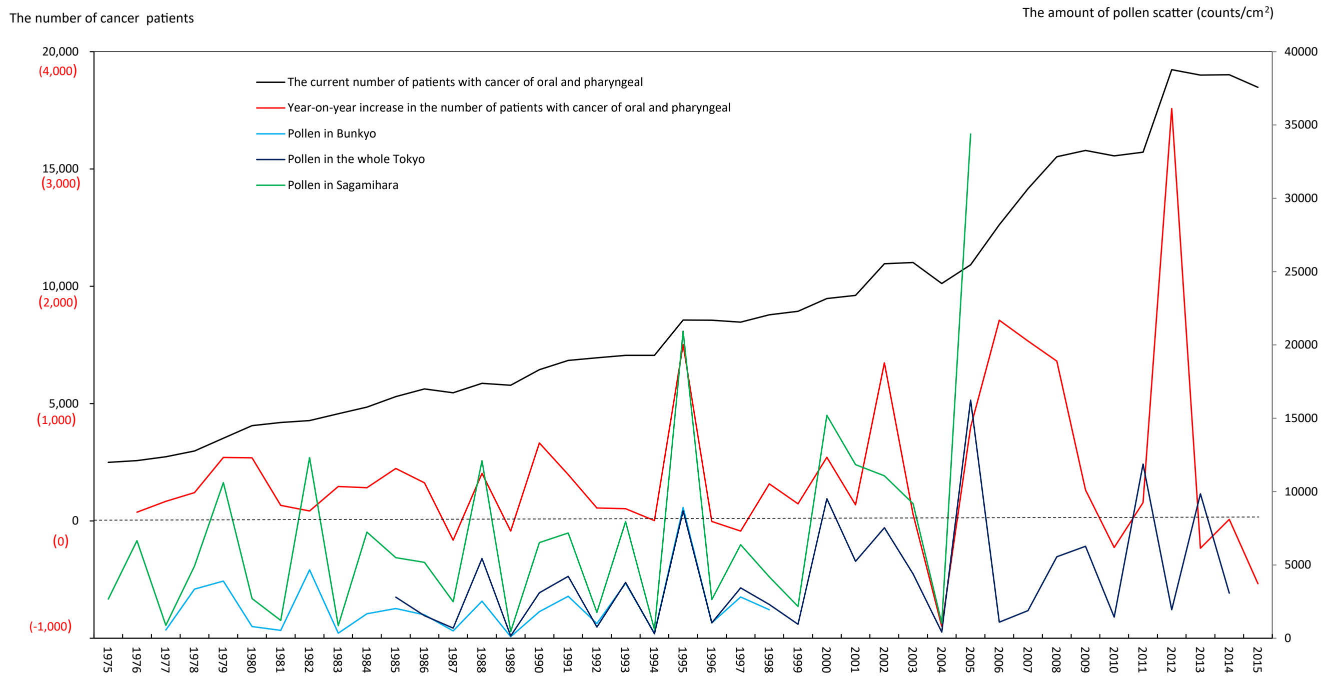

Figure 9. Total number of Japanese males and females for cancer of oral and pharyngeal at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

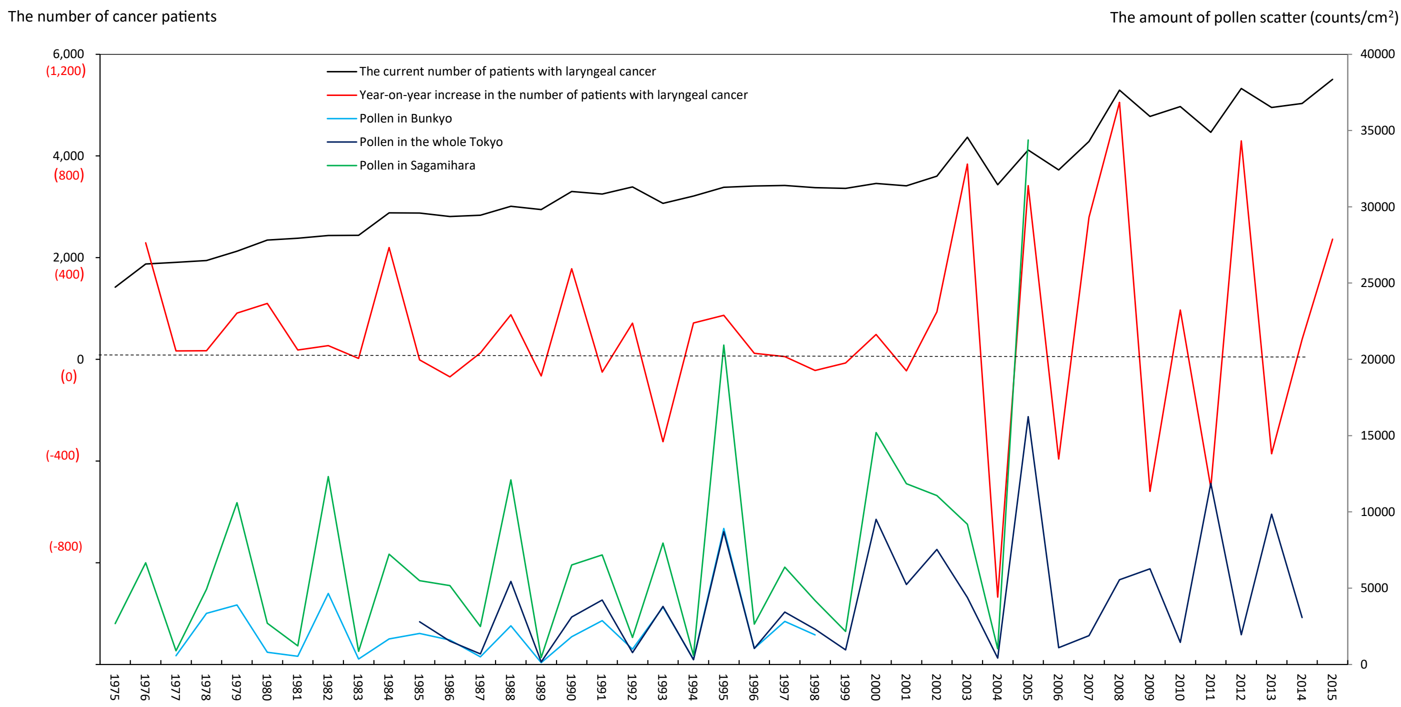

Figure 10. Total number of Japanese males and females for laryngeal cancer at the year diagnosed, its year-on-year increase, and the amount of air borne pollen scatter in 3 areas during the period from 1975 to 2015. Following explanation is the same as in Figure 1, so to be seen there.

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Table 2. *Statistical relationships between the number of nRPs in each patient-registry year and AP levels measured in the same year or prior to the patient-registry*

		Figure 1	**Figure 2**	**Figure 3**	**Figure 4**	**Figure 5**	**Figure6**	**Figure 7**	**Figure 8**	**Figure 9**	**Figure 10**
α		uterine cancer	cervical cancer	corpus uteri cancer	prostate cancer	bladder cancer	stomach cancer	GBB	mallym	o-phar. cancers	laryng. cancer
0	T				0.009015		0.043417				
	S				0.057834		0.107491			0.000711	0.012191
1	T							0.10217	0.092409	0.136811	
	S	0.111363						0.005033	0.27586		
2	T				0.106696					0.161258	
	S				0.028956						0.060179
3	T	0.134909		0.121913	0.138727		0.067635		0.023439		0.075676
	S	0.091264		0.041314			0.032259	0.142819	0.089372		0.163537
4	T										
	S										
5	T										
	S	0.049071		0.103656							
6	T	0.000295		0.000241	0.019151	0.026242	0.068328	0.017356			
	S	0.000234		0.000262	0.003926	0.003453	0.058131	0.071466			
7	T									0.0001581	0.04699
	S									0.0000090	0.076403
8	T				0.159937		0.133538				
	S				0.059515						
9	T	0.1690753	0.0389648								
	S		0.0693975								
10	T						0.190729				0.081327
	S			0.076815	0.175628		0.189973				0.056352
11	T										
	S		0.103474							0.12333	
12	T									0.075379	0.056125
	S									0.119132	0.038819
13	T										
	S	0.173366	0.08829	0.130816							
14	T										
	S										
15	T										0.100496
	S			0.091912							0.075863
16	T		0.166584								
	S	0.132919	0.048571					0.196778			
17	T									0.014517	0.002928
	S									0.012415	0.006781
18	T										
	S										
19	T					0.198784					
	S					0.0375					

A correlation analysis between the annual number of newly registered patients in each patient-registry year "x" ("x"=1975-2015), and the annual amount of airborne pollen levels in Tokyo (T) and Sagamihara (S), measured in the same year as the patient-registry year "x", and measured "α" years before the patient-registry year "x" ("α"=1-20) , for uterin cancer, cervical cancer, corpus uteri cancer, prostate cancer, bladder cancer, stomach cancer, cancer of gallbladder and bile ducts(GBB), malignant lymphoma(ML), cancer of oral and pharyngeal(PRG), and laryngeal cancer. In this Table, the data in the case of "α" =1-17 are shown. p values<0.05 are in red color. 0.05< p values <0.10 are in green color. Numerical data only for reference are also shown. Other data are deleted to blank. Corpus uteri cancer is abbreviated as corpus cancer. Gallbladder and bile ducts cancers is abbreviated as GBB. Malignant lymphoma is abbreviated as mallym. Oral and pharyngeal cancers is abbreviated as o-phar cancers. Laryngeal cancer is abbreviated as laryng.cancer.

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Statistical relationships between the number of nRPs in each patient-registry year and AP levels measured in the same year or prior to the patient-registry

We examined the statistical correlations between the annual number of newly registered in each patient-registry year “x” (“x”=1975–2015) for ten cancers and malignancies and the corresponding annual AP levels in Tokyo and Sagamihara, measured in the same year as the patient-registry data “x” as well as measured with a lag of “α” years before the patient registry year “x” (“α”=1–20). Statistically significant positive correlations were indicated by p values <0.05 (shown in red in Table 2), and marginal associations were indicated by p values between 0.05 and 0.100(shown in green). Reference data of associations with p values slightly greater than p=0.10 in one city (Tokyo or Sagamihara) and the corresponding p values of another city are also indicated. Only p values in “α=0 −17” are shown which were gotten by this calculation in this Table 2.

Our results showed statistically significant correlations between [the number of nRPs in the patient-registry year “x” abbreviated as Nos in “x” below in this column] and the amount of AP exposure measured in Tokyo, in the same year as the patient-registry year 0 for prostate and stomach cancers. Similarly, significant correlations were shown for o-phar. cancers and laryngeal cancers between Nos in “x” and AP exposure measured in Sagamihara, in the same year as the patient-registry year 0.

Regarding GBB and prostate cancers, we found significant correlations between Nos in “x” and AP exposure measured in Sagamihara, 1 and 2 years prior to the patient-registry year “x”, and as to ML we found significant correlations between Nos in “x” and AP exposure measured in Tokyo, 3 years prior to the patient-registry year “x”.

Regarding corpus uteri and stomach cancers, or uterine cancer we found significant correlations between Nos in “x” and AP exposure measured in Sagamihara, 3 or 5 years prior to the patient-registry year “x”.

With regard to uterine, corpus uteri, prostate and bladder cancers or o-phar. cancers we also found significant correlations between Nos in “x” and AP exposure measured in both Tokyo and Sagamihara, 6 years or 7 years prior to the patient-registry year “x”. As to GBB or laryngeal or cervical cancers, significant correlations were found only in Tokyo, 6 or 7 or 9 years prior to the patient-registry year “x”. In 12 or 16 years prior to the patient-registry year “x”, we found significant correlations between Nos in “x” and AP exposure measured in Sagamihara for laryngeal or cervical cancers. In 17 years prior to the patient-registry year “x”, we found significant correlations between Nos in “x” and AP exposure measured in both Tokyo and Sagamihara for o-phar. cancers and laryngeal cancer. In 19 years prior to the patient-registry year “x”, we found significant correlations between Nos in “x” and AP exposure measured in Sagamihara for bladder cancer.

There were many positive tendencies observed in Table 1. One of them is shown between Nos in “x” and the amount of AP exposure measured in Sagamihara, in the same year as the patient-registry year, 0 for prostate cancer. For ML, or stomach and laryngeal cancers 1 or 3 years in Tokyo. For laryngeal cancer, or uterine cancer and ML 2 or 3 years in Sagamihara. For stomach cancer, 6 years in both cities, and for GBB and laryngeal cancer, 6 and 7 years in Sagamihara. For prostate, cervical and corpus uteri cancers, 8, 9 and 10 years in Sagamihara. For o-phar. cancers and laryngeal cancer, 12 years in Tokyo. For cervical cancer, or corpus uteri and laryngeal cancers, 13 or 15 years in Sagamihara.

Discussion

Because of so far accumulated data, we hypothesized that 65 diseases such as KD, 40 designated intractable diseases and 24 cancers and malignancies might belong to the class of PIDs, or "pollen diseases". The starting point for many disease onsets is when PE in a given year directly after birth exceeds an individual's threshold for pollen reactivity. The time from the starting line to the onset of disease is assumed to vary depending on the disease, with some diseases developing immediately in the same year as the starting line, some developing within 1-2 years, and others taking 3-6 or 8 years to develop. Factors that determine the number of years required for the biological process from the starting point to disease onset in an individual may depend on the individual's genetic predisposition or on disease-specific pathogenic factors. Furthermore, even with similar PE, the effects vary from person to person. Some people develop Kawasaki disease, cancer, or malignant tumors, others neurological intractable diseases such as Parkinson's disease, others inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, and still others dilated cardiomyopathy or interstitial pneumonia. It is an inescapable fact that we are all headed toward the onset of these various diseases. An extensive clinical-epidemiological analysis of these issues is greatly expected.

There are still many people in Japan and around the world who are unaware of our findings and reports. Their daily habit of wearing masks and goggles, especially from February to May when pollen dispersal is high and from September to December when small amounts of cedar pollen are dispersed in advance before next spring, may help keep their innate and accumulating pollen reactivity low. We would like to recommend the daily use of masks and goggles as a useful lifestyle habit.

This spring's pollen count in Tokyo was the second highest after 2005, 2011, 2018, and 2013. While there were concerns about an increase in the number of patients with cancer/malignant tumors and designated incurable diseases, the ongoing pandemic of Omicron infection, a variant of SARS-CoV-2, may have also reduced PE, as many citizens wore masks and goggles. A preliminary report from the government is awaited to see how the number of cases of these intractable diseases has changed overall. Like seasonal influenza, the Omicron strain of SARS-CoV-2 appears to have a suppressive effect on the incidence of KD, with the number of KD cases remaining low under the Omicron pandemic through week 26 of 2023.

As we have shown in our graphs of the number of affected cases with respect to KD, 40 designated incurable diseases and 24 types of cancer and malignant tumors, we have found epidemiological evidence that the number of disease cases is linked and correlated with the number of pollen dispersal. We would like many researchers around the world to look at these results as readers and let us know if any facts have been reported that would link the number of disease cases to changes in exposure to or intake of natural and artificial synthetic substances and foods other than pollen.

In the disease area of cancer and malignancy, we have reported four papers, including this one. Our society has not considered or paid any attention to the adverse effects of PE in the living environment, to which all people are innately and continuously exposed, except for hay fever, and there has been no education on related issues in elementary, junior high, and senior high schools or medical and health science educational institutions. It is deplorable that at some point, when people reach adulthood and cancer age, they are declared to have carcinoma. We believe that we must rely on these papers to send a warning message to society as a whole to adopt a lifestyle that is firmly oriented

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toward avoiding pollen.

Human papillomavirus (HPV) has been reported to be a virus associated with cervical cancer, anal cancer, and oropharyngeal cancer [6,9,10].

Comparing the graphs for cervical cancer (Figure 2) and corpus uteri cancer (Figure 3), the increase peak of nRPs linked to the year of increased PE is more variable for cervical cancer than corpus uteri cancer, and there is a noticeable difference in the 40-year trend. The nRPs of cervical cancer are linked to the increase in PE, coinciding exactly with the same year, with a quick response peak that is always noticeable (Table 1). However, it is curious that while uterine cancer and corpus uteri cancer showed significant correlations with pollen counts 3 and 6 years earlier, cervical cancer showed no correlation with PE in any specific year, which may be because the number of cases of cervical cancer was dispersed and changed slightly from year to year.

The commonality of HPV action on cells at favorable sites for cervical and pharyngeal cancers is of interest. Through studies of hand-foot-and-mouth disease, erythema infectiosum, HHV-6, seasonal influenza [30], and SARS-CoV-2 [27-29], the author has focused on the fact that humans who become compromised hosts after pollen PE are susceptible to viruses. In HPV carriers, HPV may be activated after pollen PE and act on the host, causing the process to progress in the direction of carcinogenesis. The number of cases of cancer of oral and pharyngeal (Figure 9) showed a large increase in 2012 between 2011, when PE in Tokyo was the second highest in history, and 2013, when it was the fourth highest in history. A recent report shows a graph that shows that the percentage of treated mid-pharyngeal cancer patients whose cancer was caused by HPV began to increase in 2012, peaked in 2018, and will continue to increase through 2022 (NHK News [35]). 2018 was the third largest year of increase in PE in history, suggesting a correlation between the above cancers and PE. We thought that the graphs shown in Figure 9 for 1975-2015 and up to 2022 eloquently illustrate the possibility that PE is related to the development of oropharyngeal cancer via HPV activation.

If HPV is involved in the development of the above-mentioned cervical cancer, the fact that the biological process triggered by PE induces carcinogenesis, which is common to other cancers, will emerge and is expected to be clarified through vigorous research by researchers.

These facts remind us that various viruses are also involved in the pathogenesis of malignant lymphoma. It is hoped that experts will analyze how the state of human organs, tissues, and cells that have been exposed to pollen and have become compromised hosts will lead to the carcinogenic mechanism via virus activation.

Our assumption is that plant pollen acts as a priming agent that starts with a blow to human organs, tissues and cells and leads to the development of various human diseases. We believe that it is essential to focus our investigating efforts on these early stages of disease development dynamics, especially those that are still unknown.

To prevent the development of cancer and malignant tumors, especially to delay the age of onset in people with cancer families, it is important to reduce cumulative pollen reactivity and extend the time to onset by reducing annual PE. For this reason, it will be necessary to maintain the above-mentioned lifestyle of wearing masks throughout the year, and to install pollen-cutters. Pollen-avoidance prophylactic measures include the precaution of wearing safety masks, goggles, and transparent shields during pollen peaks from the early postnatal period, and of installing air cleaners in homes, particularly during seasons with large amounts of pollen release in spring and with small amount of forerunning pollen release of cedar pollen in September to December before next spring. These measures may help avoid or delay the first onset of cancers and malignancies, including those in young infants who have a potential risk of developing immune-mediated diseases. In addition, we suggest that the application of pollen allergen immunotherapy to reduce pollen reactivity at the level of practical medical care. On the other hand, patients with cancers and malignancies should be even recommended to avoid pollen exposure as much as possible for the purpose of preventing the aggravation of symptoms or recurrences, as well as the co-occurrence of other diseases.

Humans have been exposed to pollen since birth and are at the start-line of disease development when they are exposed to large amounts of pollen during the years when their pollen reactivity exceeds the threshold for disease onset. Some people are headed for the development of designated incurable diseases such as Parkinson's disease, ulcerative colitis, systemic lupus erythematosus (SLE), dilated cardiomyopathy, and interstitial pneumonia; others for colon cancer, lung cancer, stomach cancer, breast cancer, prostate cancer, malignant lymphoma, and others, as described above. The abstract expression of the initial process of this universal life phenomenon common to the onset of various diseases can be described using immunological expressions as follows. Namely, at the point when pollen reactivity exceeds the threshold for disease onset, the various polyclonal antibodies of the individual that have been generated against the pollen antigens over the years bind to the various autoantigens of the host that share the same epitope as the pollen antigens. This stage is time 0, where the autoimmune reaction starts. On the other hand, the host's immune system (thymus and peripheral immune cells) leaves the state of immune tolerance to the self-antigen at that point and recognizes the self-antigen as a foreign substance. Through the new changes in the individual's situation that occur at this time 0, the generating system of autoantibodies, which is different in each individual, is activated. In the meantime, the process of developing each disease progresses, and that year, or one to six years later, the patient develops a designated incurable disease, cancer, or malignancy.

It is important to pioneer an attempt to screen the pollen components that cause the breakdown of this immune tolerance state using the already established method of experimental assay system. We expect a quick turnaround on the separation, purification, and identification of components.

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Conflict of interest

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