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Cypress pollen allergy in Milan: the story of an ongoing growth

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KEY WORDS

Cypress; airborne allergy; pollen allergy; pollen sensitization; annual pollen index.

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Summary

Cypress pollen allergy was virtually absent in Lombardy about 30 years ago. A 15-year clinical survey on cypress pollen sensitization and allergy in the area north of Milan reveals that both cypress pollen sensitization and allergy increased steadily from 2003 to 2017 along with the prevalence of clinical allergy over sensitization. The pollen concentration data, recorded up from 1995 showed a dramatic increase in cypress Annual Pollen Index up from the beginning of the new millennium. Cypress pollen represents now a relevant allergen source in this area.

Impact statement

This study shows once more the consequences of global warming on one hand, and of the irresponsible politics of green by both local administrators and citizens on the other hand.

Introduction

Cypress pollen is one of the most important sources of seasonal respiratory allergy in southern Europe for many years (1). In older epidemiological studies, this type of pollen allergy seemed to be almost exclusive of Spain, Southern France, and of specific Italian regions such as Tuscany, Liguria, Apulia and Campania (1, 2). However, the increasing use of some *Cupressaceae* species (e.g., *Cupressus arizonica*) for gardening and reforestation along with the worldwide increase in temperatures has led to a growth of the epidemiological impact of pollinosis induced by this plant species, due both to a higher pollen load and an elongation of the specific pollen season (3). In effect, an Italian multicenter study performed in 2014 (4) found an unexpectedly widespread diffusion of cypress pollen allergy throughout the country, although this was markedly prevalent in the central and southern regions. Milan is the largest northern Italian town, sited in the center of the Po valley basin and has been characterized by a typical conti-

mental climate ever since. Until 30 years ago, cypress pollen was considered a negligible allergen source in Lombardy, the region of Milan (5). However, in recent years, cypress pollen allergy has gradually become an increasingly relevant cause of respiratory symptoms during the first few months of the year in a growing proportion of pollen allergic subjects. The present study reports the trends of cypress pollen allergy in a suburban area located just 5 kilometers north of Milan during 15 years of observation.

Methods

Patients

All patients presenting spontaneously for suspect respiratory allergy at the outpatient allergy center of the Clinica San Carlo, Paderno Dugnano from the beginning 2003 to the end of 2017 were considered eligible for the study. Patients were thoroughly interviewed to ascertain which kind of symptoms they complained for (either rhino-conjunctivitis, with or without bronchial

asthma) and their seasonality, with a particular focus on the period of cypress pollen allergy in this area (average from mid-end December to the end of march). All patients underwent skin prick tests (SPT) with a series of commercial extracts of airborne allergens (Allergopharma, Reinbeck, Germany), including grass, mugwort, ragweed, pellitory, plantain, birch, olive, plane, and cypress (*Cupressus arizonica*) as seasonal allergens and Alternaria, house dust mites, dog and cat dander as perennial allergens. Skin tests were carried out following established methods (6); readings were taken after 15 minutes, and skin responses were considered positive in the presence of a wheal and flare reaction exceeding 3 mm in diameter. Histamine 10 mg/mL and saline were used as positive and negative controls, respectively.

Sensitivity to cypress pollen was defined as a positive SPT in the absence of respiratory symptoms in the specific pollen season. In patients sensitized to > 3 seasonal allergenic sources including cypress, due to the risk of a false positive result caused by co-recognition of a pollen panallergen such as profilin or polcalcin (7), primary cypress pollen reactivity was confirmed by measuring IgE specific to Cup a 1 by ImmunoCAP (ThermoFisher, Uppsala, Sweden). In order to improve the specificity of the test, IgE levels exceeding 0.35 kU/L were considered positive.

Clinical allergy to cypress was defined as the presence of symptoms or rhino-conjunctivitis with or without asthma in the specific pollen season in a patient showing a positive SPT with cypress pollen or IgE specific for Cup a 1 (see above). In the presence of co-sensitization to perennial allergens such as house dust mite, animal dander, or molds the patient was considered as clinically allergic to cypress pollen only if he/she reported a marked increase in symptom severity during the specific cypress pollen season. Monosensitization to cypress pollen was defined as hypersensitivity to cypress pollen in the absence of sensitization to any other seasonal allergen source.

Follow-up study

All patients spontaneously presenting for a control visit at the allergy center at least 4 years after the first visit and who did not score positive for cypress pollen on the initial visit were considered eligible for the follow-up study. These patients underwent SPT with the whole panel of airborne allergens previously described, looking for *de-novo* cypress sensitization/allergy following the same criteria reported before.

Cypress pollen exposure

Cypress pollen data were provided by the UOC Igiene e Sanità Pubblica Milano Ovest. Pollen counts were performed according to the CEN standard methods (8). Daily average pollen concentrations were expressed as particles per cubic meter of air (p/m^3). Observation period ranged between 1995 and 2017; within this period, the Annual Pollen Integral (API) (9), was examined.

Statistics

Cypress pollen sensitization was calculated as a percentage of all subjects sensitized to any pollen source. Cypress pollen allergy was calculated both as a percentage of all subjects sensitized to any pollen source and as a percentage of cypress pollen sensitized patients. The percentage of patients monosensitized to cypress pollen was calculated as well.

Results

Results are summarized in **table I**. In total 5626 patients were diagnosed as having pollen allergy at the outpatient clinic between the beginning of 2003 and the end of 2017. Of these, 1125 (20%) were found to be sensitized to cypress pollen. Two-hundred eighty-nine (26% of cypress pollen sensitized subjects; 5% of the whole population) were diagnosed as having frank cypress allergy. **Figure 1** shows the trends of cypress sensitization and clinical allergy over time. Both sensitization and allergy showed a gradual increase. Sensitization rate increased from about 15% during the first years of observation to about 25% during the last years of the study period. Similarly, cypress allergy increased from about 3% to about 10%. The linear trend line for both sensitization and allergy showed an almost parallel pattern (**figure 1**). **Figure 2** shows the prevalence of cypress pollen allergy over sensitization during the study period. The linear trend shows a much steeper increase towards the occurrence of allergy among sensitized subjects.

Although altogether 26% of cypress pollen-sensitized subjects were clinically allergic, such proportion showed a gradual increase up to 40% during the last years of the survey.

In contrast, mono-sensitization to cypress pollen remained quite stable over time, ranging between 0% and 9% of cypress pollen sensitized population (**table I**).

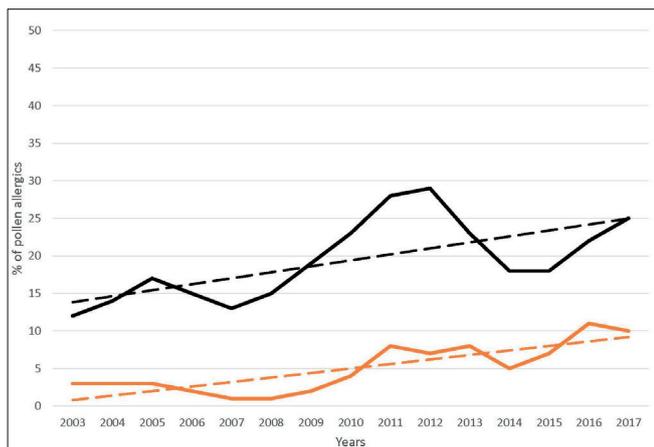
Follow-up data

In total 291 patients underwent SPT during a control visit at least 4 years after the first visit at this center. New sensitizations to cypress pollen were detected in 51/291 (18%) cases, a proportion that is very similar to that of the general study population during the last decade. One third of them (17/51, 33%) reported symptoms suggesting the occurrence of clinical allergy to cypress pollen. New cypress pollen sensitization showed a dramatic increase up from 2010 (**table II** and **figure 3**).

Cypress pollen exposure

Figure 4 shows the cypress pollen load in this area from 1995 to 2007. After a period of stability at low level between 1995 and 2000 (median API 3793 Pollen \times day/ m^3) a dramatic increase in mean API was recorded in 2001 followed by a high-level stabilization onwards (median 2001-2017 API: 8705 Pollen \times day/ m^3).

Figure 1 - Cypress pollen sensitization and allergy during the study period (2003-2017).



Black line: cypress pollen sensitization. The linear trend is the dotted line. Orange line: cypress pollen allergy. The linear trend is the dotted line.

Discussion

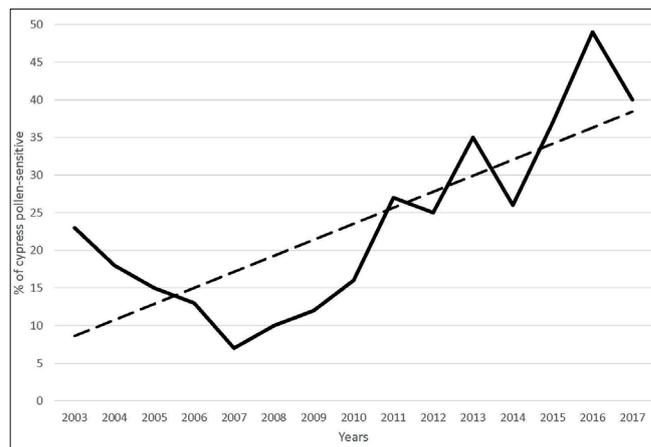
Although the present study does not have a strict epidemiological value, as it was not carried out on the general population, it nonetheless shows that both cypress pollen sensitization and allergy are gradually on the rise in the north of Italy. One limit might be the relatively small study population both in the year by year analysis of trends and in the follow-up part of the study but one strength is that the data came from a single geographical area, and were collected using the same methodology throughout the years by one single operator.

As short as 30 years ago, cypress pollen was still considered a negligible allergen source in this area (5).

Nowadays about one fourth of patients with pollen allergy presenting at this allergy center are sensitized to cypress pollen. During the last decade, there has been an impressive increase in poly-sensitizations to airborne allergens, in many cases due to the sensitization to pollen pan-allergens (profilin, polcalcin) (10).

However, the increase in cypress pollen sensitization observed in the present study cannot be ascribed to plant panallergen co-recognition, as patients showing multiple skin reactivity to seasonal airborne allergens underwent *in vitro* component-resolved diagnosis and were included into the cases series only in the presence of Cup a 1 IgE reactivity. Further, since cypress pollen extracts for SPT seem to contain little or no pollen panallergens (7, 11), patients scoring positive on SPT with such extracts are probably primarily sensitized to cypress pollen allergens. Another point is the improved sensitivity of SPT with commercial cypress pollen extracts after the replacement of the formerly employed *Cupressus sempervirens* with

Figure 2 - Clinical allergy/sensitization to cypress pollen during the study period (2003-2017).



The dotted line represents the linear trend.

the much more allergenic *Cupressus arizonica* as source material (12). The main reason for this impressive increase is probably the much heavier cypress pollen burden. In fact, in this geographic area the median annual cypress pollen index more than doubled up from the beginning of the new millennium. This observation is in keeping both with the significant uptrend of the number of days with cypress pollen concentrations exceeding 1 p/m^3 in the surroundings of Milan (13), and with previous studies performed in Japan where the policy of planting millions of cedar trees between the early 1950s and early 1970s eventually resulted in a dramatic increase in the prevalence of specific pollen sensitization and allergy (14). In our study, an interesting coincidence of high pollen burden, and marked increase in the prevalence of cypress sensitization both in the general population and in the follow-up group occurred in the years 2010-2012. This period was followed by a period of more moderate pollen burden (2014-2017) associated with a reduction of the percentage of sensitized patients detected. Interestingly, the increase in cypress pollen sensitization was followed by a marked increase in its clinical expression over the years, which reached about 40% at the end of the study period. This finding also is probably the consequence of the increasing cypress pollen burden in this area in recent years. The increasing relevance of cypress pollen allergy in this area has been associated with a marked increase in the number and proportion of patients prescribed cypress pollen immunotherapy over the years (data not shown).

The massive increase of cypress pollen in this area could be due to the more frequent planting of cypress trees, particularly in private gardens, for ornamental purposes. It could also be one further indirect consequence of the ongoing global warming trend,

Table I - Cypress pollen sensitivity and allergy in Milan 2003-2017.

Year	N° patients	Sensitized	%	Allergic	%	Monosensitized
2003	111	13	12	3	3	0
2004	155	22	14	4	3	0
2005	343	60	17	9	3	2
2006	507	76	15	10	2	2
2007	452	59	13	4	1	0
2008	346	51	15	5	1	1
2009	358	69	19	8	2	2
2010	426	100	23	16	4	0
2011	434	121	28	33	8	1
2012	342	99	29	25	7	2
2013	479	111	23	39	8	4
2014	445	82	18	21	5	2
2015	412	76	18	28	7	7
2016	433	94	22	46	11	6
2017	383	94	25	38	10	5

as showed by Ziska *et al.* (15) for airborne allergenic pollen abundance and seasonality across the northern hemisphere. Indeed they found that the ongoing increase in temperature extremes (T_{min} and T_{max}) might already be contributing to extended seasonal duration and increased pollen load for multiple aeroallergenic pollen taxa in diverse locations across the northern hemisphere.

Figure 3 - Proportion of new sensitizations to cypress pollen in patients undergoing SPT > 3 years after the first visit.

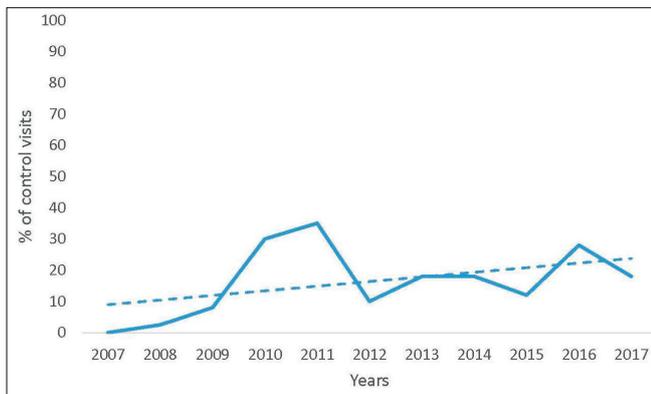


Table II - Detection of de-novo cypress pollen sensitization during follow-up visits.

Year of control visit	No. follow-up visits	No. patients scoring positive for cypress pollen (%)
2007	11	0 (0%)
2008	11	1 (9%)
2009	25	2 (8%)
2010	33	10 (30%)
2011	40	14 (35%)
2012	29	3 (10%)
2013	50	9 (18%)
2014	28	5 (18%)
2015	25	3 (12%)
2016	21	6 (28%)
2017	18	3 (18%)

Specific future studies might assess the relationship between climate change and cypress pollen production in the area.

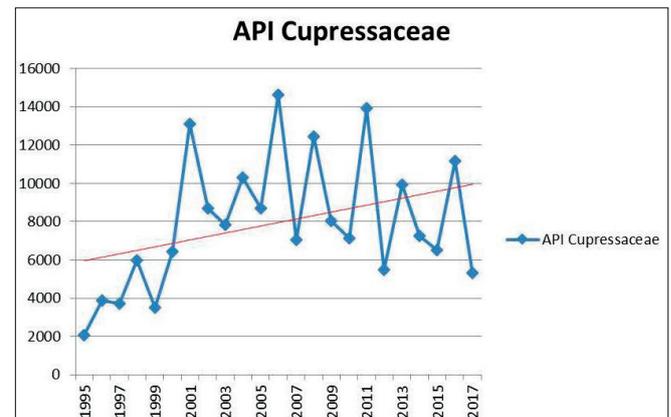
Conclusions

In conclusion, nowadays cypress pollen represents a relevant source of sensitization and seasonal respiratory allergy in this area. This is possibly one further indirect consequence of the global warming trends.

Conflict of interests

The authors declare that they have no conflict of interests.

Figure 4 - Annual cypress pollen index (API) in the area north of Milan from 1995 to 2017.



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