Allergology International. 2013;62:171-179
DOI: 10.2332/allergolint.12-RA-0523

REVIEW ARTICLE

JSA Best Presentation Award 2011

Influences of Smoking and Aging on Allergic Airway Inflammation in Asthma

Tadao Nagasaki[1] and Hisako Matsumoto[1]

ABSTRACT

Asthma is a heterogeneous disease with varying phenotypes and numerous risk factors. This condition results from complex interactions between genetic and environmental factors, and active smoking is one of these risk factors. The effects of aging should also be taken into account in these interactions. From an epidemiological standpoint, smokers and/or elderly patients with asthma are not small part in the total population with asthma. Furthermore, both smoking and aging are important risk factors for severe asthma. This review discusses the potential effects of smoking and aging on healthy subjects and patients with asthma, particularly from the perspective of inflammatory changes. First we show evidence that smokers and the elderly have increased neutrophil counts in their airways, which may have impacts on their clinical characteristics of elderly smokers with asthma. Secondly, on the basis of our recent findings on the interactions between smoking and aging in patients with asthma, we propose that IgE/eosinophilic inflammation should not be underestimated in elderly smokers with asthma, particularly those who are atopic. This review may expand our understanding of the effects of smoking and aging on asthma with a new perspective of an old issue.

KEY WORDS

aging, asthma, eosinophils, inflamm-aging, neutrophils, smoking

INTRODUCTION

It is well known that current smokers with asthma have poorer disease control[1-3] and show an excessive declines in forced expiratory volume in 1 second (FEV_1)[4] compared with never-smokers with asthma. Smoking may also impair therapeutic responses to inhaled[5] and oral corticosteroids[6] in patients with asthma. Currently, mechanisms underlying the characteristics of smokers with asthma are mostly explained by the induction of neutrophilic airway inflammation[7-9] and goblet cell hyperplasia,[10] whereas studies on the relationship between smoking and eosinophilic inflammation in patients with asthma have yielded inconsistent findings.[7,8,10,11] Nonetheless, considering that smoking is related to higher serum IgE levels in the general population[12-14] and that relatively young patients with asthma are enrolled in studies on smokers with asthma,[7,8,11] the involvement of IgE/eosinophilic inflammation in smokers with asthma should be re-evaluated in all age groups.

In the first part of this review, we summarize the evidence for the effects of smoking on asthma. We also address the impact of ex-smoking on the pathophysiology in this condition. Next, we review evidence for the effects of aging on asthma and offer insights into the interactions between smoking and age on IgE/eosinophilic inflammation in patients with asthma.

ASTHMA AND SMOKING

EPIDEMIOLOGY

The prevalence of smokers among adult patients with asthma is similar to that among the general popula-

[1]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
Conflict of interest: No potential conflict of interest was disclosed.
Correspondence: Hisako Matsumoto, MD, PhD, Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606–8507, Japan.
Email: hmatsumo@kuhp.kyoto–u.ac.jp
Received 6 December 2012. Accepted for publication 30 January 2013.

tion. In Western countries, 17%-35% patients with asthma are current smokers, while 22%-43% patients are ex-smokers.[15] In a survey of Japanese adult patients with asthma (n = 400) in 2005, Adachi *et al*. reported that the percentage of current smokers with asthma was 20.5%, which was similar to the general population (21.7% in 2009 according to the Ministry of Health, Labour and Welfare, Japan), while that of ex-smokers with asthma was 24.5%.[16] In another recent study in Japan, Ikeue *et al*. reported that the percentage of current smokers among patients with asthma who visited emergency department due to asthma attack was 34.8%.[17] In our university hospital, 15.0% patients with asthma were current smokers while approximately 21.2% were ex-smokers as shown later.

Passive smoking is a risk factor for the development of asthma. Studies on maternal smoking during pregnancy, parental smoking during childhood, and passive smoking in the workplace consistently demonstrate that passive smoking is related to the onset of asthma and respiratory symptoms.[18-20] Recent studies, including a population-based incident case-control study, show that active smoking also causes asthma in adulthood,[21-23] although it did not increase the risk of asthma onset in earlier studies.[24,25] Furthermore, in a recent longitudinal study, allergic patients who smoked were more prone to newly develop asthma of greater severity.[26] Ex-smoking may also be a risk factor for the development of asthma, as Piipari *et al*. showed that ex-smoking increased the risk of asthma by 1.34 in males and 2.38 in females.[22] However, some analyses do not support this risk of asthma onset among ex-smokers.[26]

CLINICAL CHARACTERISTICS

Current smokers with asthma consistently have more severe symptoms and poorer asthma control than never-smokers with asthma,[1-3,15,27] while ex-smokers have poorer asthma control than never-smokers.[1] Current smoking or passive smoking increases admission rates and decreases quality of life in patients with asthma.[28] The mortality rate is higher among current smokers with asthma than among never-smokers with asthma.[29] Current smokers are less likely to manage their asthma compared with never-smokers, possibly because they lack knowledge about asthma, use inhaled corticosteroids less frequently, and attend asthma education programs less frequently compared with never-smokers.[30-32]

DECLINES IN LUNG FUNCTION

The combination of current smoking and asthma has a synergistic[4] or an additive effect on the decline in FEV_1.[33] In a 15-year follow-up of adults with asthma in the Copenhagen City Heart Study, among male patients with asthma aged 40-59 years, current smokers and never- or ex-smokers showed an average annual decline in FEV_1 of 58 ml and 33 ml, respectively.[4]

THERAPEUTIC RESPONSES IN SMOKING ASTHMATICS

Current smokers with asthma, and to a lesser extent, ex-smokers with asthma are resistant to oral corticosteroids, although their airways show reversibility to an inhaled short-acting β_2 agonist.[6] Similarly, current smokers with asthma are insensitive to inhaled corticosteroid treatment,[5,34] particularly when low doses of inhaled corticosteroids are used.[35] Several mechanisms for corticosteroid resistance in smokers with asthma have been suggested: (a) increased production of tumor necrosis factor-α with overexpression of glucocorticoid receptor β, (b) increased production of interleukin (IL)-4, (c) overexpression of nuclear factor-κB, (d) decreased histone deacetylase activity, and (e) increased numbers of neutrophils and CD8+ T cells.[6]

In contrast to treatment with corticosteroids, current smokers with asthma may benefit from treatment with a leukotriene receptor antagonist. After 8 weeks of treatment with a leukotriene-receptor antagonist, morning peak flow increased to a greater extent in current smokers with asthma than in never-smokers with asthma.[33] Smoking-induced increases in urinary excretion of leukotriene E4 in patients with asthma may have been involved in this effect.[36]

IMMUNE SYSTEM AND AIRWAY INFLAMMATORY CELL PHENOTYPES

Cigarette smoking alters immune inflammatory responses in many ways. Smoking compromises host defense by suppressing innate immune responses in conjunction with impairing mucociliary clearance and epithelial junction.[37] Meanwhile, cigarette smoke activates resident cells toward a pro-inflammatory status and recruits inflammatory cells into the airways.[38] The effects of smoking on innate immunity in asthmatic airways have not been completely determined. However, it is interesting to note that among several Toll-like receptors (TLRs) that play key roles in innate immune responses, the expression of TLR2, which recognizes gram-positive bacteria, fungi, and rhinovirus capsids,[39] may be altered in smokers with asthma compared to never-smokers with asthma.

In never-smokers with asthma, the mRNA expression of TLR2 in sputum, but not of TLR3 or TLR4, was increased compared to healthy subjects.[40] TLR2 expression was higher during acute asthma attacks, particularly viral-induced asthma attacks, than in the stable condition.[40] Of note, for patients with fatal asthma who smoked, the expression of TLR2, but not of TLR3 or TLR4, in the small airways was lower than that in never-smokers with fatal asthma.[41] This was consistent with findings of decreased TLR2 expression in smokers.[42] Although the subsequent changes in adaptive immune responses have not been shown, suppression of TLR2 may be involved in the altered the immune system in smokers with asthma.[43]

During the development of adaptive immune-inflammatory responses, dendritic cells play an important role in the differentiation of Th-1- and Th-2 type inflammation. Dendritic cells that develop under nicotine exposure have a defect in their Th-1-promoting capacity and promote Th-2 responses, which are augmented in a Th-2-biased environment.[44] Indeed, smoking skews the immune inflammatory responses toward Th-2-type inflammation in healthy subjects.[45,46] Serum immunoglobulin E (IgE) levels[12-14] and blood eosinophil counts[14,47,48] of current smokers are higher than those of never-smokers in the general population.

Cigarette smoking significantly alters the types of airway inflammatory cells. Recent studies on Th-17-type inflammation show that IL-17 levels are increased in the airways of smokers. Because IL-17 recruits and activates neutrophils,[49] systemic and local increases in neutrophil counts in healthy current smokers[50-52] may be partly induced by Th-17-type inflammation[53] concomitant with the release of the neutrophil chemoattractant IL-8 from epithelial cells.[54] At the same time, airway inflammation in smokers cannot be simply described as neutrophilic inflammation. Among individuals without asthma, in addition to neutrophils, the number of eosinophils that infiltrate the small airway submucosa is greater in current smokers than never-smokers,[52] and the number of neutrophils is correlated with the numbers of eosinophils.[52]

Several studies that investigated bronchial biopsies[9,10] and induced sputum samples[7,8] from patients with asthma showed that smoking induced neutrophilic airway inflammation[7-9] but did not aggravate eosinophilic inflammation.[7,8,10] However, these studies excluded elderly asthma patients, presumably to exclude the comorbidity of chronic obstructive pulmonary disease (COPD). This is an important point for analysis, although it should be interpreted carefully as addressed below. In addition, Tsukioka *et al*. reported that total IgE levels and specific IgE levels against mites, cedar pollen, and *Candida* were higher in current smokers with asthma than never-smokers.[55] In murine models of allergy, tobacco smoke exposure induces bronchial hyper-reactivity, eosinophilia, and Th2-type inflammation,[56-58] which supports that IgE/eosinophilic inflammation can be induced in current smokers with asthma.

Fractional exhaled nitric oxide (FeNO) is considered to be a useful biomarker of eosinophilic airway inflammation.[59] However, cigarette smoke is known to consume NO that is produced in the airways via reactions with superoxide anion and/or peroxidase-dependent mechanisms.[60] Therefore, FeNO levels in current smokers are low[61-63] and are not considered to be a reliable marker of eosinophilic airway inflammation. Studies on FeNO levels in ex-smokers have yielded inconsistent findings.[62,64,65]

SMOKING CESSATION

Needless to say, smoking cessation is the best treatment for smokers with asthma. In a cross-sectional study, the number of goblet cells and mucus-positive epithelium were increased in current smokers with asthma compared with never-smokers with asthma, however, there was no increase in ex-smokers.[10] FEV_1 in smokers with asthma improved within a week after smoking cessation, and this improvement increased further for an additional six weeks.[66] Patients who had quit smoking for at least a year exhibited restored responses to an oral corticosteroid, with increased morning PEF values.[6] In addition, sputum neutrophil counts were decreased within six weeks of smoking cessation.[66] Therefore, many characteristics of smokers with asthma may be normalized after smoking cessation. However, the question remains if smoking cessation completely reverses airway inflammation or immune system responses. Indeed, the levels of several sputum mediators were not decreased after smoking cessation.[67] In addition, the adjuvant effects of cigarette smoking on allergic subjects cannot be neglected because these effects may cause persistent eosinophilic inflammation after smoking cessation. Recall challenge with ovalbumin one month after the last concurrent exposure to smoking can result in ovalbumin-induced antigen-specific memory and significantly augments eosinophilic inflammation in mice models.[68]

ASTHMA IN THE ELDERLY

CLINICAL CHARACTERISTICS

Asthma may emerge at any age and at a similar rate in all adults (approximately 5%-10%).[69] Enhanced longevity in the general population may result in increased numbers of elderly patients with asthma. The term elderly adult is usually defined on the basis of chronological, biological, or sociocultural perspectives, and the cutoff age defining an individual as elderly ranges from 60 to 65 years.[70]

Elderly patients with asthma have high rates of hospitalization[71] and mortality,[29,72] possibly because of comorbidities,[72] underdiagnosis, and inadequate treatment.[71,73,74] Although elderly patients with asthma are typically characterized as nonatopic, atopy is not uncommon among these patients according to some reports.[75,76] Indeed, elderly patients with asthma are sensitized to allergens at a higher rate compared with age-matched controls (50% vs. 26%, respectively).[77]

DECLINES IN LUNG FUNCTION

Lung function is at its maximum around 20 to 25 years of age and begins to decline thereafter, with annual declines of 25-30 ml in FEV_1. Of note, the estimated rate of decline is not linear with age and can be greater in the elderly.[78] The putative mechanisms for impairment of lung function in the elderly are a loss

Table 1 Inflammation in smoking asthmatics

Authors, Published year	Subjects, Smoking status, Condition of treatment	Pack-years	Age, Mean (range) or mean ± SD	Samples	Effects of smoking
Boulet LP, 2006[7]	22 current smokers 27 never-smokers No use of ICS	14.0 ± 7.6 0 ± 0	31 (20-44) 29 (20-42)	Induced sputum	Neutrophil counts ↑ Eosinophil counts →
Chalmers GW, 2001[8]	31 current smokers 36 never-smokers No use of ICS	21.0 ± 16.6 0 ± 0	36.3 ± 10.6 36.0 ± 8.9	Induced sputum	Neutrophils ↑ (both counts and proportions) Eosinophils ↓ (both counts and proportions)
St-Laurent J, 2008[9]	12 current smokers 12 never-smokers No use of ICS	16.7 ± 2.2 0 ± 0	32.7 ± 2.3 25.8 ± 2.3	Bronchial biopsies	Neutrophil elastase, IFN-γ, and IL-8 ↑
Broekema M, 2009[10]	35 current smokers 46 ex-smokers 66 never-smokers 44% used ICS	3 (0-64) 15 (0.4-47) 0 (0-0)	50 (21-64) 52 (25-68) 47 (19-71)	Bronchial biopsies and induced sputum	Neutrophils → in biopsies (current and ex) Eosinophils ↓ in biopsies (current and ex) Sputum neutrophil counts ↓ (current) Sputum neutrophil counts → (ex) Sputum eosinophil counts → (current and ex)
Sunyer J, 2003[11]	301 current smokers 406 ex-smokers, 713 never-smokers		34.5 ± 9.5	Blood	Eosinophil proportions ↓
Nagasaki T, 2013[91]	46 current smokers 65 ex-smokers 196 never-smokers No use of ICS	30 ± 19 27 ± 22 0 ± 0	47 ± 13 61 ± 15 49 ± 20	Blood	Neutrophil counts ↑ Eosinophil counts ↑

of chest wall compliance and decreased supporting tissue, such as elastic fibers, around alveolar ducts,[78] which may result in enlarged air spaces and increased air trapping. Elderly patients with asthma have an accelerated rate of decline in FEV_1 compared with healthy elderly individuals[4]; furthermore, they may have pronounced impairments in the small airways.[79] Pentosidine may be involved in one of the mechanisms underlying the accelerated decline in the lung function of elderly patients with asthma, although further studies are warranted.

IMMUNE SYSTEM AND AIRWAY INFLAMMATORY CELL PHENOTYPES

Immunosenescence or inflamm-aging is defined as changes in innate and adaptive immune responses associated with increasing age.[75,76] Age-related changes in immune function may alter susceptibilities to antigens, infection, malignancy, and autoimmunity. In the general population, serum total and allergen-specific IgE levels decrease with increasing age.[12,75,80] Bronchoalveolar lavage fluid (BALF) samples from elderly healthy never-smokers without allergies showed increased airway neutrophilis[81] and CD4+ T cells[82] when compared with samples from younger populations. The effects of increasing age on the balance between Th-1 and Th-2 cytokines can be altered by many factors.[83,84]

There are few reports regarding age-related processes in the immune system, including airway inflammatory cell types, of patients with asthma[85-87]. One study suggested that elderly patients with asthma had significantly increased percentages of sputum neutrophils.[86] In addition, increased airway neutrophils in elderly patients with asthma corresponds to increased levels of sputum neutrophil-related mediators such as matrix metalloproteinase 9, neutrophil elastase, and IL-8,[86] but not leukotriene B_4.[87] With regard to eosinophils, an earlier study showed that eosinophil activity was decreased in elderly patients with asthma.[85] Antigen-sensitized and antigen-challenged aged mice showed higher numbers of eosinophils in BALF than younger mice.[88]

Although FeNO reflects eosinophilic airway inflam-

mation, some caution may be necessary when interpreting FeNO levels in the elderly. Gelb *et al*. showed that FeNO and alveolar NO levels increased with increasing age in healthy subjects who had never smoked.[89] They speculated that the increase in NO levels in the elderly could be because of a decrease in capillary blood volume and decreased NO diffusion. Nonetheless, associations between higher FeNO levels and increasing age have not yet been established.[62,65,89]

SMOKING AND IMMUNOSENESCENCE IN PATIENTS WITH ASTHMA

As described above, several clinical studies on asthma found that neutrophilic inflammation may be the main characteristic of current smokers with asthma.[7-9] However, relatively young patients, mostly in their thirties,[7-9] were examined in these studies, probably to avoid patients with COPD as a comorbidity (Table 1). Mitsunobu *et al*. showed that exsmoking increased the rate of atopic predisposition among elderly patients with asthma.[90] Therefore, the effects of smoking on eosinophilic inflammation in patients with asthma, including the elderly, remain undetermined.

Table 2 Relationships between IgE/eosinophilic inflammation and age in never-smokers

	Correlation coefficient	*p* value
†IgE, IU/mL	-0.31	<.0001
†Blood eosinophil counts, /L	-0.16	0.028
†FeNO, ppb	-0.14	0.05

†Log-transformed. FeNO, fractional exhaled nitric oxide.
From reference 91.

To determine the effects of smoking on IgE/eosinophilic inflammation in elderly patients with asthma, we performed a cross-sectional analysis of the associations of serum IgE levels, blood eosinophil counts, and FeNO levels with smoking and age in steroid-naïve patients with asthma (n = 307).[91] Current smokers were excluded when analyzing factors that contributed to FeNO. We found that serum IgE levels, blood eosinophil counts, and FeNO levels consistently decreased with increasing age in never-smokers (Table 2). When patients were stratified on the basis of age, IgE levels and blood eosinophil counts were higher in current smokers, followed by ex-smokers and never-smokers only in the elderly group (≥64 years of age)[70] (Fig. 1, 2). In addition, exsmokers exhibited higher FeNO levels compared with never-smokers in the elderly group (Fig. 3). For younger patients (<64 years of age), significant differences with regard to smoking status were only ob-

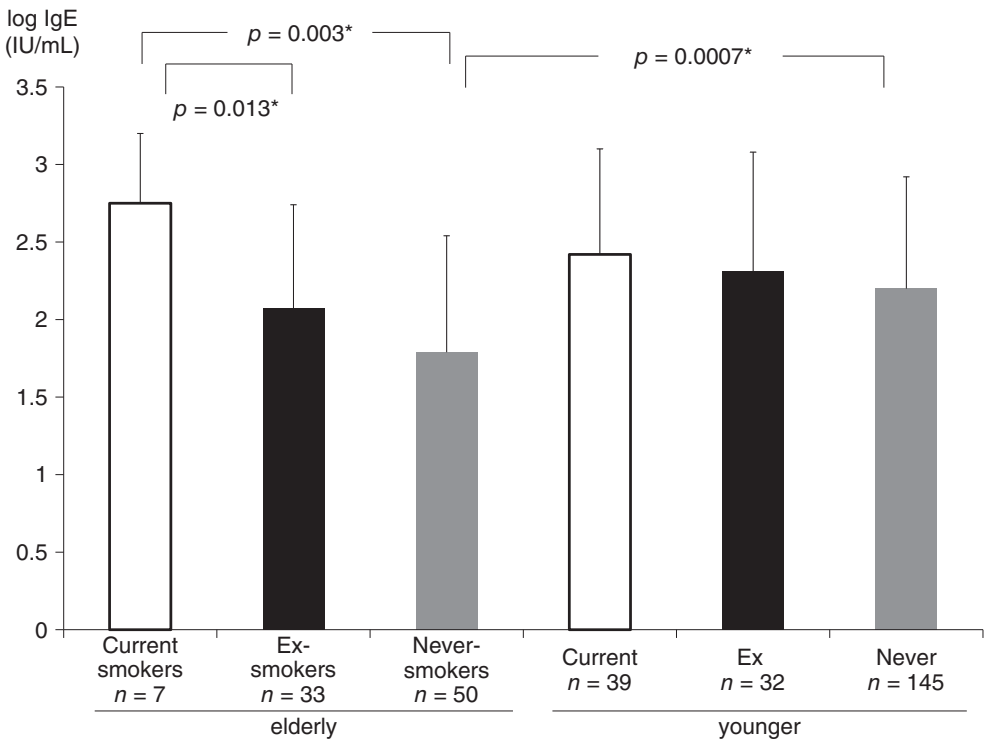

Fig. 1 Relationships between log-transformed serum IgE levels and smoking status when data were separately analyzed in the elderly patients (≥64 yr) (p = 0.003 using the Kruskal-Wallis test) and younger patients (<64 yr) with asthma. *Using the Wilcoxon rank-sum test. From reference 91.

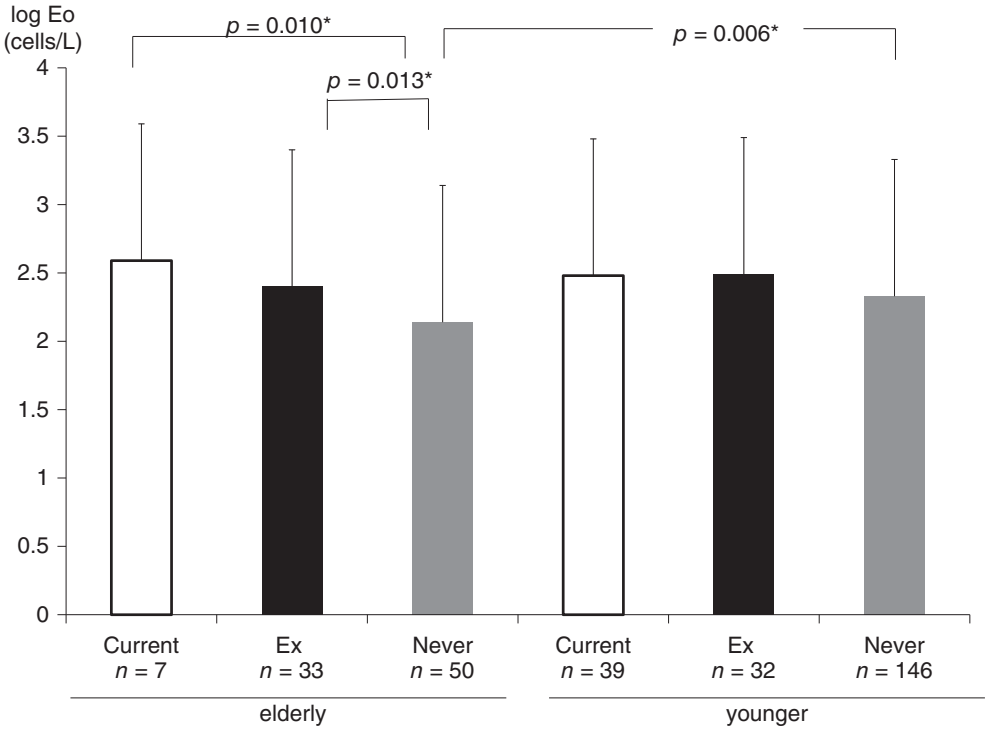

Fig. 2 Relationships between log-transformed blood eosinophil counts and smoking status when data were separately analyzed in the elderly patients ($p = 0.005$ using the Kruskal-Wallis test) and younger patients with asthma ($p = 0.050$ using the Kruskal-Wallis test). *Using the Wilcoxon rank-sum test.

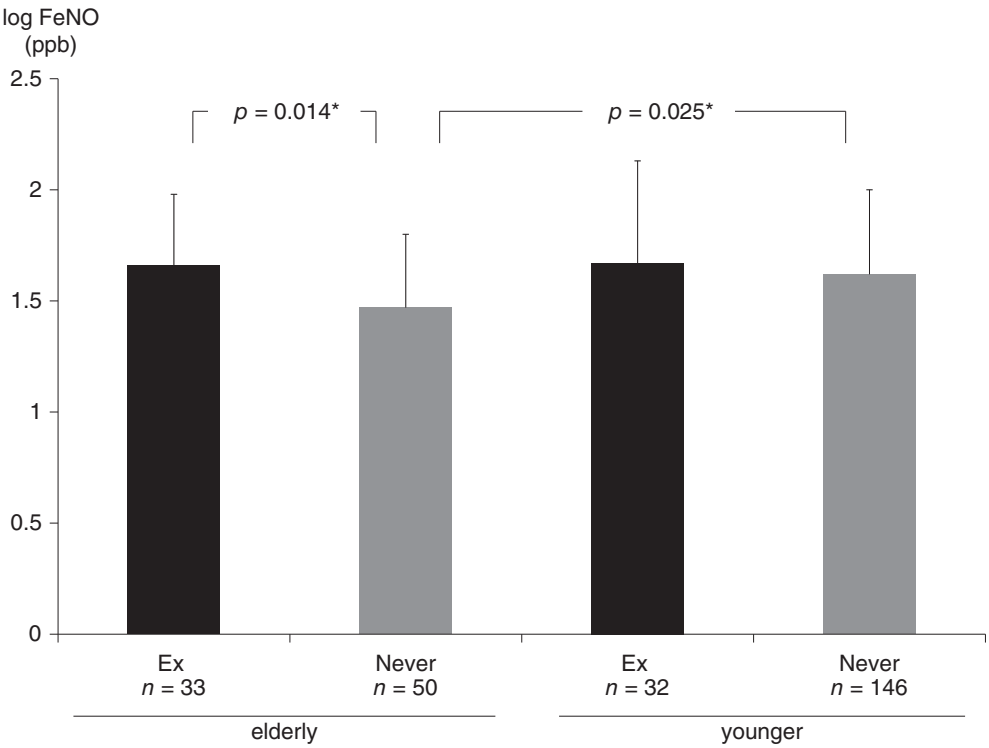

Fig. 3 Relationships between log-transformed fractional exhaled nitric oxide (FeNO) levels and smoking status when data were separately analyzed in the elderly and younger patients with asthma. *Using the Wilcoxon rank-sum test.

served for blood eosinophil counts (p = 0.05). Association analyses using continuous variables yielded similar findings, which were more pronounced when analyses were confined to atopic patients with asthma (data not shown).[91]

These findings may suggest that current and ex-smoking attenuates age-related decreases in IgE levels and maintain eosinophilic inflammation, particularly in atopic asthmatics. One possible mechanism underlying persistent eosinophilic inflammation in current and ex-smokers is thymic stromal lymphopoietin (TSLP), a pro-allergic cytokine induced by smoking, viral infection, and/or allergen exposure, which promotes Th2-skewed immune responses. We found that sputum TSLP levels (n = 139) were weakly but positively correlated with smoking pack-years (ρ = 0.29; p = 0.0005) and the percentage of sputum eosinophils (ρ = 0.17; p = 0.048). Moreover, sputum TSLP levels in current smokers (14.1 ± 17.7 pg/mL; p = 0.008) and ex-smokers (14.4 ± 22.6 pg/mL; p = 0.016) were significantly higher than those in never-smokers (6.4 ± 15.7 pg/mL).[91] TSLP may be involved in persistent eosinophilic inflammation in current and ex-smokers.

CONCLUSIONS

Asthma is a common disease, even among smokers and elderly individuals. Smokers or older patients with asthma may have altered baseline airway inflammation with increased neutrophilic inflammation compared with never-smokers or younger patients. However, it is possible that current smoking and ex-smoking attenuates age-related decreases in IgE levels and maintains eosinophilic inflammation, particularly in atopic patients with asthma. Clinically, the presence of both neutrophilic and eosinophilic inflammation should be fully recognized during the management of elderly smokers with asthma. This review may expand our understanding on the effects of smoking and aging on asthma by offering insights into their interactions in patients with atopic asthma.

ACKNOWLEDGEMENTS

This study received JSA Best Presentation Award 2011 from the Japanese Society of Allergology.

REFERENCES

1. Pedersen SE, Bateman ED, Bousquet J, Busse WW, Yoxall S, Clark TJ. Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the gaining optimal asthma control study. *J Allergy Clin Immunol* 2007;**120**:1036-42.
2. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Cook EF. Determinants of future long-term asthma control. *J Allergy Clin Immunol* 2006;**118**:1048-53.
3. McCoy K, Shade DM, Irvin CG *et al*. Predicting episodes of poor asthma control in treated patients with asthma. *J Allergy Clin Immunol* 2006;**118**:1226-33.
4. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;**339**:1194-200.
5. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;**57**:226-30.
6. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003;**168**:1308-11.
7. Boulet LP, Lemiere C, Archambault F, Carrier G, Descary MC, Deschesnes F. Smoking and asthma: Clinical and radiologic features, lung function, and airway inflammation. *Chest* 2006;**129**:661-8.
8. Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, Thomson NC. Smoking and airway inflammation in patients with mild asthma. *Chest* 2001;**120**:1917-22.
9. St-Laurent J, Bergeron C, Page N, Couture C, Laviolette M, Boulet LP. Influence of smoking on airway inflammation and remodelling in asthma. *Clin Exp Allergy* 2008;**38**:1582-9.
10. Broekema M, ten Hacken NH, Volbeda F *et al*. Airway epithelial changes in smokers but not in ex-smokers with asthma. *Am J Respir Crit Care Med* 2009;**180**:1170-8.
11. Sunyer J, Springer G, Jamieson B *et al*. Effects of asthma on cell components in peripheral blood among smokers and non-smokers. *Clin Exp Allergy* 2003;**33**:1500-5.
12. Barbee RA, Halonen M, Kaltenborn W, Lebowitz M, Burrows B. A longitudinal study of serum IgE in a community cohort: Correlations with age, sex, smoking, and atopic status. *J Allergy Clin Immunol* 1987;**79**:919-27.
13. Omenaas E, Bakke P, Elsayed S, Hanoa R, Gulsvik A. Total and specific serum IgE levels in adults: relationship to sex, age and environmental factors. *Clin Exp Allergy* 1994;**24**:530-9.
14. O'Connor GT, Sparrow D, Segal MR, Weiss ST. Smoking, atopy, and methacholine airway responsiveness among middle-aged and elderly men. The normative aging study. *Am Rev Respir Dis* 1989;**140**:1520-6.
15. Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004;**24**:822-33.
16. Adachi M, Ohta K, Morikawa A, Nishima S, Tokunaga S, Disantostefano RL. [Changes in asthma insights and reality in Japan(AIRJ) in 2005 since 2000]. *Arerugi* 2008;**57**:107-20(in Japanese).
17. Ikeue T, Nakagawa A, Furuta K *et al*. [The prevalence of cigarette smoking among asthmatic adults and association of smoking with emergency department visits]. *Nihon Kokyuki Gakkai Zasshi* 2010;**48**:99-103(in Japanese).
18. Skorge TD, Eagan TM, Eide GE, Gulsvik A, Bakke PS. The adult incidence of asthma and respiratory symptoms by passive smoking in uterus or in childhood. *Am J Respir Crit Care Med* 2005;**172**:61-6.
19. Cook DG, Strachan DP. Health effects of passive smoking. 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997;**52**:1081-94.
20. Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P. Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European community respiratory health survey: A cross-sectional study. *Lancet* 2001;**358**:2103-9.
21. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization

and smoking. *Am J Respir Crit Care Med* 2000;**162**:920-4.
22. Piipari R, Jaakkola JJ, Jaakkola N, Jaakkola MS. Smoking and asthma in adults. *Eur Respir J* 2004;**24**:734-9.
23. Gilliland FD, Islam T, Berhane K *et al*. Regular smoking and asthma incidence in adolescents. *Am J Respir Crit Care Med* 2006;**174**:1094-100.
24. Vesterinen E, Kaprio J, Koskenvuo M. Prospective study of asthma in relation to smoking habits among 14,729 adults. *Thorax* 1988;**43**:534-9.
25. Troisi RJ, Speizer FE, Rosner B, Trichopoulos D, Willett WC. Cigarette smoking and incidence of chronic bronchitis and asthma in women. *Chest* 1995;**108**:1557-61.
26. Polosa R, Knoke JD, Russo C *et al*. Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol* 2008;**121**:1428-34.
27. Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the genetics and environment of asthma. *Eur Respir J* 2000; **15**:470-7.
28. Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. *Chest* 1999;**115**:691-6.
29. Marquette CH, Saulnier F, Leroy O *et al*. Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. *Am Rev Respir Dis* 1992; **146**:76-81.
30. Radeos MS, Leak LV, Lugo BP, Hanrahan JP, Clark S, Camargo CA Jr. Risk factors for lack of asthma self-management knowledge among ed patients not on inhaled steroids. *Am J Emerg Med* 2001;**19**:253-9.
31. Janson C, De Marco R, Accordini S, Almar E, Bugiani M, Carolei A. Changes in the use of anti-asthmatic medication in an international cohort. *Eur Respir J* 2005;**26**:1047-55.
32. Yoon R, McKenzie DK, Miles DA, Bauman A. Characteristics of attenders and non-attenders at an asthma education programme. *Thorax* 1991;**46**:886-90.
33. James AL, Palmer LJ, Kicic E *et al*. Decline in lung function in the Busselton health study: The effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005; **171**:109-14.
34. Lazarus SC, Chinchilli VM, Rollings NJ *et al*. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;**175**:783-90.
35. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;**60**:282-7.
36. Gaki E, Papatheodorou G, Ischaki E, Grammenou V, Papa I, Loukides S. Leukotriene e(4) in urine in patients with asthma and COPD—the effect of smoking habit. *Respir Med* 2007;**101**:826-32.
37. Auerbach O, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking, 1955-1960 vs. 1970-1977. *N Engl J Med* 1979;**300**:381-6.
38. Birrell MA, Wong S, Catley MC, Belvisi MG. Impact of tobacco-smoke on key signaling pathways in the innate immune response in lung macrophages. *J Cell Physiol* 2008;**214**:27-37.
39. Triantafilou K, Vakakis E, Richer EA, Evans GL, Villiers JP, Triantafilou M. Human rhinovirus recognition in non-immune cells is mediated by Toll-like receptors and MDA-5, which trigger a synergetic pro-inflammatory immune response. *Virulence* 2011;**2**:22-9.
40. Wood L, Simpson J, Wark P, Powell H, Gibson P. Characterization of innate immune signalling receptors in virus-induced acute asthma. *Clin Exp Allergy* 2011;**41**:640-8.
41. Ferreira DS, Annoni R, Silva LFF *et al*. Toll-like receptors 2, 3 and 4 and thymic stromal lymphopoietin expression in fatal asthma. *Clin Exp Allergy* 2012;**42**:1459-71.
42. Droemann D, Goldmann T, Tiedje T, Zabel P, Dalhoff K, Schaaf B. Toll-like receptor 2 expression is decreased on alveolar macrophages in cigarette smokers and COPD patients. *Respir Res* 2005;**6**:68.
43. Venarske DL, Busse WW, Griffin MR *et al*. The relationship of rhinovirus-associated asthma hospitalizations with inhaled corticosteroids and smoking. *J Infect Dis* 2006; **193**:1536-43.
44. Nouri-Shirazi M, Guinet E. A possible mechanism linking cigarette smoke to higher incidence of respiratory infection and asthma. *Immunol Lett* 2006;**103**:167-76.
45. Vassallo R, Tamada K, Lau JS, Kroening PR, Chen L. Cigarette smoke extract suppresses human dendritic cell function leading to preferential induction of Th-2 priming. *J Immunol* 2005;**175**:2684-91.
46. Cozen W, Diaz-Sanchez D, James Gauderman W *et al*. Th1 and Th2 cytokines and IgE levels in identical twins with varying levels of cigarette consumption. *J Clin Immunol* 2004;**24**:617-22.
47. Taylor RG, Gross E, Joyce H, Holland F, Pride NB. Smoking, allergy, and the differential white blood cell count. *Thorax* 1985;**40**:17-22.
48. Kauffmann F, Neukirch F, Korobaeff M, Marne MJ, Claude JR, Lellouch J. Eosinophils, smoking, and lung function. An epidemiologic survey among 912 working men. *Am Rev Respir Dis* 1986;**134**:1172-5.
49. Kawaguchi M, Adachi M, Oda N, Kokubu F, Huang SK. IL-17 cytokine family. *J Allergy Clin Immunol* 2004;**114**: 1265-73.
50. Kuschner WG, D'Alessandro A, Wong H, Blanc PD. Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. *Eur Respir J* 1996;**9**:1989-94.
51. Van Eeden SF, Hogg JC. The response of human bone marrow to chronic cigarette smoking. *Eur Respir J* 2000; **15**:915-21.
52. Lams BE, Sousa AR, Rees PJ, Lee TH. Immunopathology of the small-airway submucosa in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**158**:1518-23.
53. Shan M, Cheng HF, Song L *et al*. Lung myeloid dendritic cells coordinately induce TH1 and TH17 responses in human emphysema. *Sci Transl Med* 2009;**1**:4ra10.
54. Mio T, Romberger DJ, Thompson AB, Robbins RA, Heires A, Rennard SI. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. *Am J Respir Crit Care Med* 1997;**155**:1770-6.
55. Tsukioka K, Toyabe S, Akazawa K. [Total and specific IgE levels in adolescents and adults with bronchial asthma]. *Nihon Kokyuki Gakkai Zasshi* 2010;**48**:409-18(in Japanese).
56. Van Hove CL, Moerloose K, Maes T, Joos GF, Tournoy KG. Cigarette smoke enhances Th-2 driven airway inflammation and delays inhalational tolerance. *Respir Res* 2008; **9**:42.
57. Seymour BW, Schelegle ES, Pinkerton KE *et al*. Secondhand smoke increases bronchial hyperreactivity and eosinophilia in a murine model of allergic aspergillosis. *Clin Dev Immunol* 2003;**10**:35-42.

58. Seymour BW, Pinkerton KE, Friebertshauser KE, Coffman RL, Gershwin LJ. Second-hand smoke is an adjuvant for t helper-2 responses in a murine model of allergy. *J Immunol* 1997;**159**:6169-75.

59. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: Clinical application and interpretation. *Thorax* 2006;**61**:817-27.

60. Ichinose M, Sugiura H, Yamagata S, Koarai A, Shirato K. Increase in reactive nitrogen species production in chronic obstructive pulmonary disease airways. *Am J Respir Crit Care Med* 2000;**162**:701-6.

61. Dweik RA, Boggs PB, Erzurum SC *et al*. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. *Am J Respir Crit Care Med* 2011;**184**:602-15.

62. Travers J, Marsh S, Aldington S *et al*. Reference ranges for exhaled nitric oxide derived from a random community survey of adults. *Am J Respir Crit Care Med* 2007; **176**:238-42.

63. Verleden GM, Dupont LJ, Verpeut AC, Demedts MG. The effect of cigarette smoking on exhaled nitric oxide in mild steroid-naive asthmatics. *Chest* 1999;**116**:59-64.

64. Malinovschi A, Janson C, Holmkvist T, Norback D, Merilainen P, Hogman M. Effect of smoking on exhaled nitric oxide and flow-independent nitric oxide exchange parameters. *Eur Respir J* 2006;**28**:339-45.

65. Matsunaga K, Yanagisawa S, Hirano T *et al*. Associated demographics of persistent exhaled nitric oxide elevation in treated asthmatics. *Clin Exp Allergy* **42**:775-81.

66. Chaudhuri R, Livingston E, McMahon AD *et al*. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med* 2006;**174**:127-33.

67. Lapperre TS, Postma DS, Gosman MM *et al*. Relation between duration of smoking cessation and bronchial inflammation in COPD. *Thorax* 2006;**61**:115-21.

68. Trimble NJ, Botelho FM, Bauer CM, Fattouh R, Stampfli MR. Adjuvant and anti-inflammatory properties of cigarette smoke in murine allergic airway inflammation. *Am J Respir Cell Mol Biol* 2009;**40**:38-46.

69. Reed CE. Asthma in the elderly: Diagnosis and management. *J Allergy Clin Immunol* 2010;**126**:681-7; quiz 88-9.

70. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010;**376**:803-13.

71. Banerji A, Clark S, Afilalo M, Blanda MP, Cydulka RK, Camargo CA Jr. Prospective multicenter study of acute asthma in younger versus older adults presenting to the emergency department. *J Am Geriatr Soc* 2006;**54**:48-55.

72. Bellia V, Pedone C, Catalano F *et al*. Asthma in the elderly: Mortality rate and associated risk factors for mortality. *Chest* 2007;**132**:1175-82.

73. Enright PL, McClelland RL, Newman AB, Gottlieb DJ, Lebowitz MD. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular health study research group. *Chest* 1999;**116**:603-13.

74. Diette GB, Krishnan JA, Dominici F *et al*. Asthma in older patients: Factors associated with hospitalization. *Arch Intern Med* 2002;**162**:1123-32.

75. Busse PJ, Mathur SK. Age-related changes in immune function: Effect on airway inflammation. *J Allergy Clin Immunol* 2010;**126**:690-9; quiz 700-1.

76. Hanania NA, King MJ, Braman SS *et al*. Asthma in the elderly: Current understanding and future research needs—a report of a national institute on aging (NIA) workshop. *J Allergy Clin Immunol* 2011;**128**:S4-24.

77. Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD. Characteristics of asthma among elderly adults in a sample of the general population. *Chest* 1991;**100**:935-42.

78. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging* 2006; **1**:253-60.

79. Kanazawa H, Tochino Y, Kyoh S, Ichimaru Y, Asai K, Hirata K. Potential roles of pentosidine in age-related and disease-related impairment of pulmonary functions in patients with asthma. *J Allergy Clin Immunol* 2011;**127**:899-904.

80. Freidhoff LR, Meyers DA, Marsh DG. A genetic-epidemiologic study of human immune responsiveness to allergens in an industrial population. *J Allergy Clin Immunol* 1984;**73**:490-9.

81. Meyer KC, Rosenthal NS, Soergel P, Peterson K. Neutrophils and low-grade inflammation in the seemingly normal aging human lung. *Mech Ageing Dev* 1998;**104**:169-81.

82. Meyer KC, Soergel P. Variation of bronchoalveolar lymphocyte phenotypes with age in the physiologically normal human lung. *Thorax* 1999;**54**:697-700.

83. Sakata-Kaneko S, Wakatsuki Y, Matsunaga Y, Usui T, Kita T. Altered Th1/Th2 commitment in human cd4+ t cells with ageing. *Clin Exp Immunol* 2000;**120**:267-73.

84. Sandmand M, Bruunsgaard H, Kemp K *et al*. Is ageing associated with a shift in the balance between type 1 and type 2 cytokines in humans? *Clin Exp Immunol* 2002;**127**: 107-14.

85. Mathur SK, Schwantes EA, Jarjour NN, Busse WW. Age-related changes in eosinophil function in human subjects. *Chest* 2008;**133**:412-9.

86. Nyenhuis SM, Schwantes EA, Evans MD, Mathur SK. Airway neutrophil inflammatory phenotype in older subjects with asthma. *J Allergy Clin Immunol* 2010;**125**:1163-5.

87. Nyenhuis SM, Schwantes EA, Mathur SK. Characterization of leukotrienes in a pilot study of older asthma subjects. *Immun Ageing* 2010;**7**:8.

88. Busse PJ, Zhang TF, Srivastava K, Schofield B, Li XM. Effect of ageing on pulmonary inflammation, airway hyperresponsiveness and t and b cell responses in antigen-sensitized and -challenged mice. *Clin Exp Allergy* 2007; **37**:1392-403.

89. Gelb AF, George SC, Camacho F, Fraser C, Flynn Taylor C, Shakkottai S. Increased nitric oxide concentrations in the small airway of older normal subjects. *Chest* 2011; **139**:368-75.

90. Mitsunobu F, Ashida K, Hosaki Y *et al*. Influence of long-term cigarette smoking on immunoglobulin E-mediated allergy, pulmonary function, and high-resolution computed tomography lung densitometry in elderly patients with asthma. *Clin Exp Allergy* 2004;**34**:59-64.

91. Nagasaki T, Matsumoto H, Nakaji H *et al*. Smoking attenuates the age-related decrease in IgE levels and maintains eosinophilic inflammation. *Clin Exp Allergy*. DOI: 10.1111/cea.12073.