Prevalence of asthma and wheezes among snow crab workers in western Japan: a cross-sectional study

Masanari Watanabe1, Jun Kurai1, Hiroyuki Sano2, Hiroya Kitano3, and Eiji Shimizu1

1Department of Respiratory Medicine and Rheumatology, Tottori University Faculty of Medicine, 36-1 Nishi-cho, Yonago, 683-8504, Japan; 2Department of Respiratory Medicine and Allergology, Kinki University Faculty of Medicine, 377-2 Ohnishi-gashi, Osakasayama, 589-0014, Japan; 3The Board of Directors, Tottori University, 36-1 Nishi-cho, Yonago, 683-8504, Japan

Abstract: Objectives: Few reports are available concerning the prevalence of asthma among snow crab workers in Japan. The object of this study was to estimate the prevalence of asthma and wheezes among Japanese snow crab workers and their associations with exhaled nitric oxide (FeNO) and YKL-40. Methods: Forty-nine snow crab workers enrolled in this study, which was cross-sectional by design and was conducted using a translated version of the European Community Respiratory Health Survey questionnaire. The levels of FeNO and serum YKL-40 were measured between September and October 2014. Results: The prevalences of current asthma and wheezes were 10.2% (95% CI, 3.4 to 22.2) and 12.2% (95% CI, 4.6 to 24.8), respectively. There was no association between these prevalences and the duration of snow crab employment. Six subjects’ FeNO levels exceeded 50 ppb, and nine subjects’ levels exceeded 25 ppb. Twelve subjects’ (25.5%) serum YKL-40 levels exceeded 77.2 ng/mL, which was 2 standard deviations above the mean for healthy subjects. However, there were no significant relationships among the prevalences for asthma and wheezes, FeNO, and serum YKL-40. Conclusions: This study provides information concerning the prevalences of asthma and wheezes among Japanese snow crab processing workers. J. Med. Invest. 63 : 74-79, February, 2016

Keywords: asthma, ECRHS, prevalence, snow crab processing, wheezes

INTRODUCTION

Occupational asthma (OA) is a substantial cause of occupational lung disease in many industrialized countries (1, 2). Its prevalence has been difficult to establish with precision due, in part, to ambiguous definitions and diagnostic criteria, as well as challenging work settings and limited surveillance data. Generally, OA has been implicated in 9 to 15% of adult asthma cases (3-6). The clinical and pathologic features of OA do not differ from non-occupational asthma. OA investigations have the potential to provide beneficial information about the effects of genetic, environmental, and behavioral interactions in adult onset asthma.

Snow crab harvesting and processing is an important industry in Japan; however, it is one of the most important causes of OA. It has been estimated that snow crab workers account for approximately 16% of all OA cases (7-9). The pathophysiology of snow crab OA is mediated through an immunologic mechanism involving an immunoglobulin E (IgE)-dependent mechanism (9-12). Specific IgE antibodies to crab meat and cooking water are induced by exposure to the crab proteins in dust, steam, and vapor that are generated by cleaning, steaming, boiling, washing, sawing, or crushing crab in processing plants (9-12). During these activities, crab proteins can become airborne and penetrate an individual’s airways. Existing research on OA in general suggests that snow crab OA is likely to be significant (13, 14). However, the socioeconomic impacts of snow crab OA have been poorly studied, especially in Japan.

Asthma is characterized by chronic airway inflammation, reversible airway narrowing, and airway hyperresponsiveness (15). Airway eosinophilic inflammation is one characteristic feature. Fractional-exhaled nitric oxide (FeNO) is a new method representing an eosinophilic airway inflammation that significantly correlates with sputum eosinophilia and asthma severity, instead of a sputum eosinophil count that is easily influenced by corticosteroid therapy (16). YKL-40, also called human cartilage glycoprotein-39 (HC gp-39), is produced at many cell inflammation sites and is secreted from macrophages and smooth muscle cells (17). In addition to FeNO, YKL-40 is associated with asthma severity, pulmonary function, and airway remodeling (17, 18).

In Japan, few studies have estimated the prevalence of asthma and wheezes among snow crab processing workers using a standardized questionnaire. Additionally, recent technological developments have led to improvements in the handicraft production of snow crab processing. The current prevalence of asthma and wheezes among snow crab processing workers may differ from that experienced in the past. To determine the prevalence of asthma among Japanese snow crab processing workers, a cross-sectional study was conducted in Western Japan with a standardized questionnaire. We also measured pulmonary function, the levels of FeNO, and the amount of YKL-40 that replenished according to the diagnosis and severity of asthma.

MATERIALS AND METHODS

Study design

The primary outcome variable was the prevalence of asthma and wheezes. The object of this study was to estimate the prevalence of asthma and wheezes among Japanese snow crab workers and their associations with exhaled nitric oxide (FeNO) and YKL-40.
wheezes among Japanese snow crab processing workers. A cross-sectional study was conducted using the European Community Respiratory Health Survey (ECRHS) questionnaire. We asked one snow crab processing company located in Sakaiminato City, Japan, to cooperate in this cross-sectional study. This company had 49 employees (15 male and 34 female), and all employees agreed to participate in the study. Door to door surveys were conducted in 2014, from September to October. This study was approved by an institutional ethics committee (Ethics Committee of Tottori University, Approval Number 2061), and all subjects gave their written informed consent before participating.

**Questionnaire**

To evaluate asthma symptoms, we asked questions similar to those appearing in the ECRHS. The Japanese version of the one-page ECRHS questionnaire was prepared, and the first page of this originally two-page questionnaire was prepared for a Stage One repeat study (19, 20). The validity of the questionnaire was guaranteed by first translating the Japanese version back into English (21). The questionnaire items can be found at http://www.ecrhs.org. In addition to assessing respiratory health, this questionnaire included demographic questions on age, gender, height, weight, and smoking history.

Whether a patient had ever experienced asthma that was confirmed by a doctor was assessed according to a positive answer to the question: “Have you ever had asthma?” (Q5), which was followed by: “Was this confirmed by a doctor?” (Q5.1). Current presence of asthma was defined according to the following criteria: [1] affirmative responses to Q5 and Q5.1, and [2] an affirmative response to the “Having at least one asthma-related symptom in the last 12 months” item (22). The subject who answered affirmatively to at least one question out of Qs1-4 was considered to have asthma-related symptoms. If subjects had had asthma-related symptoms in the past that remitted, they were excluded from the current asthma category.

**Measurement of pulmonary function and FeNO**

Pulmonary function tests were performed three consecutive times with a dry spirometer (Spiroshift SP-350COPD, Fukuda Denshi, Tokyo, Japan), and the highest values were recorded. The following parameters were measured: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and predicted FEV1%. FeNO was measured using NObreath (Bedfont Scientific, Maidstone, Kent, UK), following American Thoracic Society/European Respiratory Society recommendations (23).

**Measurement of YKL-40**

YKL-40 serum concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) kit for human chitinase 3-like 1 immunoassay (R&D Systems, Minneapolis, MN, USA). Samples were run in triplicate and were read using an automated ELISA reader (Model 680, Bio-Rad, Philadelphia, PA, USA).

**Statistical analysis**

The results are shown as means± standard deviations (SDs). SPSS Statistics software (Japanese ver. 21.0 for Windows; IBM Japan, Tokyo, Japan) was used for all statistical analysis. The prevalence of current asthma with 95% confidence intervals (CI) was estimated for all the participants aged 20-69 years. Fisher’s exact tests were performed to assess the differences in prevalence between males and females. Differences in YKL-40 and FeNO according to employment duration were analyzed by a Kruskal-Wallis one-way ANOVA. A χ2-test was performed to estimate the difference in YKL-40 between smokers and non-smokers. Associations among YKL-40 and FeNO levels were assessed using linear regression analysis. All quoted P values are two-sided, and the significance level was set at 0.05.

**RESULT**

Table 1 presents the characteristics of the subjects. The prevalences of current asthma and wheezes were 10.2% (95% CI, 3.4 to 22.2) and 12.2% (95% CI, 4.6 to 24.8), respectively (Table 2). None of the subjects were undergoing treatment for asthma or other respiratory diseases. Table 3 shows the prevalence of asthma-related symptoms. Table 4 presents the prevalence of wheezes according to total duration of employment as a snow crab processing worker. There were no statistically significant differences between employment duration in terms of current asthma or wheezes prevalence. Table 5 shows pulmonary functioning according to presence of current asthma and wheezes and the significance was not detected. Table 6 presents pulmonary functioning according to total duration of employment as a snow crab processing worker. There were no statistically significant differences in pulmonary functioning based on employment duration. Figure 1A shows the relationship between the levels of YKL-40 and the duration of employment. Two samples were missing YKL-40 measurements due to blood clotting. The levels of YKL-40 in subjects who had worked in this profession for more than 20 years were significantly higher than those in the <1 year- and 1 to 4-year groups. In contrast, there were no significant differences between smokers and non-smokers (Fig. 1B). Figure 2 shows the levels of

| Table 1. Descriptive characteristics of the study population |
|-----------------------------------------------------------|
| Variables | n (%) |
| Gender (male/female) | 49 (30.6/69.4) |
| Mean age (in years)± S.D. | 47.73 ±14.51 |
| Smoking history | |
| Non-smoker | 26 (53.1) |
| Past smoker | 4 (8.2) |
| Current smoker | 19 (38.8) |
| Duration of employment as snow crab worker | |
| < 1 year | 17 (34.7) |
| 1-4 years | 11 (22.4) |
| 5-9 years | 6 (12.2) |
| 10-19 years | 7 (14.3) |
| ≥ 20 | 8 (16.3) |
| Pulmonary function | |
| FVC (L) | 3.21 ± 0.89 |
| FEV1% (%) | 80.92 ± 6.54 |
| Predicted FEV1% (%) | 97.20 ± 16.8 |

Data are shown as the mean± S.D., or as numbers with percentages in parentheses (%). FEV1 : forced expiratory volume in 1 second ; FEV1% : ratio of FEV1 to FVC ; FVC : forced vital capacity ; S.D. : standard deviation.

| Table 2. Prevalence of current asthma and wheezes |
|------------------------------------------------|
| Total (% 95% CI) |
| Current asthma | 10.2 (3.4-22.2) |
| Wheezes | 12.2 (4.6-24.8) |

Data are presented as percentages with 95% CI in parentheses. CI : confidence interval.
FeNO dividing into employment duration and demonstrates that no significant relationships were found between them. In five subjects who did not experience wheezes over the previous 12 months, FeNO levels exceeded 50 ppb. The FeNO levels of one subject who had experienced wheezes within the previous 12 months exceeded 50 ppb. In contrast, the FeNO levels of four out of six subjects who had experienced wheezes did not exceed 25 ppb. Figure 3 shows the relationship between the levels of YKL-40 and FeNO. No significant associations were found.

DISCUSSION

Asthma is a serious global health problem affecting all age groups (24). Its prevalence is increasing in many countries. Certain occupational exposures are associated with asthma. Previous studies of occupational exposures among various groups of workers have suggested that asthma prevalence may be notably high among snow crab processing workers (7-9). However, few reports exist concerning the prevalence of asthma among snow crab processing workers in Japan. As far as we know, this is the first study to estimate the prevalences of asthma and wheezes among Japanese snow crab processing workers using a standard questionnaire. The prevalences of current asthma and wheezes among Japanese snow crab processing workers were 10.2% (95% CI, 3.4 to 22.2) and 12.2% (95% CI, 4.6 to 24.8), respectively. These data provide fundamental information concerning respiratory and public health among Japan’s harvesting and processing workers.

Table 3. Prevalence of asthma-related symptoms

| Variables                          | Total % (95% CI) |
|------------------------------------|------------------|
| (Q1) Wheezes                       | 12.2 (4.6-24.8)  |
| (Q1.1) Wheezes with breathlessness | 6.1 (1.3-16.9)   |
| (Q1.2) Wheezes without a cold      | 8.2 (2.3-19.6)   |
| (Q2) Waking with chest tightness   | 0 (0-7.3)        |
| (Q3) Waking with shortness of breath | 2 (0.1-10.9)  |
| (Q4) Waking with cold              | 16.3 (7.3-29.7)  |
| (Q5) Ever had asthma               | 12.2 (4.6-24.8)  |
| (Q5.1) Ever had asthma confirmed by a doctor | 12.2 (4.6-24.8)  |

Data are presented as percentages with 95% CI in parentheses. CI : confidence interval.

Table 4. Prevalence of wheezes by snow crab worker employment duration

| Employment duration as snow crab worker | < 1 year % (95% CI) | 1-4 years % (95% CI) | 5-9 years % (95% CI) | 10-19 years % (95% CI) | ≥ 20 % (95% CI) | P value |
|----------------------------------------|---------------------|----------------------|----------------------|------------------------|-----------------|---------|
|                                        | 11.8 (1.5-36.4)     | 18.2 (2.3-51.8)      | 0 (0-39.3)           | 28.6 (3.7-71)          | 0 (0-31.2)      | 0.399   |

Data are presented as percentages with 95% in parentheses. CI : confidence interval.

Table 5. Pulmonary function in the study population

| Variables            | Subjects without current asthma and wheezes (n=42) | Subjects with current asthma (n=5) | Subjects with wheezes (n=6) |
|----------------------|----------------------------------------------------|-----------------------------------|-----------------------------|
| FVC (L)              | 3.21 ±0.95                                         | 3.30 ±0.45                        | 3.10 ±0.39                  |
| FEV1% (%)            | 80.86 ±6.70                                        | 81.20 ±4.77                       | 80.23 ±4.77                 |
| Predicted FEV1% (%)  | 96.71 ±17.0                                        | 97.00 ±8.66                       | 80.23 ±5.82                 |

Data are shown as the mean± SD. FVC : forced vital capacity ; FEV1% : forced expiratory volumes in one second (FEV1) and ratio of FEV1 to FVC. SD : standard deviation.

Table 6. Pulmonary function according to snow crab worker employment duration

| Variables             | < 1 year | 1-4 years | 5-9 years | 10-19 years | ≥ 20 | P value |
|-----------------------|----------|-----------|-----------|-------------|------|---------|
| FVC (L)               | 3.83 ±0.84| 2.86 ±0.85| 2.72 ±0.67| 3.90 ±0.49  | 2.96 ±0.88 | 0.638   |
| FEV1% (%)             | 80.98 ±5.86 | 81.56 ±7.40 | 84.82 ±5.83 | 81.42 ±5.91 | 76.93 ±7.14 | 0.914   |
| Predicted FEV1% (%)   | 98.76 ±13.70 | 89.55 ±14.20 | 96.17 ±12.61 | 102.35 ±13.21 | 97.88 ±28.00 | 0.098   |

Data are shown as the mean± S.D. FEV1 : forced expiratory volume in 1 second ; FEV1% : ratio of FEV1 to FVC ; FVC : forced vital capacity ; S.D. : standard deviation.
There have been few studies on the prevalence of asthma and asthma symptoms among Asian countries using a standardized questionnaire. Recently, Fukutomi et al. conducted a population-based cross-sectional study of the prevalence of asthma and wheezes by administering the ECRHS questionnaire to Japanese adults (19). They found that the prevalences of asthma and wheezes among Japanese adults aged 27-79 years were 4.2% (95% CI, 9.7 to 10.5%) and 10.1% (95% CI, 9.7 to 10.5%), respectively. The prevalences of asthma and wheezes among Japanese snow crab processing workers in this study were higher than those among other Japanese adults. Several studies have demonstrated that snow crab processing workers have a high prevalence of asthma and wheezes in
Western countries (7-9). The results of this study suggest that the occupational exposure in Japanese harvesting and processing may account for a substantial proportion of asthma experienced by snow crab processing workers.

YKL-40 is a chitinase-like protein that is released from neutrophils and macrophage (25, 26). It is involved in inflammation, tissue remodeling, and host defense (25, 26). It is also known to increase in the serum and lungs of patients with asthma and is correlated with asthma severity and airway remodeling (27, 28). In this study, there were no significant differences between the YKL-40 levels of subjects with and without wheezes. However, twelve subjects in this study (24.5%) exceeded the mean YKL-40 serum value, which was 36.0±20.6 ng/mL in healthy subjects, based on the information from the ELISA kit for YKL-40 (www.RnDSystems.com), plus 2 SDs (77.2 ng/mL).

Additionally, YKL-40 in subjects who had worked in the industry for more than 20 years was significantly higher than in those who worked in the industry for less than 5 years. Studies have shown that the intensity of exposure according to duration and amount is an important determinant of sensitization and asthma caused by respiratory sensitizers (3). Snow crab is graded as moderate a moderate sensitizer based on evidence from the Royal College of General Practitioners’ three-star system for rating OA caused by worksites (29). Snow crab processing plants may present severe enough risk to be able to increase serum YKL-40 levels.

Based on the general recommendations of the recently published ATS Clinical Practice Guideline, if a FeNO-value is below 25 ppb, there is thought to be no steroid-sensitive inflammation present (30). In contrast, a value greater than 50 ppb is likely to be associated with steroid-sensitive airway inflammation, which is substantially reflected in eosinophilic airway inflammation (30-32). It is also well acknowledged that smoking reduces FeNO (33). Although five subjects did not experience wheezes, based on their questionnaire responses, their FeNO values exceeded 50 ppb. This suggests that their airways were inflamed. This inflammation could be associated with environmental exposure from the snow crab processing. Previous studies showed that FeNO did not have any diagnostic value in non-eosinophilic asthma (30-32). Although a value greater than 50 ppb is likely to be associated with environmental exposure from the snow crab processing workers have a relatively high rate of asthma and wheezes compared to other Japanese adults. No other Japanese study has yet investigated the prevalence of asthma among snow crab processing workers. Additionally, as far as we know, this is the first study to assess the levels of fractional exhaled nitric oxide FeNO and YKL-40 among snow crab processing workers. This study may provide fundamental health information regarding OA in Japanese snow crab processing workers.

In conclusion, this cross-sectional study used a Japanese version of the ECRHS questionnaire to determine the prevalences of current asthma and wheezes among Japanese snow crab processing workers. As compared to other Japanese adults, Japanese snow crab processing workers have more than two times the risk of prevalent asthma.

ACKNOWLEDGMENTS

We would like to thank Esumi (Tokyo, Japan) for their statistical analysis support and Editage (www.editage.jp) for their English language editing.

CONFlict OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

JK, MW, HS, and ES conceived the study. JK, MW, HS, and HK participated in the design. JK and MW collected the data. JK and MW performed the analysis. JK and MW drafted the manuscript. ES contributed to the final approval of the version to be published. All authors had full access to all study data and take full responsibility for the data integrity and analysis accuracy.

REFERENCES

1. Meredith S, Nordman H: Occupational asthma: measures of
frequency from four countries. Thorax 51 : 435-40, 1996
2. Mannino DM : How much asthma is occupationally related? Occup Med 15 : 359-368, 2000
3. Mapp CE, Boschetto P, Maestrelli P, Fabbri LM : Occupational asthma. Am J Respir Crit Care Med 172 : 280-305, 2005
4. Blanc PD, Toren K : How much asthma can be attributed to occupational factors? Am J Med 107 : 580-587, 1999
5. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp CE, Milton D, Schwartz D, Toren K, Vieg G : American Thoracic Society statement : occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 167 : 787-797, 2003
6. Maestrelli P : Natural history of adult-onset asthma : insights from model of occupational asthma. Am J Respir Crit Care Med 169 : 331-332, 2004
7. Cartier A, Malo JL, Forest P, Lafrance M, Pineau L, St-Aubin JJ, Dubois JY : Occupational asthma in snow crab-processing workers. J Allergy Clin Immunol 74 : 261-269, 1984
8. Gauthier D, Cartier A, Housse D, Horth-Susin L, Jong M, Swanson M, Lehrer S, Fox G, Neis B : Occupational asthma and allergy in snow crab processing in Newfoundland and Labrador. Occup Environ Med 67 : 17-23, 2020
9. Housse D, Gauthier D, Neis B, Cartier A, Horth-Susin L, Jong M, Swanson MC : Gender and snow crab occupational asthma in Newfoundland and Labrador, Canada. Environ Res 101 : 163-174, 2006
10. Cartier A, Malo JL, Ghezzo H, McCants M, Lehrer SB : IgE sensitization in snow crab-processing workers. J Allergy Clin Immunol 78 : 344-348, 1986
11. Malo JL, Chretien P, McCants M, Lehrer S : Detection of snow crab antigens by air sampling of a snow crab production plant. Clin Environ Exp Allergy 27 : 75-78, 1997
12. Weytjens K, Cartier A, Malo JL, Chretien P, Essiembre F, Lehrer S, Swanson M : Aerosolized snow crab allergens in a processing facility. Allergy 54 : 892-893, 1999
13. Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, Blanc PD, Brooks SM, Cowl CT, Daroowalla F, Harber P, Lemiere C, Liss GM, Pacheco KA, Redlich CA, Rowe BB, Heitzer J : Diagnosis and management of work-related asthma : American College Of Chest Physicians Consensus Statement. Chest 134 : 1S-41S, 2008
14. Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, Maestrelli P, Rooyackers J, Schlunssen V, Vandenplas O, Wilken D : ERS Task Force on the Management of Work-related Asthma. Guidelines for the management of work-related asthma. Eur Respir J 39 : 529-545, 2012
15. Ohla K, Ichinose M, Nagase H, Yamaguchi M, Sugita H, Tohda Y, Yamauchi K, Adachi M, Akiyama K : Japanese Society of Allergology, Japanese Guideline for Adult Asthma 2014. Allergol Int 63 : 293-333, 2014
16. Kharitonov SA, Davies R, Robbins RA, Logan-Sinclair R, Robbins RA, Yates D, Keatings V, Barnes PJ : Increased nitric oxide in exhaled air of asthmatic patients. Lancet 343 : 133-135, 1994
17. Kim MA, Shin YS, Pham le D, Park HS : Adult asthma biomarkers. Curr Opin Allergy Clin Immunol 14 : 49-54, 2014
18. Lai T, Chen M, Deng Z, L Y, Wu D, Li D, Wu B : YKL-40 is correlated with FEV1 and the asthma control test (ACT) in asthmatic patients : influence of treatment. BMC Pulm Med 15 : 1, 2015
19. Fukutomi Y, Nakamura H, Kobayashi F, Taniguchi M, Konno S, Nishimura M, Kawagishi Y, Watanabe J, Komase Y, Akazawa A, Yakiyama K : Nationwide cross-sectional-population-based study on the prevalences of asthma and asthma symptoms among Japanese adults. Int Arch Allergy Immunol 153 : 280-287, 2010
20. de Marco R, Zanolini ME, Accordini S, Signorelli D, Marinoni A, Bugiani M, Lo Casco V, Woods R, Burney P : A new questionnaire for the repeat of the first stage of the European Community Respiratory Health Survey : a pilot study. Eur Respir J 14 : 1044-8, 1999
21. Watanabe J, Taniguchi M, Takahashi K, Nakagawa T, Ooya Y, Akazawa A, Yakiyama K : Validation of ECHRS Questionnaire in Japanese to use for nation-wide prevalence study of adult asthma (in Japanese). Arerugi 55 : 1421-1428, 2006
22. Janson C, Chinn S, Jarvis D, Burney P : Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. Eur Respir J 10 : 1795-1802, 1997
23. American Thoracic Society, European Respiratory Society : ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 171 : 912-930, 2005
24. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2014 (revision). Bethesda : National Institutes of Health, 2014
25. Voit B, Price PA, Johansen JS, Sorensen O, Benfield TL, Nielsen HJ, Calafat J, Borregaard N : YKL-40, a mammalian chitinase member of the chitinase family, is a matrix protein of specific granules in human neutrophils. Proc Assoc Am Physicians 110 : 351-360, 1998
26. Kirkpatrick RB, Emery JG, Connor JR, Dodds R, Lysko PG, Rosenberg M : Induction and expression of human cartilage glycoprotein 39 in rheumatoid inflammatory and peripheral blood monocyte-derived macrophages. Exp Cell Res 237 : 46-54, 1997
27. Kim MA, Shin YS, Pham le D, Park HS : Adult asthma biomarkers. Curr Opin Allergy Clin Immunol 14 : 49-54, 2014
28. Rathcke CN, Vestergaard H : YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res 55 : 221-227, 2006
29. Baur X : A compendium of causative agents of occupational asthma. J Occup Med Toxicol. 2013 ; 8 : 15, 2013
30. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Lehigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR : American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline : interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 184 : 602-615, 2011
31. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, Pavord ID, Paton J, Reddick CE, Taylor DR, Zamel N : Exhaled nitric oxide in pulmonary diseases : a comprehensive review. Chest 138 : 692S-692S, 2010
32. Schneider A, Faderl B, Schwarzbach J, Welker L, Taylor DR, Pacheco KA, Redlich CA, Rowe BB, Heitzer J : Diagnosis and management of work-related asthma : American College Of Chest Physicians Consensus Statement. Chest 134 : 1S-41S, 2008
33. Baur X : A compendium of causative agents of occupational asthma. J Occup Med Toxicol. 2013 ; 8 : 15, 2013
34. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Lehigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR : American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline : interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 184 : 602-615, 2011
35. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, Pavord ID, Paton J, Reddick CE, Taylor DR, Zamel N : Exhaled nitric oxide in pulmonary diseases : a comprehensive review. Chest 138 : 692S-692S, 2010
36. Schneider A, Faderl B, Schwarzbach J, Welker L, Taylor DR, Pacheco KA, Redlich CA, Rowe BB, Heitzer J : Diagnosis and management of work-related asthma : American College Of Chest Physicians Consensus Statement. Chest 134 : 1S-41S, 2008