

Original article

Incidence and host determinants of work-related rhinoconjunctivitis in apprentice pastry-makers

Background: The authors recently assessed the incidence and determinants of immunologic sensitization to flour in apprentice pastry-makers. The aim of this work was to determine the incidence of work-related rhinoconjunctivitis (RC) symptoms and their determinants.

Methods: For this 188/230 entrants (81.7%) were evaluated before starting exposure to flour, and again 10.8 and 16.8 months after. Questionnaires and skin prick testing to common and work-related allergens were administered at each visit. Bronchial responsiveness to methacholine was assessed at baseline in all subjects and in a subgroup at follow-up.

Results: Thirty subjects (16.1%) reported new work-related RC symptoms (13.1 per 100 person-years); in three subjects (1.6%), these were accompanied by incident skin prick test reactivity to flour-derived allergens. Skin prick test reactivity to grass pollens (OR = 3.0, 95% CI, 1.3–6.7) and to pets (OR = 2.5, 95% CI, 1.1–5.9), persistent rhinitis (OR = 3.1, 95% CI, 1.1–8.4), seasonal RC (OR = 2.5, 95% CI, 1.1–5.5), RC on contact with pets (OR = 2.3, 95% CI, 1.03–5.0) and skin prick test reactivity to wheat flour (OR = 10.5, 95% CI, 2.3–46.8), assessed at baseline, were significantly associated with the incidence of work-related RC symptoms. Multivariate logistic regression analysis yielded significant OR of skin prick test reactivity to wheat flour at baseline (OR = 7.1, 95% CI, 1.7–35.1) and persistent rhinitis (OR = 3.9, 95% CI, 1.01–9.6) for the incidence of work-related RC symptoms. Increased bronchial hyperresponsiveness at follow-up was more frequent, although not significantly, in subjects positive to skin prick test to flour on entry and reporting new work-related symptoms (3/5), than in other subjects (4/17).

Conclusions: The incidence of work-related RC symptoms among apprentice pastry-makers was high (16.1% 30/186), while a minority (3/30) also developed skin prick test reactivity to flour. Skin prick test reactivity to wheat flour and persistent allergic rhinitis on starting exposure to flour are significant determinants for the development of work-related RC symptoms.

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Bakers are at risk of sensitization and work-related symptoms due to flour-derived allergens, mites and enzymes (1–3). Prevalence rates of sensitization vary from 5 to 28% for wheat flour and from 2 to 16% for alpha-amylase. Rhinoconjunctivitis (RC) symptoms are commonly encountered in bakers; in his extensive review, Houba and colleagues quote prevalence figures that vary from 7 to 30% (1). However, only a minority of these subjects also shows evidence of immunologic sensitization. For example, in a recent cross-sectional survey of 679 employees, Smith and collaborators found that 22% reported upper respiratory tract symptoms but only 2.6% had occupational RC as diagnosed by occupational physicians with skin prick tests and interviews (4).

Few longitudinal studies have been performed in bakers. De Zotti and co-workers followed 125 trainee

bakers for up to 30 months after their training began; of these, 47 (38%) subjects completed the survey. The cumulative incidence of sensitization to wheat or alpha-amylase was 10.1% at 30 months. The cumulative incidence of work-related symptoms (rhinitis and/or chest symptoms) was 9.0% at the end of the study (5). Cullinan and colleagues prospectively followed a cohort of 300 workers who had not been exposed to flour prior to their current occupation. Twelve percent developed skin prick test reactivity to flour and/or alpha-amylase, 29%, RC symptoms and 12%, chest symptoms during the period since entering the workforce (6).

The present study, also set up in the early nineties (7), was designed as a prospective study in which the cohort members were recruited when entering their apprenticeship in pastry making; the host characteristics assessed at

the first visit are therefore considered as pre-exposure. The aim of this study was to assess the incidence of work-related RC symptoms both alone and in conjunction with specific skin prick test reactivity to flour—hereafter referred to as probable occupational rhinoconjunctivitis—as well as to identify their determinants. An ancillary objective was to appraise changes in bronchial responsiveness in subjects who developed the study outcomes.

Material and Methods

Subjects

The recruitment procedure has been described in detail elsewhere (7). Briefly, the sampling unit consisted of teaching institutions offering a vocational program in pastry making within 480 km of Montreal, Quebec. From the nine schools corresponding to these criteria, the two with the largest number of full-time students were chosen, and five were selected at random from among the remaining schools. The total number of students potentially registered in pastry making at these institutions was 207 per year. In September 1991, that represented 69% of Quebec's first-year students in this program. Recruitment of 230 students took place between September 1993 and November 1995; two schools were offering a 12-month program (64 subjects) and five, an 18-month program (166 subjects) in pastry making. All students starting a vocational program in these institutions were invited to an information session presented by two of the authors (DG and J-LM). The students were eligible for the cohort study provided that they had not been exposed to flour in an apprenticeship or a job for 3 months or more before entering the career program, as assessed during a preliminary visit. The protocol was approved by the Ethics Committee of Sacré-Coeur Hospital. All subjects gave written consent to their participation in the study.

Methods

The study subjects took part in a baseline assessment when entering the program and to one or two subsequent visit(s). The first follow-up assessment took place, on average, 10.8 months after entering the program for all subjects and the second, on average, 16.8 months after entering the 18-month program. At each visit, the students answered a respiratory symptom questionnaire derived from the standardized questionnaire of the International Union against Tuberculosis and Lung Diseases (IUATLD) (8). At each follow-up visit, nasal, ocular, respiratory, and skin symptoms on exposure to flour in the pastry workshop were assessed, allowing us to establish whether the symptomatology was work-related. Work-related nasal symptoms included runny nose, stuffy nose and sneezing, while ocular symptoms included itchy eyes, watery eyes and red eyes.

Skin tests were done with the prick method (9), using 11 common inhalants: mixed trees, mixed grass, and ragweed pollens; *Alternaria*, *Aspergillus*, and *Hormodendrum*; feathers; *Dermatophagoides farinae* and *D. pteronyssinus*; and cat and dog dander (Omega, Montreal, Canada). Histamine phosphate (1/200 g/ml) was used as a positive control, and diluent (glycerine, 50%), as a negative control. The largest wheal diameter was assessed 10–15 min after introducing the antigen. A positive reaction was defined as a wheal ≥ 3 mm in the absence of reaction to the diluent and in the presence of a positive reaction to histamine phosphate. Atopy was defined as at least two positive reactions to 11 common inhalants.

Skin prick tests were also performed with extracts from aeroallergens potentially present in the student's work areas. These

consisted of mixed flours, wheat and bran flour and alpha-amylase (Omega, Montreal, Canada). The criterion for a positive reaction to a specific allergen was the same as for common allergens.

All extracts were obtained before the beginning of the study in sufficient amounts to perform the estimated number of skin tests through the end of the project. Each glycerinated extract was prepared from the same batch. The same nurse performed skin prick testing throughout the study.

New specific skin prick test reactivity was defined as a change in skin reactivity to at least one flour extract (from absent to present). The incidence of work-related RC symptoms was defined as the onset of work-related nasal and/or ocular symptoms during follow-up. The incidence of probable occupational RC was defined as the incidence of both a positive skin prick test to at least one flour allergen and work-related RC symptoms.

Spirometry with the assessment of FEV1 and forced vital capacity (FVC) was carried out using a Collins apparatus (Survey/1 Plus Collins, Baintree, MA, USA) according to published standards (10). Methacholine inhalation tests were performed using a Wright's nebulizer (Roxon Meditech Ltd, Montreal, Quebec, Canada) (output = 0.14 ml/min) at tidal volume breathing for 2 minutes according to guidelines slightly modified from those of the European Respiratory Society (11). The procedure for performing the methacholine test was modified as described elsewhere to take into account the lack of an onsite physician (12). The maximum concentration of methacholine administered was 32 mg/ml. The provocative concentration causing a 20% fall in FEV1 (PC₂₀) was interpolated from individual dose-response curves drawn on a semi-logarithmic scale using non-cumulative doses.

Reference values for FEV1 and FEV1/FVC were taken from Knudson and co-workers (13). Bronchial hyperresponsiveness (BHR) was set at 16 mg/ml (14).

The methacholine challenge test was repeated at follow-up visits and until the end of the study for subjects who developed skin prick test reactivity to one of the work-related allergens, as well as for a sub-sample of subjects with negative skin tests to the specific allergens or with no new positive test. The latter group was constituted of up to two subjects matched with skin prick test positive cases on the basis of atopy (yes/no), baseline PC₂₀ (≤ 16 vs. > 16 mg/ml), and school attended.

Statistical analysis

The study outcomes were incidence of work-related RC symptoms and incidence of probable rhinoconjunctivitis. The incidence was expressed (1) as a proportion of the subjects who attended at least one of the follow-up visits, and (2) by person-years at risk in the cohort (i.e., the number of subjects who attended at least one of the follow-up visits and for the period during which they remained at risk [time to the end of the study or time to the development of RC symptoms or time to leaving the apprenticeship]). Independent variables in the analyses were assessed at baseline: atopy, age, sex, smoking, immediate skin reaction to grass pollen, immediate skin reaction to pets, PC₂₀ (≤ 32 vs. > 32 mg/ml), persistent rhinitis, rhinitis on contact with pets, rhinitis in the pollen season (seasonal rhinitis), respiratory symptoms suggestive of asthma under usual conditions, or such conditions as cold air and exercise, and respiratory symptoms on contact with pets and pollen, and physician-diagnosed asthma. Univariate logistic regression analyses were first carried out separately for comparison between the subjects with incident work-related RC symptoms and the other subjects in the cohort who remained disease-free up to the end of the study. We used the -2 log-likelihood test with a P -value < 0.1 as a criterion to retain each variable that was included in the multivariate logistic regression analysis. Odds ratios (OR) and 95% confidence intervals

(CI) were estimated. Statistical analyses were performed using the SPSS software package (version 9.1 for Windows, Chicago, IL, USA).

Results

The baseline and follow-up characteristics of this cohort are summarized in Table 1. Of the 230 subjects who attended the initial assessment, 191 (83.0%) attended the first follow-up assessment; among the 166 subjects in the 18-month program for whom a second follow-up visit was scheduled, 101 (60.2%) attended that visit. Three apprentices reported work-related RC on entry; these subjects were excluded from the analyses, leaving 188 subjects in whom this outcome could be detected during the study. The majority of students were women. Nearly 50% of students were atopic and 14% had had a previous diagnosis of asthma. A minority of subjects (15%) were smokers. From 20 to 25% of the students reported respiratory symptoms. A smaller proportion of students who quit the apprenticeship were skin prick test positive to grass pollen at baseline assessment compared with those who remained in the cohort (22.2% vs. 33.3%). Eleven subjects showed skin prick test reactivity to at least one program-related allergen (wheat, bran and/or mixed flours).

Eight subjects (8/186, 4.3%) developed skin prick test reactivity to flour-derived allergens during the study (Table 2) (15). The most frequent causal agent of skin reactivity was wheat. No subject developed skin prick test reactivity to alpha-amylase; the flour used did not contain detectable amounts of this enzyme preparation based on results obtained through radioimmunoassay techniques on dust samples collected in the breathing zone of participants (16).

Thirty subjects developed work-related RC symptoms, 25/191 at the first follow-up assessment and 5/101 at the second (Table 2). All 30 subjects developed nasal symptoms (19 reported one nasal symptom and 11, two). Of these, eight also had ocular symptoms (four reported one ocular symptom and four, two). Three of these 30 subjects also reported new work-related respiratory symptoms suggestive of asthma (wheezing). Five were skin prick test positive to a work-related allergen on entry in the study, and three others developed skin prick test reactivity during the study. There were therefore three subjects ($3/186 = 1.6\%$, or 1.3 per 100 person-years) who satisfied our definition of incident probable occupational RC. These three subjects had a normal PC_{20} (> 16 mg/ml) on entry and did not acquire bronchial hyperresponsiveness nor work-related respiratory symptoms during the follow-up. In contrast, among the five subjects with skin prick test reactivity to a work-related agent on entry and incident work-related RC symptoms, two developed bronchial hyperresponsiveness; two were hyperresponsive to methacholine on entry and remained so, with one of

Table 1. Selected characteristics of the apprentices on entry into the cohort study by status of participation in the follow-up evaluation

	Participants (<i>n</i> = 188)*	Non-Participants (<i>n</i> = 39)
General		
Sex, M/F (<i>n</i>)	45/143	11/28
Age, years, mean $\pm$ SD	27.3 $\pm$ 9.9	30.7 $\pm$ 10.3
Asthma, <i>n</i> (%)	26 (13.8%)	3 (7.7%)
Current smokers, <i>n</i> (%)	28 (14.9%)	8 (20.5%)
Specific respiratory symptomatology, <i>n</i> (%)		
Wheezing	40 (21.3%)	7 (17.9%)
Dyspnea	43 (22.9%)	9 (23.1%)
Awakening with cough	14 (7.5%)	4 (10.3%)
Exercise-induced respiratory Sx	51 (27.1%)	9 (23.1%)
Cold-air-induced respiratory Sx	46 (24.5%)	9 (23.1%)
Rhinitis on contact with pets	69 (36.7%)	17 (43.6%)
Respiratory Sx on contact with pets	17 (9.0%)	3 (7.7%)
Rhinitis in the pollen season	24 (12.8%)	3 (7.7%)
Respiratory Sx in the pollen season	10 (5.3%)	1 (2.6%)
Atopy†, <i>n</i> (%)	87 (47.5%)‡	19 (52.8%)§
Cat dander	36 (19.7%)‡	7 (19.4%)§
Dog dander	21 (11.5%)‡	4 (11.1%)§
Grass pollen	61 (33.3%)‡	8 (22.2%)§

Sx, symptoms.

* Number of subjects at risk of developing work-related RC symptoms (three subjects reporting this outcome at baseline were excluded).

† At least two positive reactions to 11 common inhalants.

‡ Two subjects refused skin testing.

§ Three subjects refused skin testing.

them also developing work-related respiratory symptoms; the fifth subject reacted to the diluent at the first bronchial challenge and had a normal PC_{20} at the last visit. Table 3 shows that among the subjects with incident work-related RC symptoms, both those skin prick test positive to flour on entry and those who became positive subsequently were reacting principally to wheat flour.

Table 4 gives the results of the univariate analyses. Persistent rhinitis, seasonal rhinitis (i.e., rhinitis in the pollen season), rhinitis on contact with pets, skin prick test reactivity to grass pollen, to pets, to wheat and to bran on entry, were all significantly associated with the incidence of work-related RC symptoms. Having a $PC_{20} \leq 32$ mg/ml (measurable PC_{20}) at baseline was not significantly associated with the development of work-related RC symptoms (OR = 1.7, 95% CI, 0.8–3.9). Twenty-two of the thirty (73%) incident cases of work-related RC were atopic. No factor was significantly associated with the incidence of work-related RC symptoms in the subgroup of atopic subjects. In the subgroup of non-atopic subjects, symptoms of rhinitis on contact with pets was the factor most strongly related to the incidence of work-related RC symptoms, and almost significantly, with an OR of 5.1 and a 95% CI from 0.99 to 25.6.

A multivariate logistic regression analysis was performed to evaluate the independent effect of factors found significant in the univariate analyses on the

Table 2. Incidence of specific sensitization to flour antigens and/or of work-related RC symptoms

Outcome	Prevalence on entry	Incidence during follow-up		
		<i>n</i>	%	By 100 person-years
Specific sensitization to flour	10/191*	8/186†	4.3	4.2
Work-related RC symptoms	3‡	30/188	16.0	13.1
Probable occupational rhinoconjunctivitis	0	3/186	1.6	1.3

* 191 = number of subjects present at follow-up.

† Five subjects refused skin testing.

‡ Excluded from the denominator for calculations of the incidence figures; probable occupational rhinoconjunctivitis: specific sensitization + work-related RC symptoms.

incidence of work-related RC. Being skin prick test positive to wheat flour at baseline (OR = 7.1, 95% CI, 1.7–35.1) and reporting persistent rhinitis before entering the program (OR = 3.9, 95% CI, 1.0–9.6) were the only factors that remained significantly associated with the development of work-related RC. Adjustment for age, sex and smoking did not modify these associations. Among the 25 subjects who reported persistent rhinitis, 21 also answered that they had rhinitis in the pollen season or upon contact with pets confirmed, respectively, by positive skin prick tests to pollen in 14 subjects and to cat and/or dog dander in two other subjects.

Discussion

This study shows that RC symptoms at work are common in students starting an apprenticeship in pastry making. The cumulative incidence of work-related RC symptoms after a 16.8-month follow-up was 16.1%. High prevalence figures of work-related RC symptoms in bakers have previously been reported. In a recent cross-sectional study, Smith and co-workers found that 22% of 679 bakers reported upper-respiratory-tract symptoms of some kind (4). Similar to previous findings, only a minority of our symptomatic subjects (3/30) met the definition of probable occupational RC, defined as a combination of skin prick test reactivity to a flour-derived allergen and work-related RC symptoms. Smith and collaborators found that only 3/679 subjects (0.4%) had symptoms thought to result from allergy to wheat flour (4). In a health-surveillance project of 3450 employees exposed to flour dust, the same group of researchers found that 66 employees (1.9%) had asthma or rhinitis attributable to sensitization to allergens in the workplace (17). Cullinan and collaborators examined 300 bakers not previously employed for a median period of 40 months (6). The incidence of work-related RC symptoms was 11.8 cases per 100 person-years, a figure very close to the 13.1 cases per 100 person-years found in our study. The incidence of skin prick test reactivity

Table 3. Distribution of sensitization to flour-derived allergens on entry and during follow-up according to incidence of work-related rhinoconjunctivitis symptoms

Sensitization	Work-related rhinoconjunctivitis symptoms	
	Present (<i>n</i> = 30)	Absent (<i>n</i> = 158)
Wheat flour		
On entry	5	3
During follow-up	3	2
Mixed flours		
On entry	–	2
During follow-up	–	2
Bran flour		
On entry	4	2
During follow-up	1	2
At least one		
On entry	5	5
During follow-up	3	5
Absent	22	148

to flour and/or alpha-amylase was 2.2 cases per 100 person-years, compared with 4.2 per 100 person-years for flour in the current study. In our study, incident work-related rhinitis accompanied by incident skin prick test reactivity to flour was rare (1.3 per 100 person-years), confirming the suggestion that nasal symptoms in bakers are mostly due to non-allergic inflammation characterized by activation of neutrophils and fibroblasts (18).

The follow-up period for detecting probable occupational RC was relatively short (maximum of 24 months), which can explain the low incidence figure for this outcome (1.4%). We expect that a longer follow-up period would most likely increase the incidence figures. In their series of 66/3450 employees who had both sensitization to a flour-derived allergen and work-related symptoms, Smith and co-workers estimated that the mean latency period was 7.2 years (17).

The skin prick test reactivity reported in this study was strictly to flour-derived allergens (mainly wheat flour) and not to alpha-amylase, this due to the fact that the study subjects rarely handled flour containing enzymatic additives. In contrast, among European bakers, the trend is toward increased occurrence of allergic hypersensitivity to enzymes as compared with flour-derived allergens, reflecting both the widespread practice of adding enzymes to flour (1–3) and the high antigenicity of these compounds. In the series by Smith and co-workers mentioned above, 55/66 subjects (83%) with skin prick test reactivity to an occupational allergen and work-related symptoms were positive to an enzyme, principally alpha-amylase (17). It is to be expected that a proportion of sensitized subjects would have symptoms. In our study, three of the eight subjects with new onset skin prick test reactivity to flour and four of the 10 positive to a flour allergen on entry developed work-related RC symptoms. This is slightly lower than the findings from a study carried out

Table 4. Effect of host characteristics measured at baseline on the incidence of work-related RC symptoms

	Number of subjects with characteristic		OR*	95% CI
	RC symptoms 30	No RC symptoms 158		
Persistent rhinitis	25	98	3.1	1.1–8.4
Seasonal rhinitis	16	50	2.5	1.1–5.5
Rhinitis on contact with pets	16	53	2.3	1.03–5.0
Skin reactivity to grass pollens†	16	61	3.0	1.3–6.7
Skin reactivity to pets†	11	30	2.5	1.1–5.9
Skin reactivity to allergens present in the workplace†				
Wheat flour	3	5	10.5	2.3–46.8
Mixed flours	2	0	–	–
Bran flour	2	4	12.2	2.1–69.9
At least one flour-derived allergen	5	5	6.2	1.7–23.1

* Odds ratios and 95% confidence intervals (CI) estimated by univariate logistic regression analyses.

† 186/188 subjects accepted skin testing.

in 224 individuals employed in small bakeries in the UK, in which 57 (25%) were found to be sensitized to an occupational allergen; of these, 31 (54%) had work-related symptoms (19).

Although we found some cases that fulfilled the definition of probable occupational RC (that is, work-related RC symptoms and skin reactivity to at least one flour-derived allergen), the incidence of skin prick test reactivity was low (8/186) and not different from that found in two other cohorts studied by the authors and used as controls, consisting of 394 laboratory animal technicians and 110 dental hygiene technicians (15), among whom 10 and five subjects, respectively, became skin prick test positive to flour. Sensitization may therefore have occurred at work or in the general environment. Interestingly, there was an association between the onset of skin prick test reactivity to grass pollen and that of specific skin reactivity to wheat flour.

To our knowledge, no study has assessed the effect of host risk factors on the incidence of work-related RC by multivariate analysis. We found that the presence of persistent rhinitis and skin prick test reactivity to a flour-derived allergen on entry into the program were independently associated with the incidence of work-related RC symptoms. It is logical to assume that subjects with previous persistent rhinitis symptoms may be at greater risk of developing RC symptoms on exposure to flour, which might represent, in this population an irritant-induced symptomatology, but mostly an allergic-based symptomatology. The reasons for baseline sensitization to flour are only hypothetical, but cross-reactivity with grass pollen is highly suspected to play a role, indeed 9/10

subjects (90%) skin prick test positive to flour on entry were also positive to grass pollen as compared with 30.7% among those negative to flour. Such a phenomenon further stresses the importance of obtaining information on baseline immunologic sensitization in prospective studies (7, 15). The effect of occupational factors was also considered in this study. The number of hours of work with flour in each training institution was used as an estimate of exposure. The range of time of exposure was very small, which may explain, at least in part, the lack of a significant association between the number of hours of exposure to flour and the development of work-related rhinoconjunctivitis.

To our knowledge, no study has assessed non-specific bronchial responsiveness prospectively in bakers or pastry makers. Our findings, although nonsignificant and based only on a small number of subjects, suggest that after exposure to flour begins, bronchial hyperresponsiveness may develop earlier and more often in subjects who acquired immunologic sensitization to this proteinaceous agent before entry into the apprenticeship than in those without sensitization to flour. These results need to be confirmed.

We are aware of only one other published prospective study in trainee bakers using questionnaire and skin testing (5). A follow-up survey of 125 trainee bakers was carried out at 6, 18 and 30 months after the baseline assessment. Data were available in 91, 72 and 47 subjects at those respective intervals. Ten subjects developed work-related respiratory symptoms (these may include RC and/or lower respiratory symptoms consistent with asthma) and seven of the 10 demonstrated skin reactivity to a program-related allergen at one or another of the follow-up visits. Thus, 7/125 (5.6%, and approximately 2.15 per 100 person-year) fulfilled a definition of possible occupational RC and/or asthma, an estimate close to our findings of 1.3 per 100 person-years. In addition, De Zotti and colleagues also found an association between a history of allergic disease and the development of work-related respiratory symptoms (5). We also found that seasonal and persistent rhinitis were associated with work-related RC when considered separately in a univariate analysis.

The participation rate of 83% at follow-up was satisfactory and greater than reported in previous similar studies (5). However, we cannot dismiss the possibility that the incidence of work-related RC symptoms may be slightly underestimated, given that among the 39 subjects who left the program, the proportion reporting rhinitis on contact with pets at baseline was greater than in those who remained in the program; because rhinitis on contact with pets was identified here as a risk factor for the development of work-related RC symptoms, we could speculate that those who left the program had developed similar symptoms. However, this is unlikely, as in a follow-up study of those who left the school, only four of

the 36 subjects traced (11%) reported new work-related RC symptoms before leaving the program (20).

In conclusion, the latency period for the development of symptoms and skin prick test reactivity to work-specific allergens indeed seems to be longer for pastry-making apprentices than for apprentices exposed to laboratory animals (15) or latex (21). Associated factors such as persistent allergic rhinitis and skin prick test reactivity to a work-related antigen at the beginning of exposure may suggest different types of work-related RC, a non-allergic form, as well as a specific and a non-specific allergic form. This hypothesis warrants confirmation.

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