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Epidemiology of occupational asthma

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In industrialized countries, occupational asthma has become the most common occupational lung disease. The epidemiology of occupational asthma provides important information about the general prevalence of the disease, the prevalence in different occupations, personal risk factors (eg, atopy, smoking), and the degree and type of exposures that influence the development of occupational asthma. Such information can provide the basis for establishing preventative and control surveillance programs to reduce risks for occupational asthma and to reduce its morbidity.

Epidemiologic definitions: the basics

Understanding the terminology and methods used in epidemiologic studies of occupational asthma is critical for developing studies and interpreting their results. A number of epidemiologic terms can be source of confusion. Prevalence is a measurement of the number of people in a population with a particular disease at or over a period of time. Mathematically, prevalence (P) is equal to the number of cases (C) divided by the number of persons in a population: $P = C/N$ [1]. Incidence, a term often confused with prevalence, is a measurement of the occurrence of new cases over a particular period of time [2]. Incidence usually is expressed as number of new cases per person-years; mathematically, incidence (I) is proportional to the number of new diseases in a population (A) over a net time, usually person years (PY): $I = A/PY$ [1].

To make epidemiologic studies more meaningful, many methods have been developed to adjust incidence or prevalence rates for factors such as smoking, age, gender, or race. Factor-adjusted prevalence and incidence rates can be used to calculate relative risk, which is defined as the risk for disease or death in

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Table 1
Data used to determine sensitivity and specificity

Test result	Disease	No disease	Total
Positive	A	B	A + B
Negative	C	D	C + D
Total	A + C	B + D	A + B + C + D

Abbreviations: A, true positives; B, false positives; C, false negatives; D, true negatives.

exposed people divided by the risk for the same disease in nonexposed people [1]. Odds ratio is a term that frequently is confused with relative risk. It is defined as the number of exposed people with a disease multiplied by the number of unexposed people without a disease divided by the product of unexposed people with the disease and the number of exposed people with the disease [2].

Sensitivity and specificity and how they relate to screening tests are two terms that are essential to the understanding of epidemiology. The sensitivity of a test is defined as the proportion of people with a disease that have a positive test result. Specificity is defined as the percentage of people without a particular disease that have negative test results. Data that are used to determine sensitivity and specificity are presented (Table 1) [1].

Mathematically, sensitivity can be calculated as A (true positives) divided by A plus C (true positives + false negatives) multiplied by 100. The greater the sensitivity of a test, the more likely it is that the test will detect the disease of interest. A highly sensitive test is useful for ruling out a particular disease. Conversely, specificity can be calculated as D (true negatives) divided by D plus B (true negatives + false positives) multiplied by 100. Tests with high specificity are used to confirm the presence of a disease. A delicate balance must be maintained between sensitivity and specificity. A test that is too sensitive would have too many false-positives results, and a test that is too specific would miss true-positive results [2].

Whereas sensitivity and specificity describe the accuracy of a test, positive and negative predictive values estimate the likelihood of a particular disease given a test result. The positive predictive value is the percentage of people who actually have a disease with a positive test result: A (true positives) divided by A plus B (true positives + false positives) multiplied by 100. This value gives an estimate of how likely a disease is if the test is positive. The negative predictive value is the probability of the absence of a disease when the screening test is negative: D (true negatives) divided by D plus C (true negatives + false negatives) multiplied by 100 [1].

Epidemiologic approaches and outcome measures in occupational asthma

Several different study approaches and designs are used to study epidemiology of occupational asthma. A randomized, controlled trial can provide information

about the efficacy of interventions or treatments, such as medications. Treatment trials can give information regarding the pathogenesis of occupational asthma. The strength of this study design is that all aspects are under the control of the researcher. A weakness is that random sampling of the entire eligible population usually is not achieved. The design tends to be strengthened when the researcher and subjects are blinded to the intervention. Occupational asthma cases could be included in a drug trial or be the target of a treatment trial to test a hypothesis. This type of study is considered to be observational, because the subjects' exposures to airborne contaminants rely on many different factors, such as employers, self-selection, and economics. These varieties of circumstances are beyond the control of the researcher [3].

In a cohort study, which can be used to assess incidence, a defined population is studied at a given point and then is followed to measure the number of new cases of a disease over time. This study design supplies the only source of direct evidence on host and exposure factors as determinants of occupational asthma. It may be possible to determine the level of exposure that induces asthma if the exposure is measured in enough detail. A potential weakness of this design is the survivor bias that occurs when workers with health problems leave work. Subjects who leave the workplace during the course of the study must be followed to prevent underestimation of the incidence of occupational asthma. Affected individuals may be working for such a short amount of time before quitting that they are missed as being a part of the workforce. Observational studies using cohort and prevalence designs may be strengthened by the inclusion of a similar unexposed population. Cohort studies of workers who are at risk for occupational asthma are resource demanding and are performed less frequently than are other types of observational studies [3].

Case-control studies are used to identify and study risk factors in a population. Once a case subject is identified, he or she is compared with a normal subject to evaluate host factors and environmental risks. In the study of occupational asthma, conclusions from this study design can be strengthened if used in conjunction with a cohort or prevalence study. Subjects with similar exposures can be matched to evaluate host factors, or subjects with similar host factors, such age, gender, or race, can be matched to evaluate exposure factors. Despite its strength in investigating causal factors, a case-control study of occupational asthma frequently needs to be performed in conjunction with a cohort study because of the uncertainty about whether a control group is representative of the larger populations that are examined in cohort and prevalence studies [3].

Prevalence or cross-sectional studies are usually workforce based and give information about the amount of disease and potential determinants at a given point in time (point prevalence) or about the cases up to particular time (cumulative prevalence). This study design often defines the cohort that is followed. It is prone to selection and survivor bias, because, as in cohort studies, workplace turnover can be rapid in cases of occupational asthma. This design is most often used in studies of occupational asthma; however, cause and effect cannot be distinguished using this design (eg, it cannot be determined whether

atopy or bronchial hyperresponsiveness preceded or followed the first clinical symptoms of asthma) [3].

Case series or clinical case studies that summarize clinical experience can serve as the basis for initiating a larger investigation. This study design provides material for laboratory study of mechanisms (eg, bronchial challenge), but it does not provide specific information on workplace exposure [3].

Surveys

Surveys are important tools for collecting information. Many surveys are population based and are used to gather data from a defined group of people, usually at the workplace. Surveys are used most often in conjunction with prevalence studies [3].

Questionnaires

To evaluate the risk for occupational asthma in a target population (eg, workforce), health outcomes should be measured. A questionnaire that is given or administered to each worker can achieve this task. A questionnaire permits information acquisition in a standardized and repeatable fashion. It replaces the clinical interview so that each subject's history is taken uniformly, and there are no open-ended questions or personalization of the process. Questionnaires are non-invasive and easy to administer, but they also have multiple shortcomings. Studies have demonstrated a poor correlation between bronchial hyperresponsiveness and questionnaire answers. Because bronchial hyperresponsiveness can occur without the presentation of symptoms, a questionnaire may fail to capture evidence of pathology. Workers may not have symptoms at the time of filling out the questionnaire and may develop symptoms several years later. Workers also may over- or under-report symptoms for secondary gain. In general, the questionnaire is a sensitive but not specific tool for studying occupational asthma [3].

Immunologic assessments

Immunologic assessments are important tools in the epidemiologic studies of occupational asthma, because atopy is the single most important risk factor for asthma. Skin prick testing for common inhalant allergens, such as cat, pollens, and house dust mites, are easy to perform and do not have serious side effects. High-molecular-weight proteins, such as latex, cause sensitization by producing specific immunoglobulin E (IgE) antibodies, as can some low-molecular-weight agents, such as anhydrides, which act as haptens [3,4]. Immunologic sensitization usually occurs before the development of asthma symptoms, so skin testing and measurement of blood IgE antibody levels to a specific antigen are useful and objective tools. For occupational asthma that is caused by certain low-molecular-weight agents (eg, isocyanates), specific IgE or IgG antibodies sometimes are found in only a minority of affected individuals. Use of standardized methods for skin testing or measurement of specific antibodies in these cases are not possible [3].

Spirometry

Multiple types of functional assessments can be used to measure outcomes in studies of occupational asthma. Pulmonary function testing often must be performed at the workplace, a requirement that can pose several different problems. Workplace environments are not as easily controlled as hospital and clinic environments. When using a spirometer, the temperature of the workplace and the machine must be monitored. Adequate space and electrical power must be available, and a knowledgeable technician must be on hand to handle proper machine calibration and any technical difficulties. Subjects may not give their best efforts when performing lung function tests, resulting in poor reproducibility [5].

A vast assortment of pulmonary function tests can be performed. Deciding which type to chose depends on cost, ease of testing, length of testing, reproducibility, and standardization. Common measurements used in the evaluation occupational asthma include peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV_1), forced vital capacity, and maximum midexpiratory flow rate [3].

Assessing FEV_1 in subjects before, during, and after work can be useful in detecting work-related asthma. FEV_1 results can be affected by the normal diurnal variations in lung function. Such variations are the lowest in the early morning and are greatest in the early afternoon. Several factors can affect the change in FEV_1 that occurs during the work shift, including tobacco smoke, baseline FEV_1, and immediate skin test results to common allergens. Despite these variables, measuring the cross-shift change in FEV_1 is a viable method for monitoring nonallergic airway response to a variety of exposures at work [3].

Measurement of PEF rate

Serial measurements of PEF rates (PEFRs) can be valuable in assessing occupational asthma. PEFR monitoring has been used in several different epidemiologic studies and has fair correlation with the results of specific challenge testing. Although an inexpensive and simple way to measure lung function, PEFR monitoring has some disadvantages. Workers are required to monitor PEFR three to four times per day for weeks to months at a time. Correct performance of measurements can be difficult to maintain. It takes time to demonstrate the proper technique for recording PEFR, and falsification of results may occur if measurements are recorded and performed without onsite supervision [3]. PEFR monitors are now available that can record the time and result of all patient efforts. These tools can be useful for comparing several PEFR measurements obtained at one time (to determine the reproducibility and reliability of the results).

A nonspecific challenge test with a substance, such a methacholine or histamine, or with cold or dry air (eucapnic voluntary hyperventilation) can be valuable in the assessment of obstructive lung disease. If a worker develops nonspecific bronchial hyperresponsiveness after such a challenge and has evidence of immunologic sensitization to a high-molecular-weight agent, it is likely that the worker will develop an immediate bronchial reaction when exposed to that agent. The

relationship between nonspecific bronchial hyperresponsiveness and immunologic sensitization has been recognized since the 1950s and originally was described by Tiffeneau [3]. Nonspecific bronchial hyperresponsiveness is not specific enough to diagnose occupational asthma on its own and must be used in conjunction with a questionnaire or immunologic assessment [3].

Specific challenge testing has been used successfully in the diagnosis of occupational asthma. It is associated with some problems, however. This type of testing is time consuming, and it can take up to several days to perform the graded challenges, making it difficult to use onsite. These tests can be dangerous to the patient and must be performed by an experienced physician, whereas some nonspecific challenge tests do not have this requirement. Specific challenge tests are good for confirming the diagnosis of occupational asthma once a subject is identified as at risk through other screening methods. Such testing should be performed in a safe setting, such as a hospital or well-equipped laboratory [3].

Assessment of risk

Risk factors

Many factors influence the host response after exposure to agents in the workplace. The physiochemical properties of the offending substance, the length and intensity of exposure, and the nature of the use of the substance have roles in the development of respiratory sensitization. The intensity of the exposure that causes initial sensitization in a worker is most likely much higher than the intensity that provokes symptoms in an already sensitized worker. Because of this difference, direct-reading monitors for chemicals such as formaldehyde and diisocyanates may not be sensitive enough to pick up low-level readings that could result in symptoms once sensitization has developed. Studies have shown that there is a dose–response relationship between many agents and the prevalences of sensitization, nonspecific bronchial hyperresponsiveness, and asthma. Such agents include several high-molecular-weight antigens, such as those from flour and laboratory animals, and low-molecular-weight antigens, such as those from colophony, acid anhydride, and western red cedar [3,6].

Cigarette smoking may worsen the symptoms of occupational asthma. It also causes an increased risk for sensitization and asthma through an IgE-mediated mechanism [6]. Venables and colleagues found a relationship between smoking and occupational asthma among laboratory animals that were exposed to tetrachlorophthalic anhydride [7,8]. This relation also has been found with exposure to platinum salts [9,10], snow crabs [11], green coffee beans, and ispaghula [12]. With exposure to platinum salts, smoking, and not atopy, has been shown to be the most important risk factor for occupational asthma. If the agent produces asthma through non–IgE-mediated mechanisms, nonsmokers are more commonly affected than are smokers [10].

Atopy has been shown to be the biggest risk factor for sensitization to high-molecular-weight agents, such as laboratory animals and latex [13]. However, atopic individuals who are exposed to low-molecular-weight agents are not at increased risk for occupational asthma [14,15]. Atopic workers should be warned about working in a high-risk workplace and should undergo regular screening tests so that that disease can be detected early, ideally before symptoms develop.

Genetics also have a role in the predisposition to sensitization. HLA class II markers have been studied in subjects with isocyanate-induced asthma. It was found that the presence of HLA-DQB1 * 0503 was associated with an increased risk for asthma, whereas the presence of HLA-DQB1 * 0501 was protective [6]. Other genetic markers studied include HLA B15 and DR4, which were found in workers who were allergic to laboratory animals, and HLA DR3, found in workers who were sensitized to trimellitic anyhride [6].

Epidemiologic bias in risk assessment

Several sources of bias in epidemiologic studies of occupational asthma must be considered. Bias is defined as a systemic error in a study that leads to distortion of the results. The most important type of bias in the investigation of occupational asthma is selection bias, which occurs when the study population is not representative of the target population in terms of exposure or health. This bias can result from the healthy-worker effect, in which susceptible workers are less likely to join a workplace that would place them at risk or these workers quit before they can be counted as a part of the workforce. The survivor effect also causes selection bias, because workers with asthma symptoms often quit their jobs or rearrange their duties to reduce exposure to the agent. Such workers may not be included on the list of at-risk workers or on the list of employees.

Information bias occurs during the gathering of information about exposure or the health of contrasting study groups [1]. Workers who believe that their asthma symptoms result from workplace exposures have recall bias, because they are more likely to recall all exposures at work than are workers who do not experience symptoms [3]. Confounding bias occurs when another variable is present that can cause or prevent the disease under investigation. In a study of lung function in patients with occupational asthma, smoking could be considered a confounder if the rates of tobacco use varied among patient groups. With different degrees of workplace exposure, this confounding bias would make it impossible to independently sort out the effects of the suspected occupational agent unless the information on smoking was reported and included in the analysis [3].

Screening and surveillance

Although they often are used interchangeably, the terms screening and surveillance describe different activities with different objectives [16]. According to Thorner and Remein, ‘‘[t]he basic purpose of screening for disease detection is

to separate from a large group of apparently well persons those who have a high probability of having the disease under study, so that they may be given a diagnostic workup and, if diseased, brought to treatment" [17]. Screening must be rapid, simple, and inexpensive, and it usually is performed using a survey that is given to a large number of workers who are believed to be at risk. Individuals who are identified as at risk are referred for additional testing. The goal of screening for occupational asthma is to detect the disease at a stage when treatment would be beneficial. In occupational asthma, the longer a worker is exposed to an agent after developing asthma symptoms, the less likely recovery will occur after removal from exposure to the agent. Through screening, health officials can determine whether to perform an industrial hygiene investigation of a potentially dangerous workplace [3].

Surveillance is defined as the detection of a health-related event or exposure in a target population. It involves the distribution of information to health officials. National surveys are useful for identifying possible risky occupations. They can provide incidence estimates on a larger scale than can smaller workforce-based surveys and can provide surveillance of time trends from national databases [3]. This method was used to identify the increase of occupational asthma in Sweden and in Finland during the 1980s [18–20].

Historical perspectives and estimates of the incidence and prevalence of occupational asthma

The discipline of epidemiology has been applied to the workplace since the 1700s, when Ramazzini recognized patterns of illnesses among workers who shared similar jobs. He noticed asthma symptoms in individuals who sifted and measured grain and noticed shortness of breath in individuals who worked with cotton [21]. During the Industrial Revolution, disease states such as byssinosis were described. Byssinosis was the name given to a syndrome, which included asthma-like symptoms, that was reported by cotton workers in New England [3]. Several large population-based studies of asthma have been undertaken, many of which include occupational aspects. Large community-based surveys, such as the European Community Respiratory Health Survey, estimated the attributable risk, causative fraction of workplace exposure, or both for asthma. [22]. Other studies have shown the risks for asthma in the workplace among the general population to be 3% in Spain [23] and 3.1% in New Zealand [24].

Several estimates of the occurrence of occupational asthma are based on national and regional statistics. The Sentinel Event Notification System for Occupational Risks (SENSOR) was introduced in selected U.S. states in the 1980s [25]. In this project, specialty physicians reported possible work-related cases of disease to public health investigators who then investigated any workplaces that were believed to be at risk. The most frequently identified causal agents for occupational asthma were diisocyanates (the cause of 19% of cases in Michigan and New Jersey). The work setting associated with the largest number of cases of

Table 2
Epidemiologic findings in occupational asthma from different occupational exposures

Agent-industry	Months before diagnosis	Prevalence of work-related asthma (%)	Prevalence of smoking (%)	Prevalence of atopy (%)	Determinant of the distribution of asthma symptoms	Author, year, country
Enzymes; detergent industry	Intermittent	50	52	64	Exposure, not atopy or smoking	Mitchell, 1971, Australia
Laboratory animal work	36	10	—	24	Exposure, atopy	Slovak, 1981, United Kingdom
Bakery work	26	6	57	34	Exposure	Cullinan, 1994, United Kingdom
Latex in hospitals	120	2	22	25	Skin reactivity to latex	Vandenplas, 1995, Belgium
Platinum refinery	12–24	54	63	33	Smoking, not atopy	Venables, 1989, United Kingdom
Phtahllic anhydride	1–192	18	75	29	Exposure plus atopy	Wernfors, 1986, Sweden
Toluene diisocyante	Mostly within 36	9.5	51	35	Exposure, probably not atopy	Venables, 1985, United Kingdom
Various isocyanates in secondary industry	54	20	52	—	Exposure	Seguin, 1987, Canada
Red cedar	12–24	3.4	—	—	Exposure, atopy	Ishizaki, 1973, Japan

Data from Becklake M, Malo J, Chan-Yeung M. Epidemiological approaches in occupational asthma. In: Bernstein IL, et al, editors. Asthma in the workplace. 2nd edition. p. 27–65.

occupational asthma varied in different states. For selected reporting periods, the largest number of cases occurred in the automobile industry in Michigan (40%), in the chemical industry in New Jersey (15%), and in office workers in Colorado (26%). Although SENSOR was labor intensive and was burdened with the problem of under-reporting, it increased physicians' awareness of occupational asthma. In the United Kingdom, a sentinel system was introduced in 1989 and was based on voluntary reporting of physicians across the country [26]. This project, called surveillance of work related and occupational respiratory disease (SWORD), showed a stable incidence of occupational asthma with a change in responsible agents over time. An increase in cases was seen among nurses, construction workers, and mine workers, whereas a decrease in cases was seen among laboratory technicians and hairdressers. Overall, the estimated incidence of occupational asthma in the United Kingdom is 22 cases per million people per year [23].

In Canada in the provinces of Quebec and in British Columbia, a model similar to SWORD was used to estimate cases of occupational asthma. The incidences were 20 cases per million people per year in Quebec [28] and 92 cases per million people per year in British Columbia [27]. In Sweden, the estimates were derived from national registers of self-reported asthma cases [18], and in Finland, registers of persistent and occupational asthma cases were used [22]. These incidences were 80 cases per million people per year and 156 cases per million people per year, respectively. The large differences in the incidences of occupational asthma between these countries most likely result from differences in the way the data were collected and differences in the occupations and industries in the countries [3]. Studies in the different countries consistently found that the incidence or prevalence of occupational asthma increased in the 1980s. These types of estimates are subject to underestimation (ie, not all cases are reported) and overestimation (ie, not all cases prove to be occupational asthma). In systems that rely on voluntary reporting by physicians over a long period of time, it is difficult to maintain compliance [3].

As epidemiologic data on occupational asthma has accumulated, it has become apparent that different occupational exposures may be associated with different prevalences of occupational asthma. Epidemiologic data from studies in different industries and occupations are shown (Table 2).

Summary

Information gathered through epidemiologic studies of occupational asthma is useful for the establishment of prevalence or incidence data for public health purposes, which can be used to determine which industry or workplace requires assistance from preventive services [29,30]. These studies address etiologic questions regarding exposure and host risk factors. They can establish an exposure–response relationship that provides scientific basis for setting environmental control measures. They also examine the effectiveness of preventive control measures.

In the conduct of epidemiologic studies of occupational asthma, choosing the type of study to answer the study question is important. Observational studies have predominated in studies of occupational asthma. Although these types of studies have provided much useful data, they are associated with the problem of the healthy-worker effect. In the future, use of more robust epidemiologic study designs should foster a greater understanding of occupational asthma.

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