Epidemiology and risk factors of occupational respiratory asthma and occupational sensitization

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Abstract

Information on the occurrence of occupational asthma comes from different sources; disease registries, general population studies and workforce-based studies. Each source has its strengths and weaknesses. For multi-causal diseases such as asthma, reliable information from well-designed epidemiological studies is to be preferred. However, a complication is that occupational asthma is not directly measured (diagnosed) in general population studies and an attributable risk is usually calculated on the basis of crude information about exposure. The exposure information is usually derived from questionnaire responses to questions on exposure to gases, fumes or dusts, or is based on so-called 'job exposure matrices'. Disease registry data, from occupational disease registries, allows direct estimation of the occurrence of occupational asthma. However, the information is often incomplete or difficult to interpret because of diagnostic criteria which vary and can also be dependent on compensation and insurance criteria, more related to severity of disease rather than to occurrence of disease. As a result, registries may give only crude estimates of the occurrence of disease, but at the same time allow evaluation of trends over time. Workforce-based studies have given most information about determinants of work-related asthma and allergy. An important determinant of asthma and allergy is the exposure intensity and for high-molecular-weight sensitizers atopy clearly modifies the risk. It is expected that improved phenotypical characterization of occupational asthma together with genotyping and detailed exposure assessment will give more insight in the occurrence and determinants of disease and prognosis.

General introduction

In Western countries there has been a clear shift observable over the last few decades from pneumoconiosis and cancer due to mineral dust exposures (asbestos and silica) to work-related obstructive diseases such as occupational asthma (OA) and chronic obstructive pulmonary disease (COPD) [1]. In most Western countries, OA is now the most frequently occurring occupational disease. Information about the occurrence of occupational respiratory diseases and their contribution to morbidity and mortality in the general population comes from different sources of varying quality.

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Data from these different sources are not always easily comparable since the quality of the information, and the aims for which they were gathered, differ. Nevertheless, an attempt is made in this chapter to give insight into the associations between occupational exposures to occurrence of OA. Information on determinants of OA mainly comes from workforce-based studies, and these determinants are also briefly discussed.

Occupational asthma in an epidemiological context

OA is usually defined as a disease characterized by variable airway airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular workplace environment and not to stimuli encountered outside the workplace [2]. Usually, OA with and without a latency period is distinguished. Asthma with a latency period includes all forms of asthma for which an immunological mechanism has been identified. In most cases an IgE-mediated allergy is the underlying mechanism. Causes of immunological asthma are low- and high-molecular-weight sensitizers of which more than 250 have been identified. High-molecular-weight sensitizers are usually large proteins of more than 5 kDa such as enzymes like fungal α-amylase derived from *Aspergillus oryzae*, or more heterogeneous natural substances such as latex and cereals like wheat. Most high-molecular-weight sensitizers induce the development of specific IgE antibodies. The reaction between antibody and allergen leads to an allergic inflammatory response in the airways. Few population studies exist that focus on the changes shortly after sensitization, but a small longitudinal study in laboratory animal workers suggests that bronchial hyperresponsiveness and symptoms develop soon after sensitization, and accelerated decline in lung function becomes measurable [3].

For many other substances the mechanism by which inflammation develops is often at least partially unknown. Specific antibodies against isocyanates for instance have been found in a minority of the sensitized workers, but the role of these antibodies is not completely clear, and the mechanism does not seems to be IgE mediated in all isocyanate-sensitized workers [4, 5]. Irritants induce asthma by non-immunological mechanisms and no latency period is observed in most cases. An example of OA without a latency period is the reactive airways dysfunction syndrome (RADS), which develops after exceptionally high concentrations of an irritant agent. Small work shift changes in lung function, without persistent bronchial hyperresponsiveness and eosinophilia are usually not referred to as OA, but as OA-like disorders. A typical example of an asthma-like disorder is Monday morning airway obstruction associated with endotoxin exposure in agricultural workers [6], although some nowadays may refer to this as non-allergic asthma [7, 8].

There is no consensus on the best way to identify OA in epidemiological studies. A provocation test with the suspected causal agent is generally accepted as the gold

standard, but this approach cannot be applied in large scale surveys of industry-based studies or the general population. Questionnaires form an important survey tool and many have modified these questionnaires for their own purposes by adding questions on work relatedness of symptoms [9]. Other relevant tests that can be applied in surveys are bronchial hyperresponsiveness testing, spirometry, serology and skin prick testing for evaluation of sensitization in case of immunological asthma. Records of peak expiratory flow (PEF) measurements over longer periods have been commonly used for establishing a clinical diagnosis. Unfortunately, few examples can be found of application in epidemiological studies, and the response rate for repeated PEF testing in population surveys is usually low [10].

Incidence data from monitoring systems

Considerable attention has been given to disease monitoring systems for asthma across the world since the mid-1990s when it became apparent that OA had replaced the pneumoconiosis as the leading occupational disease. A major source of information included disease registries for compensation purposes, since these also give an impression of the burden on society of OA. Point estimates from occupational disease registries indicated an incidence between 2 and 15 cases per 100 000 (Tab. 1). Differences are, among other factors, associated with differences in industrial structure between countries, differences in definition of work-related (and compensable) asthma, differences in case finding methods, and changes over time in asthma incidence. Through the voluntary Surveillance of Work Related and

Table 1. Reported occupational asthma incidence by different asthma monitoring programs and some occupational disease registries.

Reference	Country	Incidence/100 000	Range
[11, 13, 15, 17]	UK	2.0-4.3	1–183 [17]
[12]	USA	2.9	0–17
[14]	Finland	3.6	5–30
[16]	Germany	4.2	
[18]	Canada (Quebec)	6.3	
[19]	Sweden	8.1-19.1	1–77
[20, 21, 23–25]	Finland	8.1	
[22]	Canada (Br. Columbia)	9.2	
[26]	USA		5.8–20.4*

*Estimates based on capture-recapture method

Ocupational Respiratory Disease (SWORD) reporting system in the UK, occupational physicians, lung specialists and allergists voluntarily reported 3000–4500 cases of respiratory diseases. More than a quarter of the cases involved OA, which makes OA the most reported work-related respiratory disease. Diisocyanates, which are low-molecular-weight sensitizers, and high-molecular-weight allergens from animals, flour and grain appear the most important sensitizers. In Germany, only 1500 of the 5600 suspected cases could be confirmed as OA [16]. Of these, another 400 were rejected because they were not in accordance with additional clinical or non-medical criteria. In a study from the USA, OA cases reported through different disease registries in one state were evaluated using the capture-recapture method, a statistical technique that used the overlap between sources of information to obtain an estimate of the 'true' rate [26]. Reports from physicians, hospital discharge records and worker compensation claims were used, and the incidence of new onset OA was estimated between 5.8 and 20.4 cases/100 000 individuals per year, clearly higher than the directly observed incidence of 2.7 cases/100 000 individuals per year, but in range with the data from registries in other countries. Some disease registries have been able to show strong changing trends in numbers of reported cases reported, like for latex-associated respiratory allergy in Germany [27]. A strong drop in cases was associated with a targeted reduction of exposure to powdered high-protein latex gloves. Similarly, in Ontario, Canada, a program to reduce exposure to diisocyanates and to introduce medical surveillance was associated with earlier diagnosis and fewer cases in a compensation population [28].

Occurrence in general population studies

General population studies were more often explored as a means to estimate the population attributable risk for both asthma and COPD since the late-1970s and mid-1980s [29–46]. This design became popular because it was believed that general population studies were less sensitive to the healthy worker effect. A general population sample was considered superior compared to a workforce-based population sample from which workers who had developed disease had already left. General population studies allowed evaluation of associations between job title and asthma not only for the present but also for previous jobs [47]. This made a more direct evaluation of the healthy worker effect possible. In addition, introduction of so-called 'Job Exposure Matrices' – expert systems that cross-link job titles with specific occupational exposures in a qualitative or semi-quantitative way – made characterization of exposure possible in these studies. A strength of these general population studies is that exposures have been identified that were outside the classical basic high-risk industries. An example is the identification of cleaning agents as a cause of OA [48].

The early general population studies made use of self-reported exposure and some may have been affected to some extent by misclassification of exposure in the form of recall bias. Most studies were cross-sectional and used prevalence data. The studies included information on respiratory symptoms associated with asthma, lung function or bronchial hyperresponsiveness testing, and allowed calculation of the risk for developing asthma for individuals with a certain exposure. This allowed the calculation of the contribution of occupational exposures to the prevalence of asthma, the etiological fraction. Most studies estimate contributions as being between a few percent and 20%.

An important example is the large prospective one among 6837 participants from 13 countries who previously took part in the European Community Respiratory Health Survey (1990–1995) [49]. The individuals included did not report respiratory symptoms or a history of asthma at baseline. Asthma was assessed by methacholine challenge test and by questionnaire-registered asthma symptoms. Exposures were defined by high-risk occupations, an asthma-specific job exposure matrix with additional expert judgment, and through self-report of acute inhalation events. A significant excess asthma risk was seen after exposure to substances known to cause OA [relative risk (RR), 1.6; 95% CI 1.1–2.3]. Risks were highest for asthma defined by bronchial hyperreactivity in addition to symptoms (RR, 2.4; 95% CI 1.3–4.6). Asthma risk was increased in participants who reported an acute symptomatic inhalation event (fire, mixing cleaning products, chemical spill) (RR, 3.3; 95% CI 1.0–11.1). The population-attributable risk for adult asthma due to occupational exposures ranged from 10% to 25%. This is equivalent to an incidence of new-onset OA of 250–300 cases per million people per year. Although this study is among the larger general population studies, it shows some specific limitations of general population studies. Risk estimates for specific occupational groups are sometimes based on small sample sizes, leading to instability in the risk estimates for specific occupational titles or exposures. Intermediary endpoints such as specific work-related sensitization have up to now not been included in general population studies and this makes it difficult to link results to workforce-based studies. A future challenge for all general population study is adequate exposure assessment. People move more frequently from job to job and the exposure is more diffusely spread through the population in modern service economies without large basic industries. This makes characterization of the exposure on the basis of job title information more challenging and probably more detailed techniques will be required.

Occurrence of occupational asthma in workforce-based studies

Important information also comes from studies in specific workforces. For instance studies in bakers suggest sensitization rates of 5–25% for several work-related allergens [50], which is in most cases accompanied by symptoms. Similar figures

are available for workers exposure to a range of high- and low-molecular-weight allergens. Typically, workforce-based studies have a cross-sectional or cohort design and include between 100 and 1000 workers. Given the incidence of OA, these studies are usually too small to directly study the occurrence of clinically relevant OA. Therefore, asthma is defined on the basis of questionnaire responses and intermediate effects such as sensitization or hyperresponsiveness are considered as endpoints in the analysis.

The discrepancies in the magnitude of the hazard estimated by different information sources (general population studies, disease registries, and studies in specific occupational groups) is most likely due to differences in (the definition of) endpoints considered, the diagnosis, and severity of what is considered OA, and selection out of the workforce. Most evidence on determinants and modifiers of risk for OA comes from workforce-based studies. Modern workforce-based studies often involve a quantitative exposure assessment component. Phenotypical evaluation of the workers is often more detailed and specifically chosen for the type of asthma resulting from the exposure than in general population studies. The information that is generated by this type of study contributes to risk assessment and prevention.

Exposure

Allergen exposure level is a clear determinant of risk of occupational allergy and asthma. Exposure-response relationships have been shown for both high- and low-molecular-weight sensitizers. Some recent studies in specific occupational groups illustrated the existence of exposure sensitization relationships for some high-molecular-weight sensitizers. In particular, a series of European studies in bakers and laboratory animal workers shed new light on some aspects of the development of occupational allergic asthma and rhinitis due to exposure to high-molecular-weight sensitizers. A more complete overview can be found elsewhere [51–56]. A small retrospective cohort study among laboratory animal workers, who underwent a pre-employment medical examination, indicated that the time until development of symptoms was dependent on both exposure intensity and atopy [57]. The risk for developing sensitization and allergy is measurable directly after start of exposure and remains high with ongoing exposure. A follow-up study showed that the 12-year incidence rates of symptoms among workers from laboratories exposed to rodents were 2.26 (95% CI 1.61–2.91) and 1.32 (95% CI 0.76–1.87) per 100 person-years, respectively. Higher relative risks were seen with increasing hours of exposure to tasks that involved working with animal cages or with many animals at one time. The most common symptoms were related to rhinitis rather than to asthma. Incidence might be reduced by limiting exposure through reducing the number of hours per week of exposure to laboratory animals [58, 59].

Atopy

Atopy is usually defined as either specific IgE against a series of common allergens or a positive skin prick test response to the same panel of allergens. Usually, tree pollen, grass pollen, house dust mite, cat and dog allergens are considered common allergens in occupational studies. Atopy is a strong risk modifier for high-molecular-weight sensitization. This is most clearly illustrated by a large pooled European study in 650 Laboratory Animal Workers [56]. Atopic workers were at higher risk for having work-related sensitization compared to non-atopic workers. The atopic workers already had a clearly increased risk at the lowest exposure levels and there was no evidence of an exposure threshold. For non-atopic workers a steadily increasing exposure-response relationship was found. Atopy is the most important risk modifier of work-related sensitization high-molecular-weight sensitizers. There is no clear evidence that atopy is a modifier of the risk for work-related sensitization and asthma in case of low-molecular-weight sensitizers.

Atopy was until recently seen as an individual susceptibility factor with presumably a genetic background. However, atopy has no perfect penetration and cannot only be interpreted as a factor solely determined by individual susceptibility. It seems also associated with environmental factors. There is increasing evidence that farm exposures throughout life are protective against atopy, allergic rhinitis, and atopic asthma [60]. Several studies have observed a strongly decreased prevalence of allergic sensitization [61–63], hay fever [64, 65], and asthma [8] among adults with childhood and current farm exposures. According to the hygiene hypothesis, bacterial and viral infections, and environmental exposures to microbial compounds may protect from the development of allergic disease by influencing immune responses. Farmers, and children growing up on farms, are exposed to high levels of microbial pathogens causing zoonoses, and proinflammatory agents such as bacterial endotoxin and fungal $\beta(1\rightarrow3)$-glucans. It has been hypothesized that exposure to such agents may induce a shift from atopic Th2 responses to Th1 responses through stimulation of the innate immune system and regulatory T cells [66]. Protective effects of house dust endotoxin on the development of atopy and asthma have been shown in children [67–69], and more recently, studies among adults have shown similar inverse relationships between endotoxin exposure and atopic asthma [8], allergic sensitization [65, 70, 71], and hay fever [64]. Thus, the more recent studies among occupationally exposed populations have shown that, in accordance with the hygiene hypothesis, effects of early exposures can be long-lasting. However, some of these studies also suggest that immune deviation from Th2 to Th1 responses may take place throughout life, and exposure in adulthood to endotoxin and other microbial compounds seem been associated with a lower prevalence of allergy or allergic asthma. Most evidence is still based on cross-sectional studies, and longitudinal studies are needed to observe reversal of atopic status under the influence of high microbial exposures directly.

Since endotoxin and other microbial agents are potent proinflammatory agents, the downside of increased exposure can be an elevated risk of non-allergic or non-atopic asthma [72–74]. Only a few studies have explicitly reported the Janus-faced nature of endotoxin – a protective effect on atopic disease, paralleled by an increased risk of non-atopic asthma and non-specific airway hyperresponsiveness – in the same population sample. There also appears to be a clear difference in susceptibility for endotoxin exposure, measurable at the population level [75] (Fig. 1).

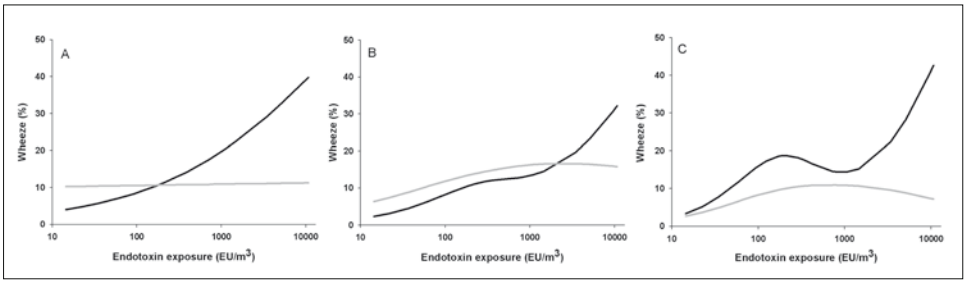

Figure 1.
Different exposure-response relationships for endotoxin exposure and wheeze for low and high responders in a whole blood stimulation assay. Low (gray line) and high (black line) responders defined on their tumor necrosis factor-α (A), interleukin-1β (B), and interleukin-10 responses (C). Exposure expressed in endotoxin units (EU) (with permission from [75]).

Smoking

One study identified smoking of cigarettes as a risk factor of work-related sensitization for high-molecular-weight sensitizers [76]. Smokers seemed at higher risk to have work-related sensitization in especially one of the three subsamples than non-smokers in this cross-sectional study. However, this finding has not been reproduced in many larger and better controlled studies [55, 56, 77]. Most evidence available at present for high-molecular-weight sensitizers indicates that smoking is not an effect modifier for the association between allergen exposure, sensitization and allergic asthma. Interesting results have recently been published for other sensitizing agents such as platinum salts. For low-molecular-weight sensitizers, such as platinum salts, smoking is an effect modifier [78–80]. The incidence of platinum salt sensitization depended on the solubility of the platinum salt, after correction for smoking habits at median levels below 0.5 $\mu g/m^3$ [79].

Genetic markers

Studies on the role of genetic markers have traditionally been conducted on relatively small samples of OA cases or within industrial cohorts, especially considering workers with exposure to specific agents such as isocyanates and red cedar wood dust. The genes associated so far with OA are HLA class II genes, genes involved in antioxidant protection, α-1-antitrypsin, and genes regulating the native immune pathways (see for review [81]). Few interactions have been demonstrated as yet but large-scale genetic studies of asthma that are now underway will likely change the situation. A first genome-wide association study (GWAS) including large working populations will be published soon, but yielded little important information on top of GWAS studies among adult asthmatics not specifically focused on occupational exposures. It is expected that a new generation of studies based on specific hypotheses (candidate interactions) in combination with improved phenotypical and environmental characterization will create more useful evidence on gene environment interactions. There is awareness about the potential use of genetic information in, for instance, pre-employment testing and asthma surveillance [82]. However, the associations between genetic markers and asthma or sensitization are based on cross-sectional analyses and usually relatively weak. Prediction of future occurrence of disease is practically not possible at the moment and present information indicates that predictions will be imprecise. A study among laboratory animal workers for instance showed that HLA-DR7 was associated with sensitization [odds ratio (OR), 1.82; CI, 1.12–2.97], respiratory symptoms at work (OR, 2.96; CI, 1.64–5.37) and, most strongly, sensitization with symptoms (OR, 3.81; CI, 1.90–7.65) [83]. HLA-DR3 was protective against sensitization (OR, 0.55; CI, 0.31–0.97). Atopy defined phenotypically, on the basis of an immunological evaluation, was more strongly associated with work-related sensitization than any of the phenotypical markers.

Prognosis

A limited number of epidemiological studies focused on the prognosis of OA [84–88]. The available studies suggest that symptoms can still be present up to 12 years after exposure cessation [84, 85]. One study describes results from an interview 6 years after diagnosis of a group of 79 individuals with OA [86]. Most had the impression that symptoms had improved, although 72% still used medication and 33% were still unemployed. Others found indications that symptoms can still worsen after exposure is terminated [24, 89]. Some have argued that exposure reduction is associated with a poorer prognosis than complete removal from exposure [90]. However, the studies underlying this statement involved a limited number of asthma cases and were poorly controlled in terms of the exposure [91, 92]. The changes in

exposure were only monitored qualitatively, and it is not known if any exposure reduction occurred objectively or that the exposure reduction was sufficiently large to have any effect.

Prevention

Information on exposure-response relationships can be used for risk assessments and will be the input of standard setting procedures in different countries. For instance, the American Conference of Governmental Industrial Hygienists and the Dutch Health Council are among the first to use data on exposure-response relationships for bio-aerosols, such as wheat allergens, to propose a standard for wheat dust levels in the air [93, 94]. It is expected that similar standards will be developed for some other high-molecular-weight sensitizers because the principles for risk assessment for sensitizing agents have recently been described [95]. Standards do exist for several low-molecular-weight sensitizers, such as toluene diisocyanate (TDI) and platinum salts, but it not the rule that these standards take into account the risk for sensitization. In addition, some of these standards were derived several decades ago, and it is not always certain what the scientific basis was for these standards and if they truly protect the workers.

Future developments

Over the last few years, new technologies have become available to measure inflammatory markers in nasal and bronchial lavage samples. Less invasive technologies are expected to become available such as exhaled nitric oxide (eNO) and measurements based on exhaled breath condensate samples or exhaled air. These developments will give more insight into the heterogeneity in phenotypes and will improve phenotyping in epidemiological studies. Some examples of this development do already exist, but usually refer to patient data and seldom come from open population studies.

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