



The Promise and Problems of E-Cigarettes

The debate about the safety of e-cigarettes is heating up in the public and scientific press. A number of cities in the United States have already extended or are considering extending the ban on cigarette smoking in public places to include e-cigarettes. The editorial page of the *New York Times* has joined the debate about whether e-cigarettes are the new approach to safe cigarettes or just another way to foster nicotine toxicity and addiction (1, 2), and references to e-cigarettes in PubMed have increased from three in 2010 to 113 by the end of 2013.

E-cigarettes, which were first developed in China in 2003, are now marketed throughout the world as a smokeless and safe way to inhale nicotine without being exposed to the many toxic components of standard cigarettes, and as an aid to smoking cessation (3–5). E-cigarettes consist of battery-powered liquid cartridges, containing nicotine and a number of other components, including in some instances tobacco itself (6). E-cigarettes create a vapor that provides a dose of nicotine that varies with the vigor of inhalation and depends on the nicotine content of the cartridge, which is often not listed. Virtually every tobacco company produces e-cigarettes, and the market for e-cigarettes is large and growing. They have been especially appealing to increasing numbers of young previous nonsmokers (7) because they are advertised as being safe, fashionable, and good tasting, often due to the addition of pleasant flavors.

Cigarette smoking is the leading cause of preventable disease and death in the United States, yet it took decades to produce any governmental regulation of the tobacco industry. Regulation of e-cigarettes in the United States has been stalled as courts have ruled that health warnings on e-cigarettes cannot be enforced because they are not strictly tobacco products, nor can they be labeled as drug-delivery devices because nicotine is not a drug (5, 8).

Nicotine, the main ingredient of e-cigarettes, is addictive (9) and has been implicated in a number of cancers (10). It crosses the placenta and alters fetal gene expression and tissue development in a variety of organs (11). Its toxic effects have been documented in many organs, and it has been shown that nicotine binds to the airway epithelial cell nicotine receptor, producing physiological changes in airway epithelial cells that are similar to those found in cystic fibrosis (12).

There is sufficient evidence about the toxicity of nicotine and the other components that have been found in e-cigarettes, including tobacco itself (7), for regulatory agencies to require a list with concentrations of all e-cigarette ingredients. Given the overwhelming evidence that nicotine is addictive, an appropriate warning about that possibility belongs on e-cigarettes.

Recent studies of airway epithelial cell gene expression have detailed the changes in gene expression that occur in smokers and documented reversal of some of these changes on cessation of smoking (13). Similar studies should be performed in e-cigarette smokers. Methods are now available to maintain differentiated

airway epithelial cells in culture (14) so that we can study the *in vitro* response to various e-cigarettes.

Several relatively small and conflicting studies of the value of e-cigarettes in smoking cessation programs have been published (15). There clearly is a need for a multicenter clinical trial of the value of e-cigarettes in smoking cessation programs, documenting nicotine capsule consumption, serum concentration of metabolic products such as cotinine, markers of systemic and airway inflammation, and rates of smoking recidivism. A recent report on e-cigarette effects on indoor air quality (16) has provided evidence of secondhand e-cigarette exposure, and this possibility needs to be explored further.

The success in marketing of e-cigarettes achieved by the tobacco industry, and the rapidity with which the smoking and nonsmoking population has embraced e-cigarettes in the United States and around the world, demands a rapid and forceful response by the regulatory, scientific, and medical communities.

This is an important time for the American Thoracic Society (ATS) to provide information to physicians, their patients, and the public detailing concerns about the safety of e-cigarettes. The ATS should play a leading role in advocating for basic and clinical research programs related to e-cigarettes, working with the Food and Drug Administration to bring about changes in the regulation of e-cigarettes, and providing information to the public about alternative smoking cessation programs. ■

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Cigarette Exposure in Very Early Life Leads to Persistent Respiratory Effects



Fifty years after the Surgeon General's Report on Smoking and Health (1), Hollams and colleagues (pp. 401–407) deliver another arrow into the bull's-eye linking cigarette smoking to deleterious health outcomes in this issue of the *Journal* (2). Their analyses using the Australian Raine birth cohort demonstrate that maternal smoking during pregnancy, as measured between 16 and 18 weeks, is associated with current asthma at age 14 years in offspring, a persistent effect that is consistent with their previous work reporting a similar association at age 6 years in the cohort children (3).

The authors demonstrate that maternal exposure to cigarette smoking is associated with current asthma, current wheeze, exercise-induced wheeze, and poorer lung function in early adolescence. A recognized caveat is that 100% of the study children born to mothers smoking during pregnancy were also exposed postnatally to environmental tobacco smoke, so it is impossible, even with the most elegantly designed and analyzed cohort, to discern prenatal versus postnatal effects. Nevertheless, from a public health perspective, exposure to cigarette smoke either pre- or postpartum should continue to be heartily discouraged. Most interestingly in these analyses, cigarette smoking during pregnancy was not associated with either atopy in the adolescents or bronchial hyperreactivity, but it was associated with a higher level of peripheral circulating neutrophils and basophils.

This article reveals the challenges in the conduct and analysis of birth cohort data. Retention is difficult. By the time of adolescence, 37% had dropped out of the cohort and an additional 23% could not provide complete data. The epidemiological issues include potential selection bias because the relationships between exposure and outcomes may vary between those who stay in a study and those who were lost to follow-up. More challenging in this article is the undertaking of an analysis that attempts to elucidate the relationship between variables that may lie on the causal pathway between early exposure to cigarette smoke (such as markers of immunological profiles, lung function, and bronchial hyperreactivity) and a diagnosis of asthma. First, all of these measures were accomplished at the same age (14 yr); therefore, the

authors had to assume that current measures were reflective of past trends. Second, these measures are associated with asthma but are not completely correlated with the disease, and may or may not be upstream on the causal pathway. Adjusting for a risk factor that is intermediate on the pathway between the exposure of interest and the disease outcome must be carefully assessed for appropriateness (4). However, in examining maternal smoke exposure and asthma, Hollams and colleagues discern in their Table 4 that even in youth with normal lung function, maternal cigarette smoking during pregnancy is associated with current asthma (2).

This article highlights the increasingly recognized need to carefully discriminate asthma and allergy phenotypes in all research endeavors, a need recognized by the authors themselves and by others in recent research (5–7). For example, similar to the early *New England Journal of Medicine* article by Braun-Fahrlander and colleagues (8) and a report by Williams and colleagues in the *Journal of Allergy and Clinical Immunology* (9), this article reveals that a risk factor is associated with one asthma phenotype but not another. Maternal cigarette smoke exposure was not associated with atopy in the cohort teens, despite the fact that atopy is highly correlated with asthma. Therefore, in asthma risk factor studies, it is becoming imperative that, for example, the phenotypes of atopic versus nonatopic asthma be distinguished to avoid masking associations. Birth cohorts that can be followed intensively are often constrained in size due to resource requirements, and consequently the number of cases of “current doctor-diagnosed asthma” is usually suboptimal for examining effect modifiers such as sex, race, and other parental and child characteristics. Unfortunately, the need to classify asthma into distinct phenotypes implies that study populations must be even larger than ever, and more data on the incidence of various phenotypes in different populations are required to estimate sample size needs when designing a study. Furthermore, analytic approaches to classifying children with asthma into discrete phenotypes are not straightforward (10). In risk factor studies, the factors themselves cannot be used in the identification of phenotype clusters. This becomes a conundrum: what is a risk factor and what is part of the