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Review

REVIEW

Cigarette Filter Ventilation and its Relationship to Increasing Rates of Lung Adenocarcinoma

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Abstract

The 2014 Surgeon General's Report on smoking and health concluded that changing cigarette designs have caused an increase in lung adenocarcinomas, implicating cigarette filter ventilation that lowers smoking machine tar yields. The Food and Drug Administration (FDA) now has the authority to regulate cigarette design if doing so would improve public health. To support a potential regulatory action, two weight-of-evidence reviews were applied for causally relating filter ventilation to lung adenocarcinoma. Published scientific literature (3284 citations) and internal tobacco company documents contributed to causation analysis evidence blocks and the identification of research gaps. Filter ventilation was adopted in the mid-1960s and was initially equated with making a cigarette safer. Since then, lung adenocarcinoma rates paradoxically increased relative to other lung cancer subtypes. Filter ventilation 1) alters tobacco combustion, increasing smoke toxicants; 2) allows for elasticity of use so that smokers inhale more smoke to maintain their nicotine intake; and 3) causes a false perception of lower health risk from "lighter" smoke. Seemingly not supportive of a causal relationship is that human exposure biomarker studies indicate no reduction in exposure, but these do not measure exposure in the lung or utilize known biomarkers of harm. Altered puffing and inhalation may make smoke available to lung cells prone to adenocarcinomas. The analysis strongly suggests that filter ventilation has contributed to the rise in lung adenocarcinomas among smokers. Thus, the FDA should consider regulating its use, up to and including a ban. Herein, we propose a research agenda to support such an effort.

Cigarette smoke is the major cause of lung cancer, containing numerous carcinogens, mutagens, and other toxicants (1–3). When the incidence of lung cancer began to rapidly increase in the 1950s through the 1970s, squamous cell lung cancers were the most common sub type for men, but these decreased over the next 40 years with the decreasing smoking prevalence (1,4–10). However, the incidence of lung adenocarcinomas did not similarly decrease for men and women, exceeding squamous cell cancers in about 1990 and currently comprising about 60% of non–small cell lung cancers (Figure 1A). In 2014, the Surgeon General's Report (SGR) on the Health Consequences of Smoking concluded: "The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since

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the 1950s" (1). It was observed that the changes in lung cancer over time followed a birth cohort effect in men, when successive generations of smokers transitioned from the use of non-filtered cigarettes to cigarettes of lower smoking machine tar yields (Figure 1B). A less obvious effect is seen for women because they generally started smoking later in the century and so mostly smoked only cigarettes with lower tar yields (Figure 1,A and C). It was further noted that the magnitude of lung cancer risk among smokers had increased over time; for example, in the American Cancer Society Cancer Prevention Studies, an almost two fold increase in risk for smoking men, and a 10-fold increase in risk for smoking women, from the 1960s to the 1980s was observed (11). Concurrently, the relative risks for adenocarcinomas increased from 4.6 (95% confidence interval [CI] = 1.7 to 12.6) to 19.0 (95% CI = 8.3 to 47.7) in men and 1.5 (95% CI = 0.3 to 7.7) to 8.1 (95% CI = 4.5 to 14.6) in women, while the risks of other lung cancer subtypes did not increase (6). Other studies similarly report increased rates and risks (6,12–14). Thus, there was a paradoxical increase for lung adenocarcinomas while squamous cell cancers decreased with decreased smoking rates.

Beginning in the 1950s, the concept was developed that lower smoking machine tar yields equate to reduced smoking-related risks. This led to the cigarette industry to progressively lower tar yields in different ways, beginning with the placement of filters on cigarettes (15–18). This was then followed by the use of less tobacco in cigarettes of the same length, use of reconstituted and expanded tobaccos, increasing cigarette paper porosity, and the placement of ventilation holes in the filter to dilute the smoke (Figure 2) (19). The 2014 SGR indicated two reasons that lowering tar yields could have increased the risk of lung adenocarcinomas: the use of filter ventilation holes and increasing amounts of tobacco-specific nitrosamines (TSNAs) in tobacco (1). Filter ventilation became the critical way for cigarettes with similar designs to have lower smoking machine tar yields, and cigarettes were marketed as "regulars" (a few "regulars" remained with 0% ventilation) and "lights" in the 1970s, and "ultralights" in the 1990s (20–23). The public health community believed that smoking cigarettes with lower smoking machine tar yields was preferable for smokers who would not quit (24–27). Lower tar yield cigarettes became the preferred choice of many smokers who perceived them to be a lower health risk because of health messaging. This perception was reinforced by the sensation of reduced harshness when smoking due to the mixing of air and smoke and reduced resistance to draw when puffing the cigarette (16,28,29). While today many countries such as the United States, Canada, and the European Union, have banned the use of "light" and "ultralight" cigarette descriptors because of the evidence that these are not safer cigarettes, filter ventilation continues to be used in almost all commercial cigarettes (16,30). In some jurisdictions, including the European Union, a maximum machine-measured tar yield is mandated for all cigarettes, attributable to the belief that lower tar yields lead to safer cigarettes, which happens to be achieved primarily through the use of filter ventilation (31–33).

There have been previous calls for regulating cigarette filter ventilation because of smokers' misperceptions that lower-tar cigarettes would cause less disease (34,35). Under the 2009 Family Smoking Prevention and Tobacco Control Act (TCA), the FDA has the authority to regulate tobacco products and issue "product standards" when there is sufficient evidence that a standard would be "appropriate for the protection of public health." The purpose of this review is to provide a weight-of-evidence review using causation criteria linking filter ventilation to an increasing risk of lung adenocarcinoma expanding the analysis to include chemistry and toxicology studies, human clinical trials, and epidemiologic studies of smoking behavior and lung cancer risk. This review will use two methods and a consensus-building process to evaluate the evidence for the causal relationship of filter ventilation to increasing risk of lung adenocarcinomas in order to provide a scientific evidence base for the regulation of filter ventilation. One method has been traditionally used for the assessment of smoking-related health risks, and the second method is more recently being advocated for the use in regulatory decision-making because of its transparency and identification of inconsistent data and data gaps (1,24,36–40).

Methods

This review is an evidence-based causation analysis, which uses a weight-of-evidence review of published scientific literature and internal tobacco company documents (experimental and human studies) to provide a comprehensive overview of filter ventilation in relation to lung adenocarcinoma. After grouping disparate types of evidence, reviews were conducted within topics. Scientific publications were identified through PubMed using the following search terms: lights, ultralights, tar, cigarettes, filter ventilation, air dilution, adenocarcinoma, Ames, tumorigenicity, nitrosamines, polycyclic aromatic hydrocarbons, inhalation, puff topography, mutagenicity, smoking machine, compensation, smoking behavior, and chemical yields. Using cigarette and any of the above terms yielded 81 382 publications, which were then narrowed to 3284 based on studies that considered tar yields (Supplementary Table 1, available online). It should be noted that a causation analysis considers all available relevant studies and does not exclude any based on some particular design or feature; rather, it weights highly the most relevant and best studies. Additionally, the online Tobacco Documents Bibliography of internal tobacco company documents archived by the library of the University of California, San Francisco's Center for Knowledge Management was searched using search strings similar to those above (41). This database includes numerous duplicates, and there are numerous unique documents providing duplicative data and methods (eg, draft reports, partial reports, interim reports, final reports, and summaries). Thus, reporting the number of documents that were considered is not informative.

Causality Assessment

Two weight-of-evidence methodologies were utilized, as described in the Supplementary Methods (available online). The first is detailed in the 2004 SGR, derived from the method applied in the 1964 SGR and subsequently used for the later reports (1,24,36). This approach is consistent with an "evidence-based causation methodology" that recognizes the importance of human data, challenges in extrapolating laboratory toxicology data to human risk, use of laboratory toxicology data to support conclusions based on mechanisms, and an integration of data ranging from the laboratory to epidemiology (37). The causation criteria, briefly, include the consideration of 1) consistency as applied to both experimental and human studies; 2) strength of association that considers the magnitude of the effect (eg, reported risk); 3) dose-response relationship; 4) specificity of the effect vs other contributing causes; 5) coherence between laboratory and human data; 6) interventions that provide direct experimental evidence using laboratory and human

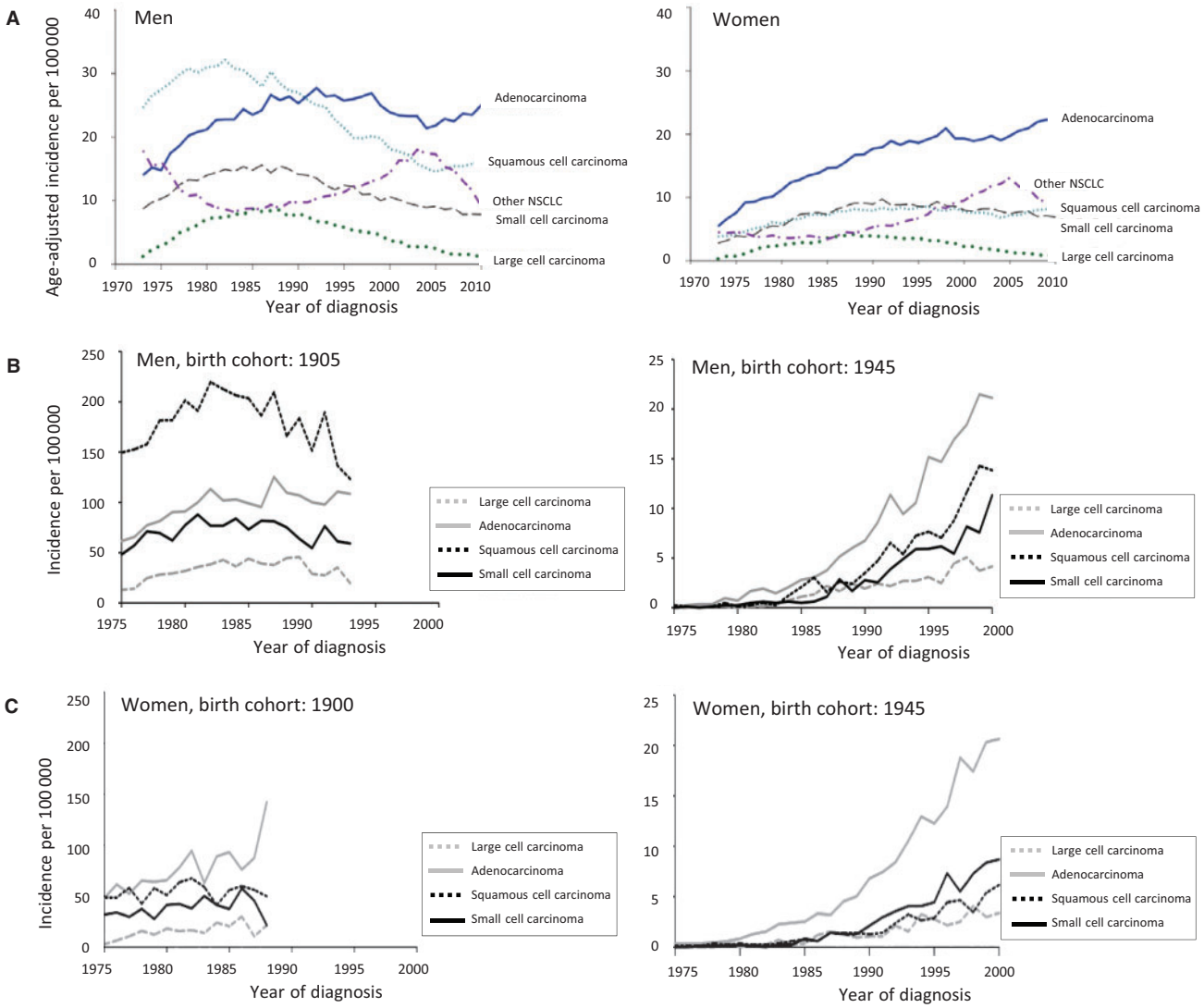

Figure 1. Trends of incidence of lung cancer among US men and women and from various birth cohorts. Adapted from the 2014 Surgeon General's Report (1). (A–C) Graphs present trends in age-standardized incidence rates in the United States from 1973 to 2010 for lung cancer for men (**A, left**) and women (**A, right**) and histologic type of lung cancers using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Among men, there has been a shift in the histology patterns, with an increase of adenocarcinomas over squamous cell carcinoma **(B)**; similar trends are seen for women **(C)**. Graphs present trends in incidence rates of lung cancer in the United States for 1905 and 1945 from birth cohorts of men **(B)** and for 1900 and 1945 from birth cohorts of women **(C)** and histologic type of lung cancers. NSCLC = non–small cell carcinoma.

studies; 7) plausibility; and 8) analogy to other known causes. While there is no particular guidance on how to weight disparate pieces of evidence, this review classifies categories of data on a scale of 0 to 3, where consistency and interventions were given a threefold weight compared with other criteria, dose-response and biological plausibility were given a two fold weight, and the others were the comparator at a one fold weight (coherence, plausibility, and analogy), so that the maximum score was 45 (Supplementary Table 2, available online). The authors evaluated the different types of evidence presented herein during numerous meetings and phone calls to reach a consensus for the various weights and rankings.

The second approach uses a mode of action (MOA), and human relevance framework for weighing the evidence has been applied (Supplementary Table 3, available online), which has evolved for risk assessment purposes from causation criteria developed in the 1960s by Sir Austin Bradford Hill (38), where more recent considerations now are applied in the context of modern scientific principles and specific defining questions (39,40). This second framework is used to enhance transparency and determine if similar conclusions result using different approaches. The MOA links the exposure of a cell to a substance that reflects the outcome of interest, for example, increasing cancer risk, and does this in the context of human relevance. This framework explicitly considers the consistency of the data from disparate types of studies, outcomes based on a sequence of events, and biological evidence of pathways that can be interrupted so that risk is not considered inevitable, and it necessitates the consideration of the dose-response relationship. Inconsistencies and data gaps are identified using a standardized template.

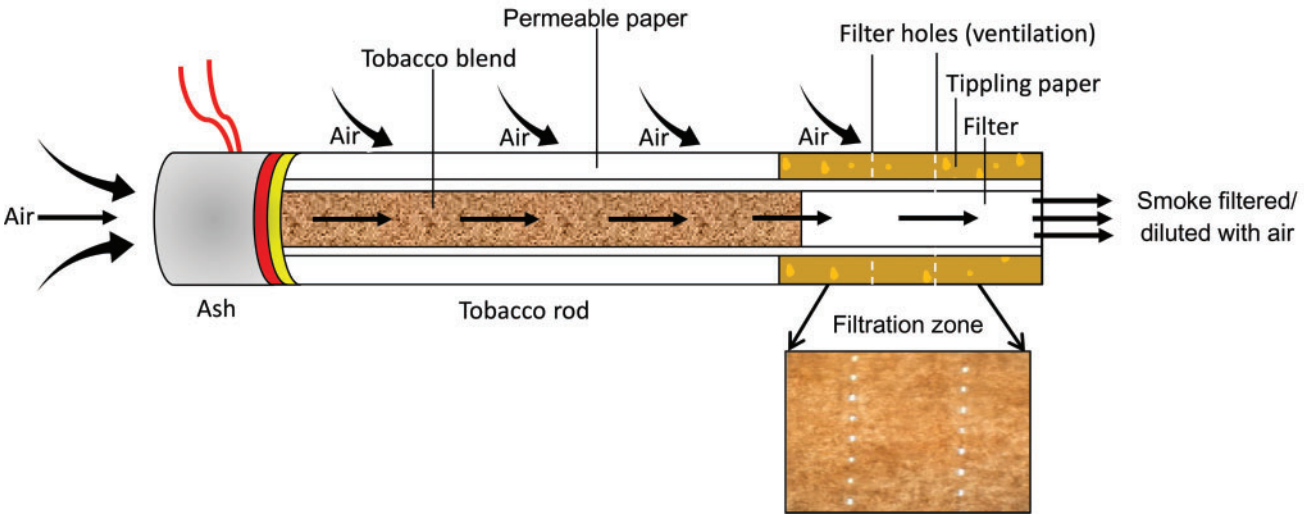

Figure 2. The modern cigarette. An adapted depicted modern cigarette as to elucidate mechanisms in and around the burning cigarette by Richard R. Baker in 1982 (https://industrydocuments.library.ucsf.edu/tobacco/docs/#id=knyy0131) (1).

Results

The published scientific literature and unpublished internal tobacco company research can be grouped by laboratory experimental data (ie, impact of filter ventilation on smoke chemistry yields, in vitro mutagenicity, and in vivo animal studies) and human studies (ie, smoking behavior, exposure including observational studies and clinical trials, and long-term epidemiology). Figure 3 provides the framework for the relationship of filter ventilation to the increased risk of adenocarcinomas.

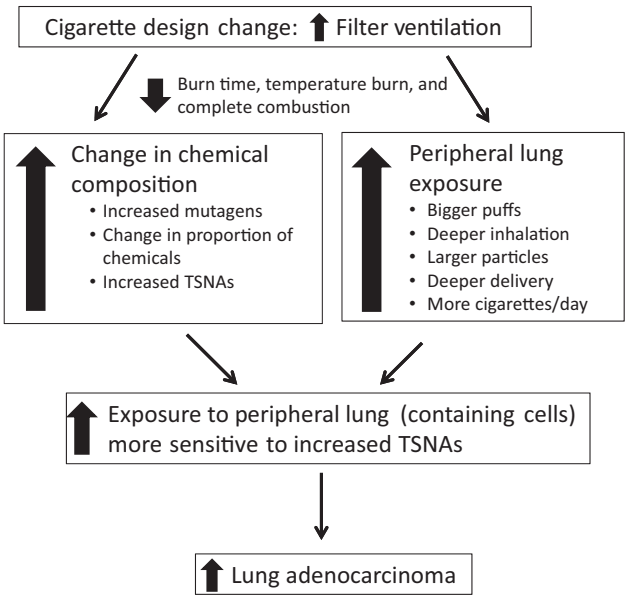

Figure 3. The framework for the relationship of filter ventilation to the increased rate of adenocarcinoma. The placement and increase of filter ventilation lead to higher levels of mutagens and carcinogens, compensation with the greater depth of inhalation, and deposition of smoke that increases exposures to in the peripheral portion of the lungs. Thus, smokers who smoke low-tar cigarettes have developed a greater risk for adenocarcinoma of the lung. TSNAs = tobacco-specific nitrosamines.

Smoking Machines and Toxicant Delivery

Smoking machines are used to generate smoke in a standardized manner for laboratory testing and were thought to be useful for comparing cigarette smoke tar yields (and constituents) in the context of relative disease risks (42–45). When cigarettes with increasing filter ventilation are smoked on a smoking machine, tar yields are lowered because the filter ventilation holes allow for the smoke to be diluted with air. Machine-measured cigarette tar yields generally decreased from an estimated average of 38 mg in 1954 to 12 mg in 1997 (Figure 4A) (46). Figure 4B shows when filter ventilation was adopted compared with other design changes that also were intended to lower tar yields (23). Filter ventilation was used in about 7% of marketed cigarettes by the end of the 1960s, but rapidly increased to 94% to 100% by 1982 (35, 47). Today, the percent age of filter ventilation used in commercial cigarettes ranges from 0% to 83%, although most smokers choose cigarettes that have 10% to 20% ventilation (10–15 mg tar yield). A small number of smokers prefer cigarettes with greater than 40% ventilation (1–6 mg tar yields) (23,30,47–49). Until 2008, US cigarettes were branded by the industry as "regulars" or "full-flavor" (>15 mg tar), "lights" (6–15 mg tar), and "ultralights" (<6 mg tar) depending on the machine-rated tar yield, in large part determined by filter ventilation (Figure 4B) (19,47,50).

While the application of filter ventilation can result in lower machine-measured tar yields, the composition of the smoke changes increases tobacco toxicant yields and adverse biological effects as follows (Figure 5) (51–55):

- As filter ventilation increases, the cigarette is burned down less rapidly on the smoking machine, and there are more puffs per cigarette (54–59).
- As the tobacco rod burns down less rapidly, there is more time for the coal to smolder and form more toxic constituents (54,55,57).
- With increased ventilation in the range of most commercial cigarettes, there is decreased air flow through the burning coal tip and lower coal temperatures, resulting in more incomplete combustion and toxic constituents (60–66). An important publication for the chemical yields of two

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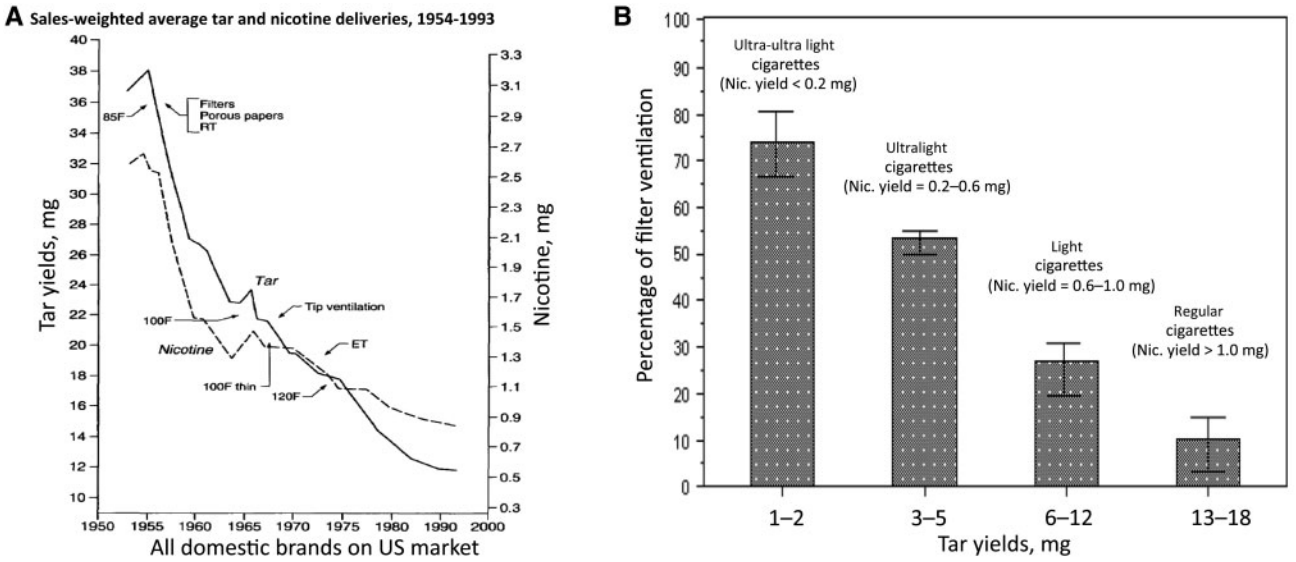

Figure 4. Sales-weighted average tar and nicotine deliveries, 1954 to 1993, and percentage of filter ventilation of cigarettes based on tar yields using the Federal Trade Commission. **A)** Tar and nicotine as measured by a smoking machine. Source: Hoffmann D, Djordjevic MV, Hoffman I. The changing cigarette. *Prev Med*. 1997;26(4):427–434. (19). **B)** Adapted from: Centers for Disease Control and Prevention. Filter ventilation levels in selected U.S. cigarettes, 1997. *MMWR Morb Mortal Wkly Rep.*, 1997;46(44):1043–1047 (22). Bars represent 95% confidential interval. Percentage of filter ventilation is the percentage of a standard puff (two second duration, 35 mL), that is, air taken into puff through the filter vents. A cigarette with no filter ventilation would produce a puff undiluted by air from filter vents; a cigarette with 80% filter ventilation would produce a puff that is 80% air from vents and 20% smoke undiluted by air from vents. Descriptors are no longer allowed by law because they are misleading and because the classification and nicotine yields vary by definition in the literature. ET = expanded tobacco; F = filter; Nic. = nicotine; RT = reconstituted tobacco.

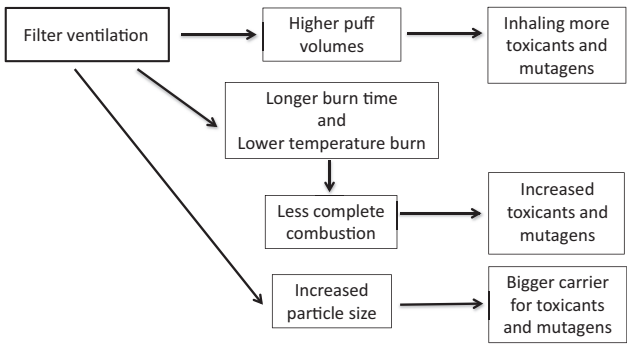

Figure 5. The relationship of filter ventilation to changes in chemical yields and toxicity. With increased filter ventilation, smokers take higher puff volumes and inhale more toxicants and mutagens, tobacco burns longer and at a reduced temperature that increases incomplete combustion with increased toxicants and mutagens, and increased particle size becomes a bigger carrier for toxicants and mutagens.

commercial cigarettes that differ by the amount of filter ventilation shows that most toxic constituents are statistically significantly increased (67). The analysis of this study was done with smoke constituent yields on a per-mg-of-nicotine basis, mimicking smoke intake for a smoker adjusting their smoking behavior to compensate for lower nicotine delivery. Among the increased toxicants was (N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), a potent lung carcinogen, in agreement with other published studies (57,64,68–72). Blocking ventilation holes decreases NNK levels (73).

- Increasing filter ventilation increases cigarette smoke mutagenicity as measured by the Salmonella Reverse Mutation Assay (Ames test), which is a highly replicated and extensively used assay for the screening of mutagenic potential (74–78) (Supplementary Figure 1, available online) (79). Filter ventilation increases mutagenicity across the full range of cigarette ventilation (69,74,80). An internal tobacco company study assessed six different design parameters to model the contribution of various design changes, including ventilation to mutagenicity, using 30 different research cigarettes (81). Filter ventilation statistically significantly increased the mutagenicity of tar independent of other cigarette designs and tobacco formulations (Figure 6) (81).
- Increased filter ventilation increases particle size in the smoke due to increased water content, condensation, and coagulation as the smoke passes through the tobacco rod (Supplementary Table 4, available online) (54,82–88). This is due to the slower burn down of the cigarette and increased residence time of the smoke, allowing for the particles to absorb more water and constituent gases.

In summary, the consistency and biological plausibility resulting from changes in combustion provide mechanistic support for a causal relationship between filter ventilation and the increased risk of lung adenocarcinoma, owing to a dose-response relationship between ventilation and increased toxicant yield. This applies to the full range of filter ventilation, including highly ventilated cigarettes with the lowest machine yields that have been previously marketed as “ultralights.”

Filter Ventilation Provides No Benefits to Smokers

Filter ventilation allows for the cigarette yields to be “elastic” when smoked by smokers. Increased puffing intensity resulted in a nonlinear increase in the concentration of tar and nicotine yields because ventilation and tar reduction depend on how fast and large the puff is (89,90). Varying puffing intensity allows smokers of ventilated cigarettes to titrate the nicotine yield, maintain their desired blood nicotine levels, and optimize nicotine reward (34,91). This process, known as “compensation,” is

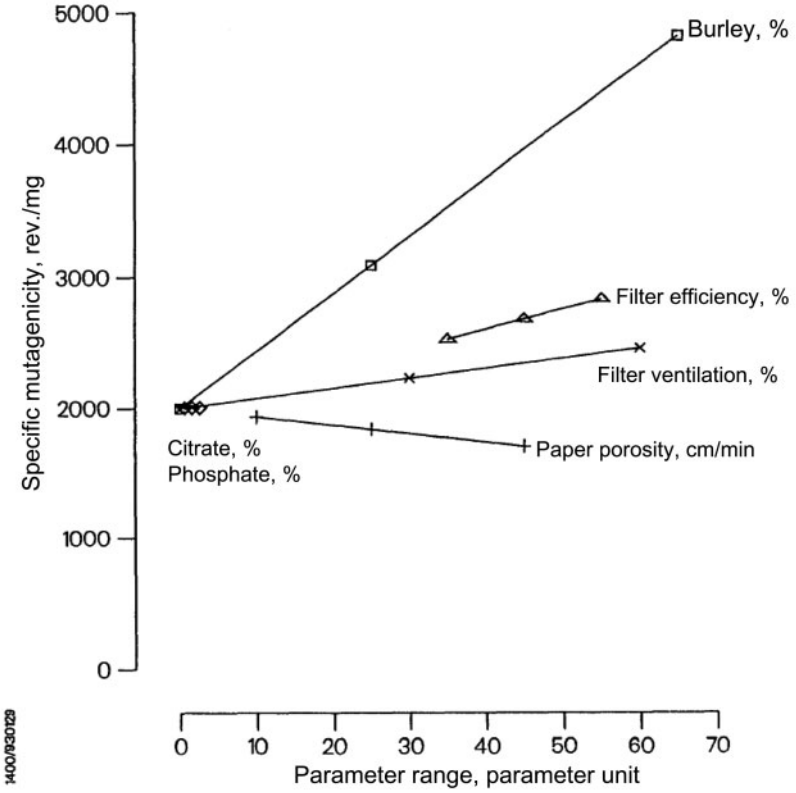

Figure 6. The increase in mutagenicity per % increase in ventilation, which was statistically significant. Source: Mutagenicity of the mainstream smoke condensate of 30 research cigarettes with differences in 6 parameters," 1993. Philip Morris Records. https://industrydocuments.library.ucsf.edu/docs/#id=thcc0126 (81).

accomplished by individual puffing styles (puff topography) of harder or longer puffs, or by blocking the ventilation holes with one's fingers (either consciously or unconsciously; most smokers are unaware of ventilation holes) (34,42,92–101). In 2006, a federal court decision determined that that the reporting of machine-rated tar and nicotine yields was "totally unreliable for measuring the actual nicotine and tar any real life smoker would absorb because it did not take into account the phenomenon of smoker compensation" (102). In November 2008, the FTC took action that prompted the removal of nicotine and tar listings from cigarette packs and ads. As of June 2010, the TCA prohibited the use of explicit or implicit descriptors on tobacco packaging or in advertising that convey messages of reduced risk or exposure, specifically including terms like "light," "mild," and "low" (103). Nonetheless, there has been no action to regulate filter ventilation, and ventilation holes in cigarette filters remain today on most cigarettes.

Replicating Human Puff Profiles on Smoking Machines

Academic studies replicating human smoking behavior on smoking machines demonstrated how none of the standardized smoking machine puffing regimens accurately predict exposure to smokers (42,104,105). For example, Djordjevic and colleagues found that smokers of 8 to 9 mg machine-rated tar yield cigarettes, when compared with 15 mg cigarette smokers, had a 2.5-fold higher intake of tar, nicotine, and TSNAs compared with the machine yield (104). Hammond and coworkers compared nicotine yields using different machine smoking regimens with actual exposure for smokers using salivary cotinine levels, showing that these are unrelated (105). While there are no published studies replicating human smoking behavior on a smoking machine by levels of ventilation, the Philip Morris Tobacco Company conducted several studies (cross-sectional and clinical trials) in the 1970s recording puffing behaviors by smokers and programming a smoking machine to replicate their profiles (106–111). They showed that filter ventilation resulted in a compensatory response by the smoker such that standard machine yields grossly underpredicted actual exposure and that compensation led to similar exposures from cigarettes with different ventilation levels.

Clinical Trials

The most direct evidence for determining a smoker's exposure from filters with different yield elasticity comes from clinical trials of smokers who switched to cigarettes with different levels of filter ventilation. These studies encompass a range of designs including smoking one or several cigarettes in a laboratory, confining smokers to an inpatient setting so that smoking is directly monitored, to longer-term switching trials in the naturalistic setting. Among these, longer-duration studies and those in the naturalistic setting are more informative because they allow smokers to adjust to taste and other cigarette characteristics and to compensate for changes in nicotine yields in the "real world." Also, studies with control groups (ie, smokers who continue to smoke their usual brand) are more informative as smokers may alter their behavior simply because they are in a study about smoking (112–119). The largest study conducted to date, which used commercial cigarettes that differ little except by filter ventilation, was conducted by Philip Morris (113). It studied 225 smokers of low-ventilation cigarettes (~10%) who

switched to higher-ventilated cigarettes (~17% or ~47%) or unswitched (controls). The smokers were first confined to an inpatient facility for eight days and had restrictions based on how much they could smoke per day. Then, they continued in a 24-week naturalistic environment study. Compared with the controls, there was no statistical reduction for switching to the approximately 17% cigarettes, and while there was some statistical reduction for some biomarkers when switching to the approximately 47% cigarette, it was much less than the expected reduction based on decreased tar yields. One limitation for this study is a high dropout rate at 24 weeks, although there are similar results for interval follow-ups. Other studies also indicate little to no difference in actual exposure reduction by filter ventilation or other methods to reduce exposures with ventilated cigarettes (eg, reduction in cigarettes per day) (89,112,113,116–118,120–122). These clinical studies are summarized in Supplementary Table 5 (available online).

Cross-Sectional Studies

These studies of general population smokers assess puff topography and exposure biomarkers at a single point in time. While clinical trials for cigarettes with different tar yields provide direct evidence for the effects of filter ventilation on exposure, there also are observational cross-sectional studies that provide corroborative data, although of lesser weight. A major limitation of these studies is that they provide little information about cause and effect because of inherent bias and confounding (eg is an observed difference in a biomarker level due to the cigarette design or due to self-selection by a smoker with innate characteristics). They also do not solely assess the effect of filter ventilation because marketed cigarettes differ by other characteristics. Nevertheless, consistent with the clinical trials, these studies (Supplementary Table 6, available online) demonstrate that exposure biomarkers are not statistically reduced when smoking cigarettes with differing tar yields and filter ventilation, except for perhaps some comparisons of the most extreme differences in tar yields (25,89,104,123–150). The largest study to date (n = 3600), also conducted by Philip Morris, was specifically designed to assess biomarker exposures by tar yields. This study showed few differences in biomarkers based on tar yields, and statistical differences were reported only for the most extreme comparisons of tar yields (137,144,151). Tar yield was substantially less of a predictor for nicotine exposure compared with number of cigarettes per day, nicotine dependence, and puff topography. Other studies, albeit smaller, show similar results (25,138,139,143,144). Separately, while machine--measured tar and nicotine levels have decreased over time, serial cross-sectional data over 25 years from the National Health and Nutrition Examination Survey (NHANES) demonstrate little overall change in daily nicotine intake among smokers, with cotinine per cigarette increasing by 42% over that time (152).

In summary, the consistency of the human clinical trials and cross-sectional studies demonstrates that lower machine tar yields do not predict lower exposures determined by biomarkers of exposure. And actually, puff volumes increase for smokers of cigarettes with more ventilation, suggesting greater exposures in the lung. Reported results in cross-sectional studies of lower biomarkers for smokers of cigarettes with the most ventilation may be due to the characteristics of the smokers choosing these cigarettes rather than the tar yields affected by ventilation (153). It can be noted that these studies do not support a causal relationship for filter ventilation and lung adenocarcinoma because they do not show increased levels of blood and urinary biomarkers. However, the above studies are somewhat limited in study design, do not measure exposure at the lung level, do not include validated biomarkers of harm, and the urine and blood studies might not be a surrogate for changes in lung exposure because of rapid absorption of carcinogens through the lung.

Effects of Filter Ventilation on Consumer Perception and Response

As early as 1955, filter ventilation was recognized by the tobacco industry to produce a smoke that is less strong, harsh, and irritating (58,154–159). This led smokers to believe that they are smoking a product that is less harmful (156,157,160). Most smokers are unaware of the presence of filter ventilation leading to this effect (161,162), although some might subconsciously partially block the holes with their fingers (23,163). These perceptions were reinforced by implicit and explicit advertising claims about safer cigarettes (20,23,34,101,162,164–181). Although tar yield descriptors are currently prohibited, the messaging remains because the coloring and packaging has not changed (180,181), and smokers retain their misperceptions about health effects based on the character and sensory effects of the smoke (20,23,34,101,162,164–179). Thus, an added adverse impact of filter ventilation is the fostering of a false belief that a lower-tar cigarette is a healthier cigarette.

Filter Ventilation, Inhalation, and Smoke Distribution in the Lung

The process of inhalation is separate from puffing for most smokers and is a multistep process of mouth-holding followed by inhalation (182–186). Filter ventilation allows smokers to have higher puff volumes and to take more frequent puffs (42), making more toxicants available to be inhaled to deeper parts of the lungs and allowing for greater retention of nicotine and toxic chemicals (42,182–184,187). To date, there are inconsistent results as to whether cigarettes with different tar yields directly influence inhalation, separate from allowing for more smoke to enter the lungs because of larger puff volumes, although the consensus within the academic community is that the depth of inhalation increases with greater filter ventilation (1,42,97,116,117,147,188–200). There is no validated method to assess inhalation for smoking, and the inconsistencies may relate to variations in methodologies, use of unnatural environments (eg, use of smoke chambers, constricting bands around the chest, and radiotracer studies), small study size, and inadequate study design (eg, single use or limited use). Importantly, many smoke constituents, such as nicotine, are rapidly absorbed through the lungs so that biomarker studies of the urine and blood might not reflect local lung exposures, and there is evidence for differential retention of particulate matter constituents such as TSNAs (97,184,186,201). Several studies have indicated that 95% to 100% of inhaled nicotine is retained, but only 60% to 97% of particulate constituents (186,201). Smoke reaching the most distal parts of the lung, where air flow decreases, allows for easier sedimentation of the particles. Also, particles may grow in size and water content in the lungs, allowing for more deposition and retention of particles with higher amounts of smoke toxicants due to filter ventilation (186,199,202). To validate this in humans, smoke distribution and retention would need to be directly measured, but these

methodologies do not exist. There is some data for smoke distribution using experimental animal studies and modeling, but these are not developed based on actual smoking behavior data, which likely underestimate deposition (199,203). These models also do not account for flow of the gas phase chemicals or account for changes in filter ventilation.

In summary, there is conflicting data to conclude that filter ventilation increases depth of inhalation. Furthermore, how particles distribute in the lung generally is unclear, and this has not been studied with respect to filter ventilation specifically. However, a logical inference is that smokers with larger puff volumes due to cigarette elasticity will make more smoke available to travel deeper into the lungs. Thus, greater depth of inhalation or a change in particle size do not necessarily need to occur to affect risk because more smoke is inhaled either way. The assumption of greater lung exposure to tobacco toxicants leading to an increased risk for lung adenocarcinomas due to filter ventilation is may not be in conflict with clinical trials and cross-sectional biomarker studies using blood and urine biomarkers because these studies do not provide information about lung exposure, distribution, or other local effects in the lung. Small differences in exposure that are distributed widely in the body may not be measurable and subject to numerous factors related to innate characteristics of the smoker and rapid transfer from the lungs to the blood stream. However, we postulate that small differences in exposure concentrated on a per-puff basis might have a large impact localized in the lungs.

REVIEW

Different Sensitivity of Distal Airway Lung Cells Leading to the Development of Different Types of Lung Cancer

Experimental studies and limited human evidence indicate that the distal airways of the lung contain cells prone to the development of adenocarcinoma and that these regions may be more sensitive to TSNAs. It should be noted that most lung carcinogenesis studies in experimental animals focus on TSNAs and polycyclic aromatic hydrocarbons (PAHs) and are limited both in number and type of animal models; other smoke toxicants increased by filter ventilation also may contribute. Experimental animal studies indicate that there are generally three types of epithelial cells in the lung, namely type I pneumocytes, type II pneumocytes primarily located in the alveolar space (more distal airways—probably the progenitors of type I pneumocytes) and Clara cells that are nonciliated and located in the terminal bronchioles (now known as club cells or bronchiolar cells and located in the more proximal region of the lung) (204,205). Although not well studied, there is evidence that type II pneumocytes are cells involved in inflammatory reactions (206), provide an inflammatory signal to recruit granulocytes and cause inflammation (207), and develop into adenocarcinoma (207–209), while the Clara cell lineage secretes anti-inflammatory proteins and reduced with smoking, and may be the precursor to both squamous cell lung cancer and adenocarcinomas (206,211,212). These cell types also have different carcinogen-metabolizing capacities (205,206,212–214). For example, more proximally located Clara cells have a greater ability to metabolize the carcinogen benzo(a)pyrene than type II pneumocytes, but the opposite occurs for TSNAs, although both cell types metabolize both carcinogens (205,215–217). Further, suggestive experimental animal studies indicate that NNK induces peripheral lung adenomas (219,220), while PAHs are more likely to induce central squamous cell tumors, although not exclusively (220–227). While there is some evidence that the Clara cells have more DNA damage than type II pneumocytes following exposure to NNK, the alveolar regions have more cell proliferation and tumors (215,223).

There are two prospective human studies assessing TSNA exposure and lung cancer risk (228–230). Neither considers filter ventilation in its analysis, but each provides important support for the relationship of TSNAs and lung cancer risk. In a case-control study nested within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Church et al. reported that a 1 standard deviation increase in urinary total NNAL (a metabolite of NNK) was associated with a 57% (95% CI = 8% to 128%) increased risk of lung cancer (229). When analyzed by lung cancer histology, the association of urinary NNAL with the risk of lung adenocarcinoma was statistically significant, but the results for other lung histologies combined were elevated, but not statistically significant. The second study, using the Shanghai Cohort Study and the Singapore Chinese Study, also showed an overall increased lung cancer risk with higher levels of NNK exposure (230,231); data for specific cancer subtypes were not provided because histological confirmation was not done for many subjects.

In summary, experimental animal studies indicate that the distal airways may be more sensitive to NNK than the proximal regions of the lung. Limited human cohort studies identify NNK as contributing to lung cancer risk, particularly for adenocarcinomas. Given that filter ventilation increases NNK (as do other factors) and that larger puffs of smoke with higher NNK levels can reach the distal airways, along with other toxicants, these studies add to the biological plausibility for a relationship of filter ventilation to increased lung adenocarcinoma.

Weight of Evidence Review and Causation Analysis

This weight of evidence review broadly uses three groups of evidence, namely laboratory experimental data, human smoking behavior studies, and the epidemiology of lung cancer. Table 1 and Figure 7 summarize our weight-of-evidence review in terms of the consistency of evidence, evidence of dose-response, temporality of exposure, strength of association, specificity of the evidence, and other causal criteria as they relate to the relationship of filter ventilation causing an increased risk of lung adenocarcinoma. In this analysis, human studies are given the greatest weight (clinical trials > cross-sectional studies; prospective studies with lung cancer outcomes for variation in ventilation would be given the greatest weight, but none directly exist), while experimental animal and toxicology studies are useful to support mechanistic associations because the direct extrapolation from the laboratory to human risk is not possible.

A mode of action and human relevance framework also was applied, which is summarized in Supplementary Table 3 (available online). In addition to what is identified for Table 1 and Figure 7, this framework also identifies what data may be inconsistent with a causal relationship and also what data are missing, for example a future research agenda.

Consistency

There is consistency within evidence categories among the experimental data, human behavior studies, and lung cancer epidemiology (with the exception of filter ventilation affecting inhalation and smoke distribution). Numerous studies from the tobacco industry and academia indicate that filter ventilation, in spite of decreasing tar yields using standardized smoking machine methods on a per-cigarette basis, increases the

Table 1. Causation analysis for filter ventilation leading to lung adenocarcinomas

Criteria	Human smoking behavior: compensation (puff topography and/or biomarker studies), increased, inhalation, and perception*	
Consistency	Compensation: +++	Both clinical trials and cross-sectional studies demonstrate compensation, although human biomarker studies using urine and blood assays indicate that circulating exposures may not be increased
	Inhalation: +	Available studies use methodologies that are not validated, and methodologies were used differently across studies, precluding an assessment of consistency
	Perception: +++	Consumer perception studies indicate that the feelings of "lighter smoke" provide a sense of health benefit
Dose response	Compensation: +++	Increasing filter ventilation increases compensatory response
	Inhalation: IA	Insufficient study of increasing ventilation on inhalation parameters
	Perception: ++	Consumer perception studies indicate that the feelings of "lighter smoke" provide a sense of health benefit, but assessing degree of response based on amount of ventilation has received limited study
Timing of exposure	Compensation: +++	Filter ventilation precedes the effect in experimental and observational studies
	Inhalation: +++	Filter ventilation precedes the effect in experimental and observational studies
	Perception: +++	Filter ventilation precedes the effect in experimental and observational studies
Strength of association	Compensation: ++	Degree of compensation commensurate with dose response
	Inhalation: IA	Inadequate study using methods that are not validated or consistent across studies
	Perception: ++	Magnitude of effect less clear based on degree of filter ventilation
Specificity	Compensation: ++	Filter ventilation causes compensation, but other cigarette design changes also may cause compensation; filter ventilation is the principal way of reducing smoking machine tar yields for conventional cigarettes
	Inhalation: IA	Inadequate study using methods that are not validated or consistent across studies and, other factors that affect nicotine yields may affect inhalation
	Perception: ++	"Lighter" smoke leads to false perceptions of health benefits, but other branding could cause misperceptions
Biological plausibility	Compensation: +++	Reduction in nicotine yield by filter ventilation causes smokers to compensate their puffing to address nicotine dependence
	Inhalation: +++	Reduction in nicotine yield by filter ventilation causes smokers to compensate their inhalation to address nicotine dependence
	Perception: +++	"Lighter" smoke reduces sensory effects, leading to false perception of health benefit
Coherence	Compensation: +++	Experimental laboratory methods consistent with human studies (trials and cross-sectional studies), although other methods to lower nicotine yields may also affect compensation; human biomarker studies using urine and blood assays indicate that circulating exposures may not be increased
	Inhalation: IA	Laboratory studies cannot assess this; inadequate study of filter ventilation for experimental human and observational studies
	Perception: +++	Experimental human studies consistent with cross-sectional studies
Human interventions	Compensation: +++	Clinical trials demonstrate compensation
	Inhalation: +	Inconsistent results for human clinical trials
	Perception: +++	Clinical trials (human laboratory studies) demonstrate the sensation of a "lighter" smoke, leading to false perceptions of a health benefit
Analogy	Compensation: +++	Other methods to lower nicotine yields may affect compensation
	Inhalation: IA	There has been inadequate study of various cigarette designs that may affect inhalation
	Perception: +++	Flavors and branding/marketing with claims for health benefits also lead to a false perception of a health benefit
Increased lung adenocarcinoma risk and rates		
Consistency	++	Numerous ecological and observational cohort studies are consistent for lower tar yields, leading to increased lung adenocarcinoma, but the direct assessment of filter ventilation on risk has not been done, nor is it feasible
Dose response	++	Lower tar yield cigarettes lead to increased risk and rates of lung adenocarcinomas, but there has been insufficient study and consistency by levels of filter ventilation, eg, risk across the full spectrum of tar and nicotine yields, including "ultralight" cigarettes
Timing of exposure	++	Rise in adenocarcinomas coincident with use of filter ventilation, but latency suggests that additional factors may contribute
Strength of association	++	Large rates and risk changes with use of cigarettes manufactured after the introduction of filter ventilation
Specificity	++	Other cigarette design changes such as increased nitrates and changes in tobacco blend also likely contribute

(continued)

Table 1. (continued)

Criteria	Human smoking behavior: compensation (puff topography and/or biomarker studies), increased, inhalation, and perception*	
Biological plausibility	+++	Changes in the way tobacco burns and smoke yields are consistent with the effects on location and cell sensitivity for lung adenocarcinomas
Coherence	++	Experimental animal studies indicate that NNK causes lung adenocarcinomas; other design changes increasing NNK could also cause increased lung adenocarcinoma risk
Human interventions	IA	Not feasible to test
Analogy	IA	Nitrates and tobacco blends could alter NNK yields, which cannot be separately tested from filter ventilation given that both design features changed simultaneously
Experimental data: increased chemical yields including NNK, increased mutagenicity, change in particle size, and sensitivity to NNK for distal lung cells		
Consistency	Smoke constituent yields: +++	Multiple published and unpublished studies demonstrate the effect for increasing chemical yields per mg/tar and per mg/nicotine, including TSNAs
	Mutagenicity: +++	Multiple published and unpublished studies demonstrate this adverse effect; tumorigenicity effects have not been studied
	Particle size: +	Multiple studies indicate an effect on particle size, including increased water content; how this affects smoke distribution in the lung is unclear
	Distal airway lung sensitivity: +	Epidemiology studies show increased risks and rates for adenocarcinoma with lowering tar yields over time, and adenocarcinomas occur more frequently in the lung periphery, where experimental studies show that the lung cells are more sensitive to NNK
Dose-response	Smoke chemical yields: +++	Numerous studies show that increasing levels of filter ventilation cause a dose-response increase in chemical yields, including NNK, per mg of tar or nicotine
	Mutagenicity: +++	Numerous studies show increasing levels of filter ventilation cause a dose-response increase in Ames mutagenicity
	Particle size: +	Increased ventilation increases particle size and water content, although how this affects lung distribution is unclear mechanistically
	Distal airway lung sensitivity: +	This has not been directly studied, although there is a dose-response effect for NNK and lung adenocarcinoma in experimental animal studies
Timing of exposure	Smoke chemical yields: +++	Laboratory experimental studies directly assess exposures leading to outcomes
	Mutagenicity: +++	Laboratory experimental studies directly assess exposures leading to outcomes
	Particle size: +++	Laboratory experimental studies directly assess exposures leading to outcomes
	Distal airway lung sensitivity: +++	Laboratory experimental studies directly assess exposures leading to outcomes
Strength of association	Smoke chemical yields: ++	Increased chemical yields cannot be extrapolated to human risk
	Mutagenicity: ++	Increased mutagenicity cannot be extrapolated to human risk
	Particle size: IA	There has been inadequate study for understanding the magnitude of effect on particle size and smoke distribution, so that extrapolation to human risk is not possible
	Distal airway lung sensitivity: IA	There has been inadequate study for understanding the magnitude of effect on lung cell sensitivity, so that extrapolation to human risk is not possible
Specificity	Smoke chemical yields: +	Other cigarette design parameters affect smoke chemistries, and some chemical constituents can be directly transferred from tobacco
	Mutagenicity: +	Other cigarette design parameters affect Ames mutagenicity
	Particle size: ++	Other cigarette design parameters affect particle size and lung distribution
	Distal airway lung sensitivity: IA	Other cigarette design parameters affect lung sensitivity, such as those that also increase NNK
Biological plausibility	Smoke chemical yields: +++	Changes in the way the tobacco column is burned increase incomplete combustion and burn time
	Mutagenicity: +++	Changes in the way the tobacco column is burned increase incomplete combustion and burn time, affecting yields that increase mutagenicity
	Particle size: +++	Changes in the way the tobacco column is burned increase chemical constituents in the particles and water content
	Distal airway lung sensitivity: +++	Peripheral lung cells in experimental animals metabolize NNK differently and have related carcinogenic effects
Coherence	Smoke chemical yields: +++	Multiple experimental studies demonstrate the effect on how tobacco is burned and increased per-nicotine yields of many constituents including NNK
	Mutagenicity: +++	Multiple experimental studies demonstrate the effect on how tobacco is burned and increased levels of some constituents' formation of chemicals that can increase mutagenicity

(continued)

Table 1. (continued)

Criteria	Human smoking behavior: compensation (puff topography and/or biomarker studies), increased, inhalation, and perception*	
	Particle size: IA	Other cigarette designs affecting particle size have not been adequately studied
	Distal airway lung sensitivity: +++	Multiple experimental studies indicate the metabolizing effects and the induction of tumors by NNK
Human interventions	Not applicable	
Analogy	Smoke chemical yields: +	Other design changes, such as filter efficiency, can affect chemical yields, but this also is affected by filter ventilation
	Mutagenicity: +	Other design changes, such as filter efficiency, can affect mutagenicity, but this also is affected by filter ventilation
	Particle size: IA	Inadequate study
	Distal airway lung sensitivity: IA	Inadequate study

*Grading of evidence based on scientific judgment: no relationship (0), limited evidence (+), strongly suggestive evidence (++), sufficient evidence (+++), or inadequate study (IA). NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; TSNAs = tobacco-specific nitrosamines.

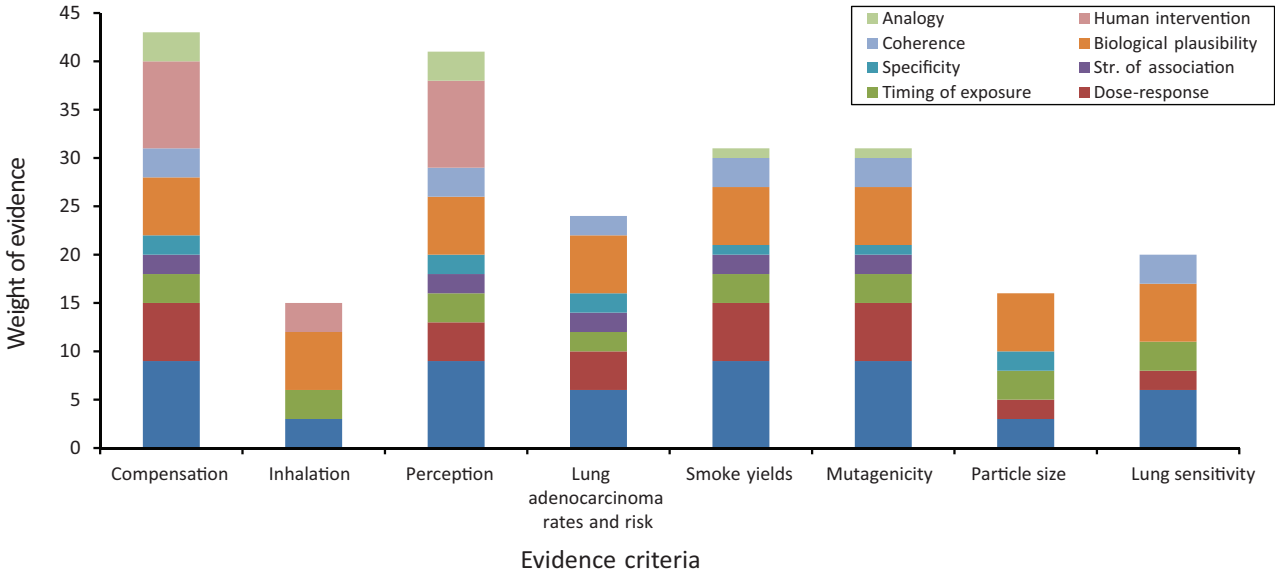

Figure 7. Evidence blocks for causation analysis. Grading of evidence showing the confidence in the weighting, from 0 to 45, based on scientific judgment: no relationship (0), limited evidence (+), strongly suggestive evidence (++), sufficient evidence (+++), or inadequate study (IA); the **taller the block**, the higher the level of evidence. Both IA and no relationship are treated as 0 and do not appear in **blocks**. Some criteria are weighted more heavily than others, as follows: Consistency and human intervention are adjusted for the greatest weight (factor of 3), dose response and biological plausibility are adjusted for a medium weight (factor of 2) and the others are unadjusted.

generation of smoke toxicants, carcinogens, and mutagens on a per-mg-of-tar-and-nicotine basis. Smoking behavior and exposures are clearly affected by smoking machine nicotine yields, such that smokers of low–nicotine yield cigarettes demonstrate an increase in puffing behavior due to the elasticity of the cigarette filter ventilation. This is borne out by both clinical trials and cross-sectional studies (see Supplementary Tables 5 and 6, available online). The effects of filter ventilation on depth of smoke inhalation are less clear for consistency or show no effect. However, the methodologies to assess depth of inhalation and particle deposition are not well developed, largely rely on methods that have not been validated, use statistical modeling that also is not validated, and do not consider gases and inhaling more smoke. Studies of smoke particle distribution consistently show increased size with ventilation (see Supplementary Table 4, available online). It should be noted that increased depth of inhalation may not be required to alter regional distribution and adenocarcinoma risk because smokers either way are increasing the amount of smoke inhaled into the lungs because of larger puff volumes.

The research data indicating the shift from squamous cell cancers to adenocarcinomas have been replicated among studies, concurrent in time with lowering tar yields and the use of filter ventilation. Other data indicate that lung cancer risk from smoking more modern cigarettes has increased over time, by considering birth cohorts of men separately from women. It is not possible to directly assess the impact of cigarette design on lung cancer risk because almost all cigarettes on the market simultaneously decreased tar yields and increased filter ventilation, although, limited prospective data associate an increase in TSNA exposure with

adenocarcinomas. It is not possible at this time to assess lung cancer risk from the highest ventilated filters ("ultralights") because these were only introduced to the marketplace in the late 1990s, so that there has not been enough latency to observe a change in risk, and relatively few smokers smoke these cigarettes.

Dose Response

There is consistency among experimental studies for increasing filter ventilation, resulting in increased toxicant yields and mutagens. Increasing filter ventilation affects smoking behavior and increases puff volumes, but the effects on inhalation are less clear and not studied based on levels of ventilation. Human studies of smoking behavior do not show increased biomarker levels with lower-tar cigarettes, and some biomarkers may decrease, but these do not assess regional lung exposure. Temporal trends of decreasing tar yields and decreasing cigarette smoking rates, concurrent with increasing risks based on birth cohorts that progressively imitate the use of ventilated filter cigarettes, are consistent with a dose-response effect, although studies directly assessing filter ventilation or risks by tar yields are not available.

Biological Plausibility and Coherence

These two criteria are met given the full range of studies from the laboratory to population-level surveillance, which provides important scientific support, although there is some uncertainty relating to human biomarker exposure studies. How filter ventilation increases tobacco toxicant yield, mutagenicity, and particle size is understood. The elasticity of filter ventilation allows for increasing puffing behavior, allowing for more of the toxicants to enter the lungs, which then exposes distal airway lung cells that are more sensitive to NNK and the development of adenocarcinomas. Coherence comes from experimental studies of specific tobacco toxicants and animal tumorigenesis, as well as mutagenicity and other cell culture studies. Human studies using biomarkers of exposure showing similar levels of exposure for smokers of cigarettes with different degrees of ventilation present some uncertainty, and while these studies are consistent with each other, they present an argument against coherence. The human studies indicate, however, that there is no difference rather than a beneficial effect. As noted above, the human studies using urine and blood biomarkers may not reflect exposures at the target organ level (ie the lung) where lung adenocarcinomas occur, and they do not use validated biomarkers of harm. Thus, this area is an important research gap to address.

Specificity

While there is highly suggestive evidence to conclude that filter ventilation has increased the rates of lung adenocarcinoma, there are other potential causes. As noted in the 2014 SGR, in addition to filter ventilation, there is suggestive evidence that increased levels of TSNAs over time also could explain the increased adenocarcinoma risks. However, one mechanism does not preclude the other, and both may be contributing (232); filter ventilation further increases NNK levels on a per-mg-of-tar-and-nicotine basis. Higher levels of NNK and other TSNAs in cigarette smoke can be driven by their increases in tobacco filler as a result of changes in tobacco blend content (eg increasing burley tobacco content), increase in nitrate content, and changes in microbial contamination (16,1,46,231–236). While most NNK yields in smoke happen as a direct transfer from tobacco, additional amounts may also be formed during tobacco burning, with nitrate-rich tobaccos potentially generating higher levels of NNK (238). While filter ventilation influences NNK levels less than changing tobacco leaf blends filter ventilation also increases other toxicant exposures.

Other Criteria

Several other causation criteria are met, although the emphasis of these is less, such as timing of exposure, where all the clinical trials and experimental studies demonstrate effects after exposure (or lack of effects); strength of association, which is inferred in some cases because the totality of the data indicates significant strength to cause a measurable change in adenocarcinoma rates and risks; and analogy, such as experimental animal studies using specific smoke constituents, such as NNK.

Discussion

This weight of evidence review and causation analysis strongly suggests that the inclusion of ventilation in cigarette filters has contributed to increased lung adenocarcinomas among smokers. There are some uncertainty and research gaps as noted below, including the potential lack of coherence between mechanistic smoking machine yields and human exposure biomarker studies (the machine studies indicate the potential for increased exposure while the human studies indicate no difference). Thus, it should not be concluded that there is sufficient evidence for causality, rather that this review leads to a conclusion that the data is highly suggestive. Importantly, the weight of evidence does not indicate a public health benefit for the inclusion of filter ventilation. The smoke from cigarettes with ventilated filters provides false perceptions to the smoker of reduced harmfulness. Filter ventilation affects how the tobacco burns, smoking behavior, and how the lung is exposed to carcinogens, so that it plausibly contributes to the increased adenocarcinomas by a cigarette that the smoker falsely believes is less harmful. Epidemiologic data provide indirect evidence for filter ventilation as a contributing factor to the increased lung adenocarcinoma rates and risks.

The FDA has the regulatory authority to issue cigarette "product standards" (Section 907(a))(4), regulating the "construction," "components," or "properties" of tobacco products. To do this, the FDA must have evidence that a product standard would be "appropriate for the protection of public health." Based on the findings from this weight-of-evidence review, we would recommend that the FDA ask cigarette manufacturers to provide clear and convincing evidence that there is a public health benefit gained by filter ventilation in filter design and that the benefits outweigh any health risks. Absent such clear and convincing evidence from any source, the FDA should consider adopting a standard to prohibit filter ventilation. Given that there are cigarettes with 0% ventilation already on the market in the United States and elsewhere, the tobacco industry can feasibly implement this change (72,238–240).

While there may be other cigarette design features that have contributed to the risk of smoking and the rise of adenocarcinomas compared with squamous cell cancers (232), it is our belief, based on the evidence reviewed herein, that filter ventilation has contributed to at least some of the increased risk. It should be noted that an FDA action regulating filter ventilation would not imply that filter ventilation is the only or most important cigarette design to impact lung cancer risk, and a filter ventilation standard could be adopted alone or in conjunction with other product standards, for example addressing NNK exposure

or other aspects of cigarette design that contribute to addiction and disease risk. If the FDA prohibits filter ventilation, it may issue complementary regulations that restrict other design methods that reduce exposures, for example using higher amounts of expanded tobaccos, decreasing rod length, using tobacco strains and curing methods to reduce TSNA formation, and using highly activated carbon filters, so long as the FDA has concluded that these other regulations would not adversely affect smoking behavior (16,242,243).

Using the SEER 9 database, we calculated the yearly age-adjusted incidence rates for adenocarcinoma, squamous cell carcinoma, and total lung cancer cases for men between 1975 and 2012. Using the CDC WONDER Population Projections (http://wonder.cdc.gov/population.html), and we computed the number of new adenocarcinomas and squamous cell cases in the overall US male population for the years 2008 to 2012. We found an excess of 32 400 adenocarcinoma cases when compared with squamous cell carcinomas (data not shown). While this may not be solely attributable to filter ventilation, this represents an adverse public health impact. Equally important, there is no existing evidence that filter ventilation reduces lung cancer risk or has any other beneficial health effect that would argue against regulation.

There are important research gaps that have been identified, including the reconciliation for coherence of human biomarker studies showing no increased exposure for smokers using cigarettes with higher degrees of ventilation and patterns of inhalation and smoke distribution in the lung. These would need to be addressed by lung biomarker studies, including biomarkers of harm, for example, using bronchoscopy to collect biospecimens as smokers switch from ventilated cigarettes to unventilated cigarettes. Importantly, prior to the regulation of filter ventilation, the FDA also will need to assess possible unintended effects of regulating filter ventilation, including a ban, for example increasing smoking initiation, delaying cessation due to perceptions that these are safer cigarettes, and that these would not likely outweigh the benefits. To date, there are no studies on the impact of removing filter ventilation on smoking behavior and perceptions, the addictiveness of unventilated cigarettes, and the resultant exposures and toxicity. This and other data gaps are indicated in Supplementary Table 3 (available online). If ventilation were removed from cigarette filters, we expect three possible results: 1) that toxic exposure will be decreased because the cigarette delivery is no longer elastic, limiting the ability of the smoker to compensate with larger puff volumes; 2) the greater amount of nicotine in smoke will result in the smoker decreasing the number of cigarettes per day and less smoke will enter the lungs; and 3) some smokers may quit smoking or transition to alternative nicotine delivery systems such as electronic cigarettes or nicotine replacement therapy because of the harshness of the cigarette smoke and perceptions of a more harmful smoke. To assess this, a combination of human and experimental animal studies could be conducted in the context of the conceptual framework for tobacco product evaluation (244). For example, clinical trials could assess smokers switching to filtered cigarettes without ventilation and with different packaging and study smoking topography, inhalation depth, and biomarkers of nicotine exposure and smoke toxicants. Because no single biomarker is available that can be used alone to predict the reduction in harm from smoking (ventilated vs nonventilated cigarettes), a panel of biomarkers of exposure to carcinogens and lung toxicants, markers of oxidative damage and inflammation should be measured in lung, blood, or/and urine. The studies also should assess smokers' perceptions, appeal, and transition to alternate products, for example electronic cigarettes and nicotine replacement therapy (behavioral economics and abuse liability). Studies would need to be done in ways to assess differing effects by race and ethnicity, gender, age, and vulnerable populations to inform the potential population-level effects. Experimental animal studies that allow for manipulations in both adolescent and adult rodents would parallel the human trials to provide evidence for the impact on smoking initiation. Another research agenda item could focus on the impact of filter ventilation on the risk of other diseases (eg chronic obstructive pulmonary disease), given shared etiologies due to tobacco toxicants. Such research would provide additional support for an FDA regulatory action.

In conclusion, the use of ventilation in the filters of cigarettes has failed to make cigarettes safer, and more than likely has made them more harmful. There is no demonstrated public health benefit, and smokers perceive these as less harmful, which in turn encourages smoking and causes harm. The FDA now has the authority to require the elimination of filter ventilation because ventilation does not serve any public health purpose and instead provides a false promise of reduced risk. This single action for banning filter ventilation by the FDA is scientifically justified and within its mandate to improve the public health. Based on these weight-of-evidence reviews, the FDA should embark on a regulatory process of data evaluation and consider regulation(s) for the use of ventilation in filters, up to and including a ban on their use.

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