



Commentary

Genetic Susceptibility to Thirdhand-Smoke-Induced Lung Cancer Development

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Abstract

Recently, potential health concerns have been raised about thirdhand smoke (THS), a much less well-understood type of smoke exposure defined as residual tobacco smoke sorbed onto indoor surfaces after active smoking has ceased. THS exposure is derived from the involuntary inhalation, ingestion, or dermal uptake of indoor pollutants. The timescale for exposure to THS pollution is generally much longer than secondhand smoke, and could stretch to days, months, or years (long-term, low-level exposure). Recent studies showed that exposure to THS at early age in mice can affect body weight, immunity, and lung cancer development. However, adverse health effects of THS in human populations remain poorly understood and many questions remain unanswered. One major question is how genetic factors influence susceptibility to THS-induced health effects, especially tumor development and whether there is an age-specific window of susceptibility for these effects. By addressing these questions, we will provide a better understanding of the effects of THS on human health and disease. This information would address critical knowledge gaps that are required for the formulation of policies related to indoor air quality.

Implications: THS, the residual tobacco smoke remaining in the environment after tobacco has been smoked, represents an underestimated public health hazard. Evidence supports its widespread presence in indoor environments. Vulnerable populations are believed to include infants and children living in a smoking household exposed to THS and/or secondhand smoke, and exposure has been identified as a risk factor for lung cancer later in life. These and future studies will provide novel and important evidence of how early-life exposure to THS affects cancer development and other diseases, which should be useful for framing and enforcing new policies against passive smoking in the world.

Thirdhand smoke (THS) has gained wide attention in the last ten years as a previously overlooked source of exposure to toxicants in secondhand tobacco smoke (SHS). The US Surgeon General Reports of 1964 (on active smoking)¹ and 1986 (on passive smoking)² warned the public about what is known about the dangers of exposure to cigarette tobacco smoke. What is THS? THS includes tobacco chemicals that remain on surfaces and in dust after active smoking has ceased, as well as constituents that are reemitted back into the gas phase and/or react with environmental pollutants to produce secondary toxicants.³ Many toxic compounds in

THS, including those produced *de novo*, have been identified in laboratory systems and in field studies.^{3–5} In comparison to its precursor SHS, THS accumulates over time, and exposure occurs through different routes including inhalation, ingestion, and dermal contact. Therefore, THS exposure occurs through routes not previously recognized. Inhalation of tobacco smoke, both by active smokers and by nonsmokers involuntarily, has been causally linked to a wide range of adverse biological endpoints and diseases. However, the adverse health effects of THS exposure remain largely unclear.

Given that young children are considered to be an at-risk population for adverse health effects associated with THS exposure due to both physiological and behavioral reasons,³ we evaluated the tumorigenic potential of short-term early-life THS exposure using a mouse model. To mimic indoor surface exposure, mice were exposed to THS materials generated using a laboratory smoking chamber. The concentrations of THS constituents in these materials were measured and estimated to be comparable to the ingestion exposure of a toddler.⁶ We observed a significant increase in the lung cancer incidence in exposed mice compared to control treated mice. Cell culture studies using human lung cancer cell lines showed that THS exposure induced tumorigenic phenotypes including increased cell proliferation and colony formation. Mechanistically, our data suggest that THS exposure increases lung cancer risk through the induction of DNA double-strand breaks.⁶⁻⁸ Taken together, our data indicate that early-life exposure to THS could be associated with increased risk of human lung cancer (Figure 1).

Many of the toxic chemical compounds in THS are also found in SHS³; it is believed that THS could cause biological and health effects similar to those from exposure to SHS, a known carcinogen. In spite of these similarities, THS components can react with its environment to generate secondary toxicants. Human exposures to THS often consist of mixtures also containing SHS. This makes characterizing the human health risks associated with THS exposure alone challenging. Genetic and life-style heterogeneities in humans are further confounding THS exposure effect studies in human populations. Studies in model systems can bridge this knowledge gap and help build a risk assessment model and identify biomarkers of THS exposure, which can then be translated to human to estimate the risk of THS exposure for human disease development.

In humans, although cigarette smoking is the primary risk factor for lung cancer, recent data show that there is a distinct population of patients with lung cancer among never smokers and the number of such patients is increasing in the United States and other countries.^{9,10} In the United States, approximately 10% of patients with lung cancer are never smokers,¹¹ whereas in Asia, >30% of patients with lung cancer have never smoked and this percentage is significantly higher in Asian women.¹² Men are more likely to develop squamous cell lung cancer, while in women lung adenocarcinoma, which is strongly associated with tobacco smoke exposure, is the most common type.^{12,13} Currently there is a strong inquiry with regard to the etiology or risk factors of this type of lung cancer. It is known that, among other factors such as air pollution and radon, SHS is a major risk factor for lung cancer in never smokers.^{14,15} In the United States, exposure to SHS caused more than 7300 lung cancer deaths each year during 2005–2009 among adult nonsmokers.¹⁶ However, a recent study showed that the high incidence of lung cancer in Asian never smokers seems unlikely to be due to SHS.¹⁷ Whether THS exposure is a contributing factor to these observations requires further investigations.

Aged THS presents a new or hidden danger to nonsmokers. Compared to fresh SHS, THS may become more toxic during its evolution from SHS. Secondary analysis of unpublished 1980s animal data from Philip Morris Tobacco Company concluded that fresh SHS can become more toxic as it ages and that concentrations of carcinogenic tobacco-specific nitrosamines (TSNAs) increased over time in aging SHS.¹⁸ Moreover, studies found that compounds in SHS sorbed onto indoor surfaces can react with common indoor pollutants and generate new and even more toxic species.¹⁸ For example, chemical transformation in SHS, that is, the reaction of nicotine with indoor nitrous acid, can form TSNAs, including

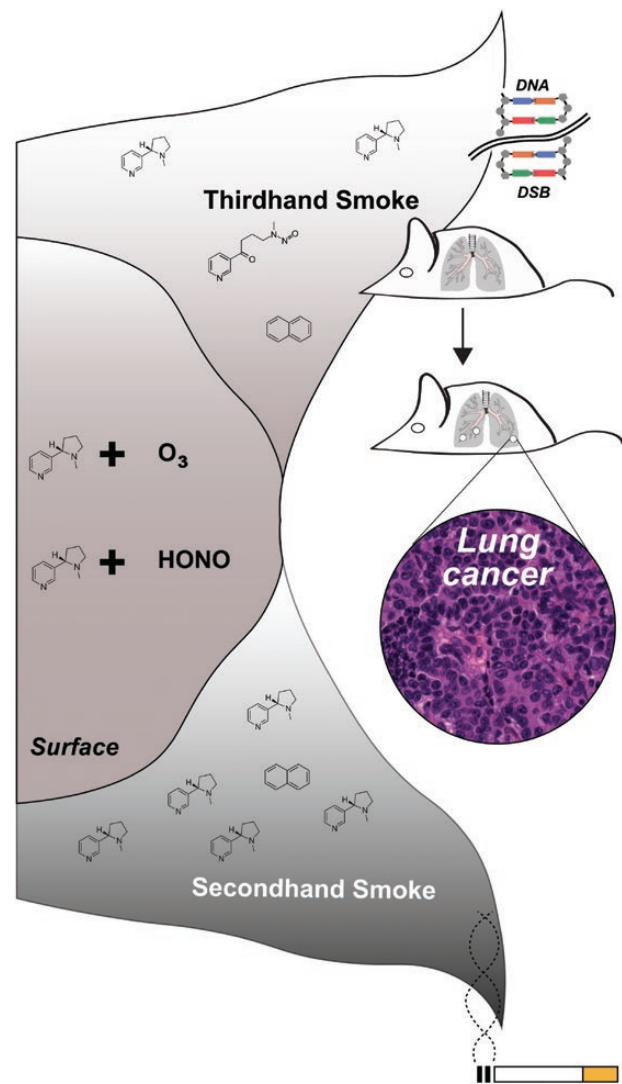


Figure 1. Schematic overview of interaction of thirdhand smoke (THS) with its environment and associated lung cancer risk. Compounds in secondhand smoke sorbed onto indoor surfaces can react with common indoor pollutants, including ozone (O_3) and nitrous acid (HONO), to produce new and even more toxic species that are components of THS. These chemicals can induce DNA double-strand break (DSB) and increase lung cancer risk.

NNA (1-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridinyl)-4-butanol), NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), and NNN (*N*'-nitrososornicotine). Nitrous acid can be generated from unvented gas appliances as well as vehicle engines. NNK and NNN are known human lung carcinogens.¹⁹ The levels of TSNAs found on indoor surfaces are hundreds of nanograms per square meter, which can further increase with frequent smoking. Therefore, we speculate that exposure to THS toxins in never smokers may contribute to the risk or development of lung cancer.

Future directions of research should include biomarker identification, genetic predisposition, and human population studies. First, it is critical to identify THS-specific exposure biomarkers. In addition to further characterizing THS to identify novel carcinogens, other biomarkers of exposure should also be explored including THS metabolites, THS-specific DNA-adducts, and THS-specific genetic and epigenetic biomarkers. Second, host genetics can influence

gene expression patterns, which can help identify susceptible populations. Finally, we will need to define the window of susceptibility of THS-induced health outcomes. These studies can be initiated in population-based model systems, which can then guide human genome-wide association studies. Data from these studies will be important to formulate novel cancer preventive strategies including educating health practitioners, families, and public health providers and organizations regarding the potential risks of environmental THS exposures and should be useful for framing and enforcing new policies against passive/indoor smoking.

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Declaration of Interests

None declared.

References

1. U.S. Department of Health, Education and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington, DC; 1964.
2. Department of Health and Human Services. *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General*. Rockville, MD; 1986.
3. Jacob P III, Benowitz NL, Destailats H, et al. Thirdhand smoke: new evidence, challenges, and future directions. *Chem Res Toxicol*. 2017;30(1):270–294.
4. Destailats H, Singer BC, Lee SK, Gundel LA. Effect of ozone on nicotine desorption from model surfaces: evidence for heterogeneous chemistry. *Environ Sci Technol*. 2006;40(6):1799–1805.
5. Sleiman M, Gundel LA, Pankow JF, Jacob P III, Singer BC, Destailats H. Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. *Proc Natl Acad Sci U S A*. 2010;107(15):6576–6581.
6. Hang B, Wang Y, Huang Y, et al. Short-term early exposure to thirdhand cigarette smoke increases lung cancer incidence in mice. *Clin Sci (Lond)*. 2018;132(4):475–488.
7. Dhall S, Alamat R, Castro A, et al. Tobacco toxins deposited on surfaces (third hand smoke) impair wound healing. *Clin Sci (Lond)*. 2016;130(14):1269–1284.
8. Hang B, Sarker AH, Havel C, et al. Thirdhand smoke causes DNA damage in human cells. *Mutagenesis*. 2013;28(4):381–391.
9. Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers—a review. *Eur J Cancer*. 2012;48(9):1299–1311.
10. Wakelee HA, Chang ET, Gomez SL, et al. Lung cancer incidence in never smokers. *J Clin Oncol*. 2007;25(5):472–478.
11. Scagliotti GV, Longo M, Novello S. Nonsmall cell lung cancer in never smokers. *Curr Opin Oncol*. 2009;21(2):99–104.
12. Toh CK, Wong EH, Lim WT, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: a retrospective analysis. *Chest*. 2004;126(6):1750–1756.
13. Yang P, Cerhan JR, Vierkant RA, et al. Adenocarcinoma of the lung is strongly associated with cigarette smoking: further evidence from a prospective study of women. *Am J Epidemiol*. 2002;156(12):1114–1122.
14. Brennan P, Buffler PA, Reynolds P, et al. Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. *Int J Cancer*. 2004;109(1):125–131.
15. Vineis P, Airolidi L, Veglia F, et al. Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study. *BMJ*. 2005;330(7486):277.
16. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. 2014.
17. Krishnan VG, Ebert PJ, Ting JC, et al. Whole-genome sequencing of Asian lung cancers: second-hand smoke unlikely to be responsible for higher incidence of lung cancer among Asian never-smokers. *Cancer Res*. 2014;74(21):6071–6081.
18. Schick SF, Glantz S. Concentrations of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in sidestream cigarette smoke increase after release into indoor air: results from unpublished tobacco industry research. *Cancer Epidemiol Biomarkers Prev*. 2007;16(8):1547–1553.
19. Hecht SS. Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. *Lancet Oncol*. 2002;3(8):461–469.