From: [redacted]
To:

Date: Sunday, July 01, 2018 03:58PM
Subject: qz.com-After conquering the US Juul e-cigarettes are going global.pdf

History: This message has been forwarded.

Juul units and capsules are made in China

The nicotine salts liquid is made in USA

Each capsule holds 59mg/ml nicotine salts

The latest 10 year study of 200,000 adults using ecigs in UK found they did not work as smoking cessation products.

The intended use of all ENDs products is to initiate and prolong nicotine addiction

Attachments:

qz.com-After conquering the US Juul e-cigarettes are going global.pdf

After conquering the US, Juul e-cigarettes are going global

qz.com/1318931/juul-e-cigarettes-having-conquered-the-us-are-heading-to-the-rest-of-the-world

Dave Gershgorn

Juul, the San Francisco-based e-cigarette company, is starting to look a lot like Google. Sure, its 68% of the US market share is inching towards Google's 87%, but it's attained that coveted pop-culture marker of becoming a verb. Just like people Google, people Juul (paywall).

But the company's success until now has been limited the US and Israel, far from the world's biggest markets for smokers. Juul is now seeking $1.2 billion in funding to tackle international markets, Bloomberg reports. The fundraising round would value the company at $15 billion, nearly four times its current $4 billion valuation.

Juul's massive market share and influence with younger smokers has also attracted scrutiny from the federal government. The company's marketing materials are currently under review by the FDA, after 11 senators accused the company of targeting teens—who reportedly love the age-restricted product— with ads for the cigarette alternative. Juul has pledged $30 million to help fight underage smoking.

That hasn't stopped teens from buying and distributing the gadgets with the fervor of any other hot commodity. "Dealers will announce on Snapchat that they've bought a hundred of them, and they'll write the price, the date, and the meeting place for kids to show up with cash," one teen told the New Yorker.

Regulatory issues aside, the future looks bright for the e-cigarette company. An analysis by Wells Fargo expects the industry to grow by 25% in 2018 (pdf), with Juul leading the charge. And in the context of the global market, the US doesn't even rank in the top 25

countries for most cigarettes smoked per year, according to the Washington Post (paywall).

The real challenge for the startup will be getting countries like China and Russia, who are among the top cigarette consumers, to start the fledgling verb of Juuling.

From: [redacted]
To: [redacted]
Cc: [redacted]

Date: Saturday, June 30, 2018 10:44AM
Subject: : Harm reduction not the way to go, Letters in Print News & Top Stories - The Straits Times

History: This message has been forwarded.

[redacted] lim_siok_peng@moh.gov.sg; sunny_lee@mha.gov.sg; jeremy.lim@duke-nus.edu.sg

https://www.straitstimes.com/forum/letters-in-print/harm-reduction-not-the-way-to-go

Harm reduction not the way to go

Published

Jun 28, 2018, 5:00 am SGT

We refer to the commentary by Dr Jeremy Lim (E-cigarettes: Neither ban nor permit, but reduce harm; June 19).

Tobacco products contain nicotine and are highly addictive. Nevertheless, we have made steady progress to bring down smoking rates. Smoking prevalence fell to 12 per cent last year. We intend to bring the number down to below 10 per cent by 2020.

Dr Lim suggests a harm reduction approach. This entails enabling, even facilitating, a person to do harm to himself, albeit to a lower degree. We should be focused on preventing harm in the first place.

Dr Lim cited the sterile needle and syringe availability programmes, which have helped control the spread of HIV infection among intravenous drug users in Australia.

Unlike Australia, Singapore does not face such a problem. Intravenous drug use accounted for less than 2 per cent of HIV cases in Singapore over the last 25 years.

This is because of our zero-tolerance approach towards drugs. We are one of the few nations in the world where the drug abuse situation is well under control.

The harm reduction approach, when it comes to drugs, in fact encourages their consumption.

In Portugal, the number of students trying drugs and drug-related deaths went up after the introduction of harm reduction strategies.

Countries go for such strategies because their anti-drug policies have failed and they need to mitigate the disastrous public health and other consequences from their failure to control drug addiction. Singapore is not in this position.

There is evidence that e-cigarette use is harmful to health, given that they contain highly toxic carcinogens like formaldehyde.

E-cigarettes can also be a "gateway" to smoking for youth, as studies in Britain, Canada and the United States have shown. A teenager who starts vaping has a higher risk of eventually progressing to smoking.

Research also suggests that e-cigarettes can re-normalise smoking in populations where smoking prevalence has been on the decline.

Given the high stakes, it would be irresponsible of the Government to make a hasty decision on e-cigarettes.

We are closely monitoring the global evidence, which will shape our policy.

We are prepared to allow e-cigarettes as a smoking cessation therapy prescribed by doctors, if there is rigorous evidence of their safety and effectiveness.

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Director, Corporate Communications

Ministry of Health

Sunny Lee

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Ministry of Home Affairs

A version of this article appeared in the print edition of The Straits Times on June 28, 2018, with the headline 'Harm reduction not the way to go'.

Attachments:

Ecigs-unfit-for-cessation-fit-for-Nic-addiction+DNA-damage.compressed.pdf


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Conclusion
In conclusion, the increased prevalence of e-cigarettes use among smokers in England has not been associated with a detectable change in cigarette consumption per day. The decline in the use of NRT has also not been associated with a change in mean cigarette intake. If use of e-cigarettes and licensed NRT while smoking act to reduce cigarette consumption, the effect is probably small.
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Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis

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ABSTRACT

Objectives Many smokers use e-cigarettes and licensed nicotine replacement therapy (NRT), often in an attempt to reduce their cigarette consumption. We estimated how far changes in prevalence of e-cigarette and NRT use while smoking were accompanied by changes in cigarette consumption at the population level.

Design Repeated representative cross-sectional population surveys of adults aged 16+ years in England.

Methods We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 from the Smoking Toolkit Study. Prevalence of e-cigarette use and NRT use in current smokers, and specifically for smoking reduction and temporary abstinence, were input variables. Mean daily cigarette consumption was the dependent variable. Analyses involved adjustment for mass media expenditure and tobacco-control policies.

Results No statistically significant associations were found between changes in use of e-cigarettes (β −0.012, 95% CI −0.026 to 0.002) or NRT (β 0.015, 95% CI −0.026 to 0.055) while smoking and daily cigarette consumption. Neither did we find clear evidence for an association between e-cigarette use (β −0.010, 95% CI −0.025 to 0.005 and β 0.011, 95%–0.027 to 0.004) or NRT use (β 0.006, 95%–0.030 to 0.043 and β 0.022, 95%–0.020 to 0.063) specifically for smoking reduction and temporary abstinence, respectively, and changes in daily cigarette consumption.

Conclusion If use of e-cigarettes and licensed NRT while smoking acted to reduce cigarette consumption in England between 2006 and 2016, the effect was likely very small at a population level.

Strengths and limitations of this study

- This is the first time series study to assess the population-level impact of the use of nicotine replacement therapy and e-cigarettes for harm reduction on cigarette consumption.
- This study uses a large representative sample of the population in England and considers both smoking reduction and temporary abstinence.
- A wide range of confounders are adjusted for including population-level interventions.
- In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed.
- Data are observational and so strong conclusions regarding cause and effect cannot be made.

INTRODUCTION

Randomised controlled trials have shown that use of non-tobacco nicotine-containing products (eg, nicotine replacement therapy; NRT) are efficacious for harm-reduction attempts.[1] Harm reduction is defined as any attempt to reduce the harm from smoking without an intention to quit completely, such as, the use of NRT for smoking reduction (ie, during attempts to cut down) or during periods of temporary abstinence (ie, during periods of time when one is unable to smoke).[1] Outside of the clinical setting where little behavioural support is provided, the use of NRT during attempts to cut down smoking appears to increase smoker's propensity to quit, but does not result in significantly large reductions in cigarette consumption.[2–4] Explanations for this include the lack of behavioural support and possible poor compliance with the medical regimen.[5 6]

In recent years, there has been an increase in the overall use of nicotine-containing products for harm reduction, with a growth in e-cigarettes more than offsetting a decline in the use of NRT.[7–9] Previous studies suggest that e-cigarettes which contain nicotine reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood, at least for some smokers.[10 11 13] Thus, although further studies are needed it is possible that e-cigarettes may be a more

effective aid for smoking reduction than licensed nicotine products.[14 15] However, it also remains possible that e-cigarettes will not result in clinically significant reductions in cigarette intake at a population level.

The aim of this study was to assess the association between changes in prevalence of e-cigarettes and NRT with changes in mean cigarette consumption per day using a time-series approach. Time-series analysis allows us to take into account underlying trends, the effect of other tobacco-control interventions, autocorrelation (whereby data collected at points closer in time tend to be more similar), and to consider possible lag effects of the independent variable on the dependent variable.[16] Where associations are found, they cannot unequivocally establish a causal association but can be indicative, as has been the case with estimating the effect of price of cigarettes on population consumption,[17] mass-media expenditure on use of specialist stop-smoking services[18] and introduction of varenicline to the market on prevalence of use of smoking cessation medication.[19] Where associations are not found, or they go in a direction opposite to that expected, this can also be informative.

Specifically, this paper assesses the association between mean cigarette consumption per day and:

1. Current e-cigarette use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.
2. Current NRT use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.

Sensitivity analyses will examine the effect of focusing only on daily e-cigarette and NRT use, given previous associations between extent of non-tobacco nicotine-containing product use and the effectiveness of harm-reduction attempts.[6]

METHODS

Design

We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 primarily from the Smoking Toolkit Study. The smoking toolkit study (STS) is a monthly survey of a representative sample of the population in England aged 16+ years.[20] This has been collecting data on smoking patterns among smokers and recent ex-smokers since November 2006. Questions on the use of e-cigarettes among all smokers were introduced in May 2011 and as aids to a quit attempt among smokers attempting to stop in July 2009. The STS involves monthly household surveys using a random location sampling design, with initial random selection of grouped output areas (containing 300 households), stratified by ACORN (sociodemographic) characteristics (https://acorn.caci.co.uk/) and region. Interviewers then choose which houses within these areas are most likely to fulfil quotas based on the probability of individuals being at home in different regions and conduct face-to-face computer-assisted interviews with one member per household. Participants from the STS appear to be representative of the population in England, having similar sociodemographic composition as other large national surveys, such as the Health Survey for England.[20]

Measures

Explanatory variables

Daily and non-daily smokers were asked the following questions:

1. Which, if any, of the following are you currently using to help you cut down the amount you smoke?
2. Do you regularly use any of the following in situations when you are not allowed to smoke?
3. Can I check, are you using any of the following either to help you stop smoking, to help you cut down or for any other reason at all?

All three questions had the following response options: nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch, electronic cigarette, nicotine mouth spray, other, none.

Current e-cigarette use was derived by an 'electronic cigarette' response to any of the three questions; e-cigarette use for smoking reduction by a response to the first question; and e-cigarette use for temporary abstinence by a response to the second question.

Current NRT use was derived by an NRT product response ('nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch or nicotine mouth spray') to any of the three questions; NRT use for smoking reduction by an NRT product response to the first question; and NRT use for temporary abstinence by an NRT product response to the second question.

Data were not recorded on NRT use for temporary abstinence between November 2006 and January 2007 and was imputed using prevalence data from February 2007.

Data were only available on the prevalence of use of electronic cigarettes among smokers from April 2011 although use specifically during a recent quit attempt were available from July 2009. Thus, prevalence of electronic cigarette use among smokers between July 2009 and April 2011 was estimated from data on use during a quit attempt; use of electronic cigarettes among smokers between November 2006 and June 2009 was assumed to be 0.1% of smokers based on other surveys which found their use to be very rare before 2009.[21 22]

Daily NRT and e-cigarette users were classified as those who reported that they used the product(s) at least once per day in response to the question: How many times per day on average do you use your nicotine replacement product or products? This question was introduced in July 2010. Prior to this time, prevalence of daily NRT use was assumed to be 60% of all users,[6] while e-cigarette prevalence was computed as above using prevalence during a quit attempt or 0.1%.

Outcome variables

Smokers taking part in the STS were also asked how many cigarettes they smoke on average per day. Non-daily smokers were asked how many cigarettes they smoked per week which was then converted to a daily figure.

Co-variables

In England, tobacco mass media campaigns have been run as part of a national tobacco-control programme. Spending was almost completely suspended in 2010 and then reintroduced in 2011 at a much lower level. Previous studies have shown that such cuts were associated with a decreased use of smoking cessation support.[18 23] Thus, advertising expenditure will be adjusted for using data obtained from Public Health England. Data on mass media expenditure was available monthly from May 2008, and yearly prior to this period, and so a monthly average was assumed. For a number of months, spending was effectively zero and was imputed as 0.1 to allow the analysis to run.

A number of tobacco-control policies were adjusted for. These included the move in commissioning of stop-smoking services to local authorities in April 2013,[24] introduction of a smoking ban in July 2007,[25] licensing of NRT for harm reduction in December 2009,[26] the publication of National Institute for Health and Care Excellence guidance on harm reduction in June 2013[27] and change in the minimum age of sale of cigarettes in October 2007.[28] Price of cigarettes is correlated 0.99 with time and will thereby be taken into account by use of differencing (ie, using the differences between consecutive observation rather than observations themselves) to make the series stationary.

Analysis

The analysis plan was registered on the Open Science Framework prior to data analysis (https://osf.io/6swk3/). All data were analysed in R V.3.2.4[29] using ARIMAX modelling.[16 30 31] Data were weighted prior to the analyse to match the population in England using a rim (marginal) weighting technique. This involves an iterative sequence of weighting adjustments whereby separate nationally representative target profiles are set (for gender, working status, children in the household, age, social grade and region). This process is then repeated until all variables match the specified targets.[20]

Two waves of data were collected in March 2007 and March 2013. These waves were averaged. No data were collected in December 2008. Mean cigarette consumption, NRT use and e-cigarette use during this period were calculated as an average of the month before and the month after. For a few months (May 2012, July 2012, September 2012, November 2012, January 2013, March 2013), data on electronic cigarettes and NRT use among smokers were not recorded. For these months, the average of the previous and next month was imputed.

The Granger causality test suggested that there was some evidence for the violation of the assumption of weak exogeneity (ie, Y can depend on the lagged values of X but the reverse must not be true) between the input and the output series. However, caution has been advised when using this and similar tests on data across a long time series,[32 33] and there was no theoretical reason we could identify for a bidirectional relationship between e-cigarette use and cigarette consumption. It was assumed that the association was spurious and likely removed following adjustment for other covariates.

Both unadjusted and fully adjusted models are reported which regressed onto mean cigarette consumption per day: (1) use of e-cigarettes among current smokers; (2) use of e-cigarettes for smoking reduction; (3) use of e-cigarettes for temporary abstinence; (4) use of NRT for harm reduction; (5) use of NRT for temporary abstinence and (6) use of NRT for smoking reduction. Sensitivity analyses were conducted which constrained the analysis to only those reporting daily e-cigarette and NRT use. We followed a standard ARIMAX modelling approach.[16 34] The series were first log-transformed to stabilise the variance, and if required, first differenced and seasonally differenced. The autocorrelation and partial autocorrelation functions were then examined in order to determine the seasonal and non-seasonal moving average (MA) and autoregressive terms (AR). For example, AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; while MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time. To identify the most appropriate transfer function (ie, lag) for the continuous explanatory variables, the sample cross-correlation function was checked for each ARIMAX model. Coefficients can be interpreted as estimates of the percentage change in cigarette consumption for every (a) percentage increase in use of e-cigarettes and NRT, (b) percentage increase in mass media expenditure and (c) implementation of tobacco-control policies.

Bayes factors (BFs) were derived for non-significant findings using an online calculator[35] to disentangle whether there is evidence for the null hypothesis of no effect (BF <1/3rd) or the data are insensitive (BF between 1/3rd and 3). A half-normal distribution was assumed with a percentage change in the outcomes of interest for every percentage increase in the input series of 0.009% based on the effect detectable with 80% power (see sample size). Sensitivity analyses were conducted using a much larger percentage change of 0.1. This was based on a meta-analysis assessing the efficacy of non-tobacco nicotine replacement products for harm reduction which reported that 21.8% of the experimental group had reduced consumption by more than 50% at final follow-up compared with 16.5% receiving placebo.[1] We therefore assumed that a 5% change in prevalence of NRT and e-cigarettes would be associated with a 0.5% change in overall cigarette consumption.

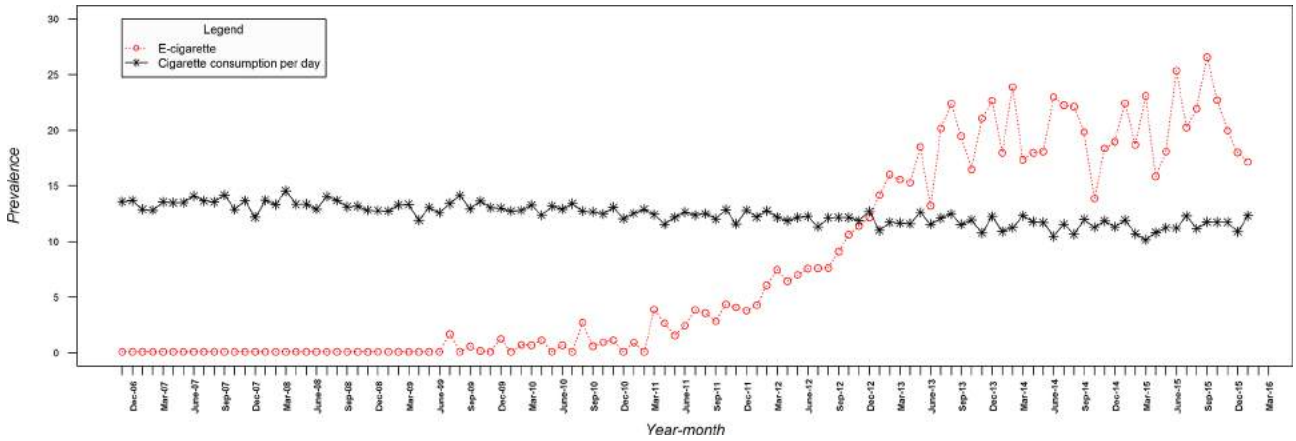

Figure 1 Monthly prevalence of cigarette consumption and e-cigarettes for harm reduction among smokers.

Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the reporting of observational studies were followed throughout.[36]

Sample size

Simulation-based power analyses suggested that this study would have 80% power to detect a change in the output series of 0.009% for every 1% change in the input series, assuming 113 monthly data collection points, MA (1) autocorrelation,[37] a baseline proportion for the input series of 0.005,[9] a baseline mean (SD) for the output series of 12.3[38] and a total change over time for the input series of 30%.[38]

RESULTS

Sample characteristics

Data were collected on 199 483 adults aged 16+ years taking part in the STS who reported their smoking status between November 2006 and March 2016. Of these, 43 608 (20.8%, 95% CI 20.6 to 21.0) were current smokers. Fifty-two per cent (95% CI 52% to 53%) of the smokers were male and 60.4% (95% CI 60% to 60.1%) were in routine or manual positions or were unemployed. The average age of smokers in this study was 42.1 years (95% CI 42.0 to 42.1).

Main analysis

Figure 1 shows that cigarette consumption declined over the study period from 13.6 to 12.3 (mean 12.4, SD 0.92). This figure also shows that current use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 17.1% at the end of the study (mean 7.8%, SD 8.82). Figure 2 shows that there was also a decline in the use of NRT for harm reduction from 12.2% to 6% (mean 14.4%, SD 4.36). Online supplementary figures 1 and 2 show the changes in e-cigarette and NRT use for smoking reduction and temporary abstinence, respectively.

Tables 1, 2 and 3 show the results of the ARIMAX models assessing the association between cigarette consumption per day with (1) e-cigarette use among current smokers and NRT use for harm reduction; (2) e-cigarette and NRT use for smoking reduction and (3) e-cigarette and NRT use for temporary abstinence. The findings were inconclusive as to whether an association was present between use of e-cigarettes and NRT for any purpose and cigarette consumption.

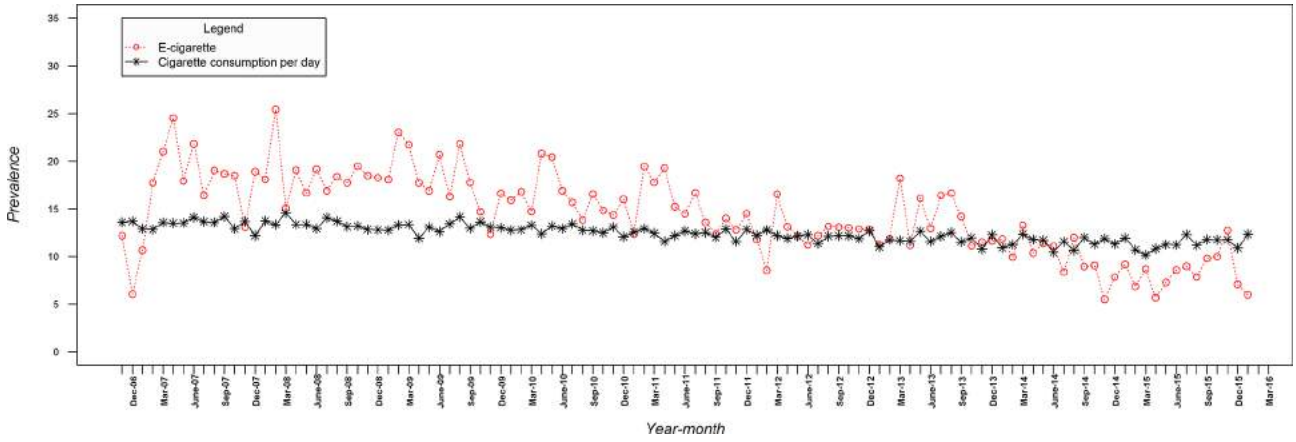

Figure 2 Monthly prevalence of cigarette consumption and nicotine replacement therapy use for harm reduction among smokers.

Table 1 Estimated percentage-point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Any current use of e- cigarettes (immediate impact)	−0.011 (−0.025 to 0.002) 0.097		−0.012 (−0.026 to 0.002) 0.091	−0.010 (−0.024 to 0.004) 0.149		−0.011 (−0.026 to 0.003) 0.130
NRT use for harm reduction (immediate impact)		0.012 (−0.028 to 0.053) 0.546	0.015 (−0.026 to 0.055) 0.475		0.003 (−0.019 to 0.025) 0.794	0.005 (−0.017 to 0.027) 0.672
Mass media expenditure (immediate impact)			<0.001 (−0.001 to 0.001) 0.984			<0.001 (−0.001 to 0.001) 0.880
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.015 (−0.070 to 0.101) 0.724			0.013 (−0.072 to 0.099) 0.756
Increase in age-of-sale (pulse effect)			−0.041 (−0.126 to 0.044) 0.342			−0.043 (−0.128 to 0.042) 0.324
Move to local authority control (pulse effect)			−0.019 (−0.105 to 0.067) 0.662			−0.027 (−0.112 to 0.058) 0.533
Licensing for NRT for harm reduction (pulse effect)			0.021 (−0.067 to 0.110) 0.639			0.020 (−0.069 to 0.109) 0.661
NICE guidance on harm reduction (pulse effect)			−0.024 (−0.109 to 0.061) 0.578			−0.028 (−0.114 to 0.057) 0.512
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR p value	NA	NA	NA	NA	NA	NA
Non-seasonal MA p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 1 Continued

	All users of nicotine replacement		Only daily users of nicotine replacement	
	Percentage change per 1 % change in the exposure (95% CI) P values			
Seasonal AR p value	NA	NA	NA	NA
Seasonal MA p value	NA	NA	NA	NA
R^2	0.65	0.66	0.65	0.64	0.66
Bayes factor e-cigarette (0.009 (0.1))	2.44 (0.46)	2.68 (0.55)	1.95 (0.35)	2.12 (0.41)
Bayes factor NRT (0.009 (0.1))	0.77 (0.14)	0.74 (0.13)	0.69 (0.09)	0.63 (0.08)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

BFs were between one-third and three when assuming a 0.009% change in cigarette consumption for every percentage change in the input series, suggesting the data are insensitive to detect very small reductions in cigarette consumption. Most BFs were less than one-third, when assuming a 0.1% change in cigarette consumption for every percentage change in the input series, suggesting evidence for the null hypothesis that NRT use and e-cigarette use among smokers has not resulted in large reductions in cigarette intake.

Sensitivity analysis

Current daily use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 11.1% at the end of the study (mean 4.5%, SD 4.91). There was also an increase in e-cigarette use specifically for temporary abstinence (from 0.1% to 8.4%; mean 3.5% SD 3.81) and smoking reduction (from 0.1% to 8.3%; mean 3.3% SD 3.64).

In contrast, there was a decline in the use of NRT for harm reduction from 7.3% to 2.9% (mean 6.5%, SD 2.35) and a decline in NRT use specifically for temporary abstinence (from 7.3% to 1.8%; mean 4.7% SD 2.29) and smoking reduction (from 6.8% to 2.6%; mean 5.8%, SD 2.46).

Tables 1, 2 and 3 also show the results of the sensitivity analyses restricted to those smokers using NRT or e-cigarettes daily. The findings were inconclusive as to whether or not an association was present between the daily use of e-cigarettes and NRT for any purpose and cigarette consumption. BFs suggested the data are insensitive to detect very small reductions in cigarette consumption, but there is evidence for the null hypothesis that NRT use and e-cigarette use among smokers have not resulted in large reductions in cigarette intake.

DISCUSSION

To our knowledge, this is the first empirical study to estimate the population association between the use of e-cigarettes and NRT among current smokers on cigarette consumption per day, using a time-series approach. There was evidence that there was no substantial association between the rise in use of e-cigarettes and decline in NRT use and changes in cigarette consumption per day.

Strengths and limitations

A strength of the study is the use of a large representative sample of the population in England, stratification of results by daily use, and the consideration of both temporary abstinence and smoking reduction. Previous studies have shown that reductions in cigarette intake are dependent on the extent of NRT use and differ as a function of the specific harm-reduction behaviour, that is, an attempt to cut down or restraining from smoking during periods of brief abstinence.[2 6]

The study had a number of limitations. First, caution should be taken when interpreting estimates of the

Table 2 Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for cutting down from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for cutting down (immediate impact)	−0.010 (−0.024 to 0.005) 0.191		−0.010 (−0.025 to 0.005) 0.191	−0.008 (−0.023 to 0.006) 0.256		−0.009 (−0.024 to 0.006) 0.229
NRT use for cutting down (immediate impact)		0.002 (−0.033 to 0.037) 0.917	0.006 (−0.030 to 0.043) 0.732		−0.002 (−0.016 to 0.013) 0.825	−0.002 (−0.017 to 0.013) 0.786
Mass media expenditure (immediate impact)			<0.001 (−0.001 to 0.001) 0.885			<0.001 (−0.001 to 0.001) 0.860
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.014 (−0.072 to 0.099) 0.755			0.012 (−0.073 to 0.097) 0.782
Increase in age-of-sale (pulse effect)			−0.043 (−0.128 to 0.042) 0.323			−0.042 (−0.127 to 0.043) 0.329
Move to local authority control (pulse effect)			−0.025 (−0.110 to 0.061) 0.571			−0.029 (−0.115 to 0.056) 0.499
Licensing for NRT for harm reduction (pulse effect)			0.018 (−0.072 to 0.108) 0.694			0.015 (−0.074 to 0.103) 0.747
NICE guidance on harm reduction (pulse effect)			−0.028 (0.058 to <0.001) 0.529			−0.027 (−0.112 to 0.059) 0.541
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR p values	NA	NA	NA	NA	NA	NA
Non-seasonal MA p values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 2 Continued

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Seasonal AR p values	NA	NA		NA	NA	NA
Seasonal MA p values	NA	NA		NA	NA	NA
R^2	0.64	0.64	0.65	0.64	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.87 (0.34)		1.79 (0.32)	1.46 (0.23)		1.61 (0.27)
Bayes factor NRT (0.009 (0.1))	0.86 (0.16)		0.81 (0.15)	0.76 (0.10)		0.76 (0.10)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

covariates, that is, impact of some of the tobacco-control policies, as interrupted explanatory variables with short time-periods prior to their introduction in ARIMAX-type models often give inaccurate estimates of the SEs.[28] Thus, although the increase in age-of-sale has been previously associated with a decline in smoking prevalence,[24] the short lead-in period may have masked any true association.[27] Second, the STS required participants to recall their average daily cigarette intake which is likely to have been somewhat inaccurate. Third, the findings may not generalise to other countries. England has a strong tobacco-control climate and relatively liberal attitude towards harm reduction and e-cigarette use. In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed. Fourth, although we are unaware of any other major population-level interventions or other events during the study period, we cannot rule out residual confounding. Fifth, participants were not asked questions regarding potentially important features of the e-cigarette (eg, nicotine content, flavouring, device type) or frequency and duration of use. It is likely that these factors may play a role in their effectiveness and should be considered in future studies.[15 39] Finally, as data were not collected on current e-cigarette use prior to April 2011, prevalence was estimated from use during a quit attempt or from previous studies.[21 22] This was necessary to ensure that the time series was long enough for an ARIMAX analysis and is an appropriate approach when data are missing completely at random.[16 40] As prevalence was low and relatively stable during this period, it is unlikely to have impacted on the reported results.

Implications of findings

The findings are in line with previous studies which show that reductions in cigarette consumption observed in clinical trials of NRT for harm reduction do not appear to generalise beyond the closely controlled trial setting.[1 2] It was hypothesised that e-cigarettes may be associated with population mean cigarette intake given that they reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood.[10 11 11 13]

The finding that e-cigarette use was not associated with reductions in consumption at a population level is consistent with previous real-world studies at the individual level. These have found little change in consumption among ever e-cigarette users[41] and that only a minority of daily users manage to reduce by a substantial amount which is not likely to be detected at a population level.[42] The findings of a recent pragmatic controlled trial, whereby 60% of participants using e-cigarettes had managed to reduce by over 50% by 6 months' follow-up, suggests that the lack of effectiveness at a population level may not be the consequence of poor behavioural support.[11]

Of course, it remains plausible that e-cigarettes may still be associated with a small effect on mean population cigarette consumption,[15] and that a reduction in harm from

Table 3 Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for temporary abstinence from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for temporary abstinence (immediate impact)	−0.010 (−0.024 to 0.005) 0.150		−0.011 (−0.027 to 0.004) 0.146	−0.010 (−0.024 to 0.004) 0.159		−0.011 (−0.026 to 0.003) 0.135
NRT use for temporary abstinence (immediate impact)		0.023 (−0.016 to 0.062) 0.241	0.022 (−0.020 to 0.063) 0.303		0.006 (−0.015 to 0.028) 0.563	0.006 (−0.016 to 0.028) 0.585
Mass media expenditure (immediate impact)			<0.001 (−0.001 to 0.001) 0.873			<0.001 (−0.001 to 0.001) 0.942
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.017 (−0.069 to 0.103) 0.696			0.014 (−0.071 to 0.099) 0.750
Increase in age-of-sale (pulse effect)			−0.036 (−0.122 to 0.050) 0.415			−0.040 (−0.125 to 0.044) 0.350
Move to local authority control (pulse effect)			−0.016 (−0.102 to 0.071) 0.721			−0.026 (−0.111 to 0.060) 0.556
Licensing for NRT for harm reduction (pulse effect)			0.023 (−0.067 to 0.114) 0.615			0.019 (−0.070 to 0.108) 0.670
NICE guidance on harm reduction (pulse effect)			−0.021 (−0.106 to 0.065) 0.638			−0.030 (−0.116 to 0.055) 0.483
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR P values	NA	NA	NA	NA	NA	NA

Continued

Table 3 Continued

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Non-seasonal MA P values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Seasonal AR P values	NA	NA	NA	NA	NA	NA
Seasonal MA P values	NA	NA	NA	NA	NA	NA
R^2	0.65	0.65	0.65	0.65	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.01 (0.59)		1.94 (0.38)	1.97 (0.35)		2.15 (0.41)
Bayes factor NRT (0.009 (0.1))		0.15 (0.02)	0.69 (0.11)		1.05 (0.18)	0.61 (0.08)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

smoking at a population level could be seen through their promotion of quit attempts[37] or by reducing smoke intake from each cigarette.[5]

Conclusion

In conclusion, the increased prevalence of e-cigarettes use among smokers in England has not been associated with a detectable change in cigarette consumption per day. The decline in the use of NRT has also not been associated with a change in mean cigarette intake. If use of e-cigarettes and licensed NRT while smoking act to reduce cigarette consumption, the effect is probably small.

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E-cigarettes are some young people's training wheels for smoking. Here's the evidence

theconversation.com/e-cigarettes-are-some-young-peoples-training-wheels-for-smoking-heres-the-evidence-80535

Simon Chapman

I started on mother's milk, soon graduated to cow's milk, went onto fizzy drinks, took a liking to beer, moved with gusto onto wine, and in my 30s settled for single malt. So, did my mother's breast milk lead me to Scotch whisky? Was it a "gateway" to all the devil's best tunes later in life?

The "gateway hypothesis" in some areas has often taken a deserved shellacking for its imprecision. It is an argument most often wheeled out over illicit drugs: a toke on a joint will be soon followed by injecting heroin.

Today the gateway hypothesis is being given a huge workout over concerns e-cigarettes might lead to kids smoking.

A series of nine recent studies has shown young people who try e-cigarettes are more likely to go on to smoke cigarettes by the next time they are interviewed. These studies all considered young people who had not smoked a cigarette, and then compared smoking between those who did, and did not use e-cigarettes at the start.

E-cigarette advocates have often dismissed these studies by saying all they show is that "children who are going to smoke in the future, will smoke in the future" and "kids who try, stuff, try stuff".

Here they are alluding to the very real issue that some children are likely to have a

constellation of existing vulnerability factors that make them more likely to use e-cigarettes and smoke.

Researchers try to tease this out by using measures of this vulnerability and then seeing whether there's still an association between using e-cigarettes and later smoking even after these factors have been taken into account.

Predictors of smoking (not including e-cigarette use) include general risk-taking, impulsiveness, low self-esteem, parental smoking, and affiliation with other risk-taking peers.

What do these studies show?

For the first time, researchers have combined the results of these nine studies, involving 17,389 people aged 14-30, and analysed the results (in a type of analysis known as a meta-analysis).

They found e-cigarette users were nearly five times more likely to smoke than those who had not used e-cigarettes. But this was reduced to a three-fold increased risk after adjusting for demographic, psychosocial and behavioural risk factors that predict cigarette smoking.

So, even after taking into account the very factors e-cigarette advocates argue would muddy the evidence, there was a three-fold increased risk of young e-cigarette users going on to smoke.

Yet, when faced with the argument that e-cigarettes may act as a catalyst to subsequent smoking, e-cigarette advocates disagree.

Typical responses contrast with what we know about the relationship between early influences on later behaviours, across a vast range of health and social problems.

For example, we search for factors that might lead to some falling in with terrorists. We try to understand the antecedents of obesity.

We know low price, tobacco advertising, parental smoking, smoking by best friends, attractive packaging, and weak, non-explicit health warnings and awareness campaigns are all associated with higher rates of smoking in some groups. This understanding has informed policy and practice and we now have a blueprint for comprehensive, effective efforts that have combined to drive teenage smoking down to its lowest ever levels.

But when research suggests using e-cigarettes might condition some children into thinking, "I wonder what the 'real thing' [ie smoking] is like?", that idea is completely out-of-bounds, apparently.

When UK researcher Peter Hajek, a long-time advocate of e-cigarettes, commented on the results of this meta-analyis, he said:

> People who drink white wine are more likely to also try red wine than teetotallers, but common sense would not suggest that this means that removing the white will reduce the drinking of the red.

But this is a poor analogy, as one of the authors of the JAMA meta-analysis suggests:

> Young people report that there is a lot of pressure among e-cigarette only users to smoke a "real" cigarette. It may be somewhat analogous to the fact that teens who use flavoured alcohol are often pressured socially to step up their game to harder forms of alcohol.

E-cigarettes, with their many teen-friendly flavours, their far less harsh "throat grab", the ease with which they can be used inconspicuously (little smell, easily hidden), and their "almost totally safe" pitch have considerable appeal to young people compared with smoking.

The 'vaping rising, smoking falling' argument

Another argument that advocates of e-cigarettes use to argue against e-cigarettes acting as "gateway" products is that in young people, vaping is rising and smoking is falling. If they acted as "gateways" to smoking, they argue, surely we'd see smoking rates in young people rising.

But this does not follow at all.

There are multiple reasons for both the rise and the fall in smoking. These include price changes, the denormalisation and growing social unacceptability of smoking, anti-smoking campaigns, the impact of advertising bans (you'd have to be over 24 in Australia to have ever seen a local tobacco advertisement after it finished here in 1993).

You can still have fewer young people smoking – teenage smoking is down to its lowest ever levels in Australia – but still be having a "gateway" effect.

If the impact of *all* factors driving smoking down in young people was greater than the impact of any "gateway" effect to smoking, the figures would still show fewer young people were smoking, which is what's happening: there's a net fall.

If the fall in young people smoking is so great, it could mask any rise in smoking caused by any e-cigarette gateway effects, which could still be substantial.

For this reason, the types of studies pooled in the JAMA meta-analysis are critical in understanding whether e-cigarettes are an important catalyst for young people to smoke.

Are e-cigarettes a gateway to smoking in 14-year-olds? New US data

theconversation.com/are-e-cigarettes-a-gateway-to-smoking-in-14-year-olds-new-us-data-46468

Simon Chapman

Electronic (e-)cigarettes are attracting massive interest for their potential in helping smokers quit, to reduce harm in those who switch from cigarettes or cut down, and in reducing the uptake of smoking in teenagers, where the argument runs that they would be best to vape instead of smoking.

Not to mention a third possibility: that they do neither.

This week saw the publication in JAMA of data from the world's first longitudinal study of young teenagers who vape. The Los Angles study reported on six- and 12-month data from a ten-school cohort of 14-year-olds who started off as non-vapers. When data from the two follow-ups were combined, 5.7% of the students who had never tried an e-cigarette had smoked cigarettes, while 32% of those who had vaped had also smoked cigarettes: a rate nearly six times higher.

What can we make of this data? Professor Linda Bauld from Scotland's University of Stirling highlighted some caveats in a Conversation article. She emphasised, as did the study authors, that this study cannot be argued to demonstrate a causal relationship between vaping and subsequent smoking (the so-called "gateway" hypothesis).

Professor Peter Hajek from the University of London was more dismissive, writing:

> It just shows that people who are attracted to e-cigarettes are the same people who are attracted to smoking. People who drink white wine are more likely to try red wine than people who do not drink alcohol.

Far more likely, of course. But by no means not exclusively. Every year millions drink alcohol for the first time. Most then diversify their drinking, so early experimental drinking is nearly always followed by consumption of other alcoholic drinks. Hajek's argument here is disturbingly parallel to that used by the tobacco industry for decades that tobacco advertising was only directed at smokers and that non-smokers (including children) were completely impervious to its appeals.

Hajek's seductive analogy attempts to shut down any possibility that among kids now rushing into vaping in the United States (where e-cigarette use is now more prevalent than smoking), there may be large numbers of kids who in the absence of access to e-cigarettes would have never smoked.

The heavily promoted appeal of e-cigarettes is that they are virtually risk-free (although only time will tell here). It is likely that some kids who resolve not to smoke because they know it's stupidly dangerous think "here's a safe way to almost smoke … to have all the benefits of the 'smoking performance', all the benefits of a hip new trend without the risks". But once dependent on nicotine via e-cigarettes, it is not hard to imagine many kids being desensitised toward a new curiosity about smoking.

Hajek points out that smoking has been declining in US high school students for a decade, and that the decline has accelerated during the time that vaping has increased. He says:

> it shows that e-cigarette experimentation is certainly not creating new smokers or slowing the decline in smoking prevalence. It may in fact be contributing to it.

This is a possibility, but Hajek then returns to his tobacco industry-like reasoning:

> Vaping is strikingly non-attractive to non-smokers and virtually none progress to becoming daily vapers – unlike experimentation with cigarettes which leads to about half of experimenters becoming daily smokers.

The movement from experimenting to daily use with cigarettes was for decades facilitated by unregulated nicotine chemistry, massive advertising, beautiful packaging, and allowing smoking in every conceivable setting (normalisation), the very strategies that e-cigarette advocates are now aggressively championing for vaping.

The business model for the success of vaping of course relies on many young people commencing and not just casually using e-cigarettes. And with predictions that the major tobacco companies now buying up the most successful e-cigarette start-ups will have 75% of the e-cigarette market within ten years, that business model will be one of dual use (smoking and e-cigarette use, not e-cigarettes instead of smoking).

Indeed, a recent study with a 12 month follow-up of vapers found that by far the most common outcome was dual use (smoking and vaping), not exclusive vaping. Of 192 daily vapers in the study, 160 (83%) were dual using at 12 months (see Table 3).

The JAMA study did not provide data on vaping or smoking frequency among its young subjects and Bauld writes:

> On top of this, the way e-cigarette and tobacco use were measured was very basic, only determining whether people had "ever" or "recently" used them, not whether this was regular or sustained use. Importantly, the age group in the study had just moved to secondary school – a time of transition and trying new things.

But this age group has very few regular or long-term smokers. It is an age where smoking tends to be intermittent. But if we were dealing here with such evidence of uptake following sustained marketing of a new form of cigarette, big alarm bells would be ringing about what we'd be likely to see as the cohort aged.

Bauld correctly notes that the numbers in this study – just 222 non-smoking e-cigarette users – were very small, so caution is indicated. Obviously a larger study would be preferable, but we regularly see outbreaks of unbridled optimism about e-cigarettes from studies with equal or far smaller numbers.

A recent English national study, for example, demonstrated that vapers using "tank" systems daily for 12 months had a statistically significantly higher smoking cessation rates (27.54%) while there were no such differences when comparing non-daily tank users, cigalike e-cigarette users and smokers not using any type of e-cigarette. But there were only 19 daily tank vapers who quit in that study (see Table 3).

The Los Angleses cohort cannot prove nor disprove the gateway hypothesis. Indeed, it's challenging to imagine any study design which could settle it. But it should provide major pause to those who blithely dismiss concerns about e-cigarette uptake as a minor issue of non consequence.

E-cigarette use in Australia is negligible compared to the United States and England. But Australia has the lowest smoking prevalence of any nation.

Finally, the seeming no-brainer that just cutting down cigarettes via e-cigarettes rather than quitting is beneficial is unfortunately also not supported by large prospective studies.

Editor's note: please ensure your comments are courteous and on-topic.

E-cigarettes are a gateway to real cigarettes for Britain's young

theconversation.com/e-cigarettes-are-a-gateway-to-real-cigarettes-for-britains-young-82466

Mark Conner

Young people in Britain who use e-cigarettes (vape) are nearly four times more likely to start smoking cigarettes than their non-vaping peers, our latest study has found.

When e-cigarettes first entered the market a decade ago, they were considered to be as dangerous as cigarettes. But views have changed since then, and e-cigarettes are now widely believed to be a far safer option than smoking.

In 2015, Public Health England published a detailed review of the evidence around the safety of e-cigarettes and said, at best guess, they were 95% less toxic than conventional cigarettes.

But concerns remain because e-cigarettes usually contain the addictive ingredient of cigarettes: nicotine. While recognising the harm reduction impact of e-cigarettes, it is important to ask what role, if any, e-cigarettes play in encouraging non-smoking adolescents to try their first cigarette.

For a number of years, my colleagues and I have been tracking data from several thousand schoolchildren in England to assess the impact of various anti-smoking interventions. We set about trying to identify any associations between e-cigarette use and starting to smoke within a year.

We started by looking at those children, aged 14 and 15, who had not smoked. We asked them to fill out a questionnaire at the start of the survey, and then a year later. Of those who had tried an e-cigarette, just under 34% reported having a cigarette within a year compared with just under 9% who had not. In other words, there was an almost fourfold increased chance of starting to smoke among those young people who had used an e-cigarette. This is worrying because it is known that once someone starts to smoke, the chances that they will continue to smoke are high.

Would they have started smoking anyway?

Last year, researchers in the US published their findings on smoking among a group of teenagers (average age 17) in southern California. As with our study in England, they were surveyed at the start of the study and again 16 months later. The US researchers found that e-cigarette users had six times risk of starting to smoke compared with their peers, who had not used an e-cigarette.

Perhaps these young people were going to smoke anyway, whether e-cigarettes existed or not? It is a question that gets to the heart of the risks that might be associated with e-cigarette use among the young.

We looked at those adolescents whose friends did or did not smoke, because having friends who smoke is a known risk factor for starting smoking. The data – which surprised us – suggested that e-cigarette use was a greater risk factor in starting to smoke in those *without* friends who smoked, compared with those *with* friends who smoked.

> Using e-cigarettes meant they were five-and-a-half times more likely to start smoking in the group with no friends who smoked but only one-and-a-half times more likely to start smoking in the group with most or all friends who smoked.

Again, the picture in the US seems very similar to what we found in the UK. Researchers there found associations between e-cigarette use and starting to smoke among those young people who during the initial survey stated they had no intention of starting to smoke.

Once people take up smoking, they tend not to stop. Sasa Prudkov/Shutterstock

So what do the associations suggest is going on? The unanswered question is whether the young people who go on to smoke are simply experimenting or whether they are becoming regular smokers.

The long-term trend in the UK is for e-cigarette use to go up while smoking declines. Future research is now needed to disentangle these apparently contrary findings, and whether there is any link between the intensity of e-cigarette use among adolescents and cigarette use.

E-cigarettes are expanding nicotine addiction in England, too

One of the arguments coming from Public Health England and the other e-cig cheerleaders there is that youth use is very low.

A new study using data collected in the UK between June 2015 and April 2016 of schoolchildren (mean age 14.1, n=499) shows that, like everywhere else, a substantial number of kids using e-cigarettes have never smoked cigarettes. In fact, at 52.6%, this is the highest fraction of never smokers reported by adolescent e-cig users.

This observation, combined with the substantially stronger gateway effect for smoking McNeill and colleagues reported in their longitudinal study of UK youth, may be another reflection of the likelihood that all the enthusiasm for e-cigs among much (but not all) of the British health establishment is recruiting kids to a lifetime of nicotine addiction.

The new paper is “More than half of adolescent E-Cigarette users had never smoked a cigarette: findings from a study of school children in the UK” by Fulton E, Gokal K, Griffiths S, Wild S (Public Health. 2018 Jun 2;161:33-35. doi: 10.1016/j.puhe.2018.04.014. [Epub ahead of print]).

Here is the abstract:

OBJECTIVES: Electronic cigarettes (ECs) are known for their use as a smoking cessation aid; however, experimental use in adolescence is a growing international concern. The proportion of adolescent EC users who have never used tobacco is rising. EC use is associated with later tobacco initiation in young people. Understanding adolescent beliefs about ECs is needed to inform public health campaigns and school education regarding the EC and the associated risks.

STUDY DESIGN: A cross-sectional questionnaire-based design was used.

METHODS: As part of a larger study, questionnaires to assess beliefs about ECs and current use were distributed to 499 school pupils aged 11-16 years in a county in England, UK.

RESULTS: More than half of EC users had never used tobacco (52.6%), a substantially greater proportion than previously reported in the literature. Adolescents were aware that ECs were less harmful than tobacco but many were unaware that they contain nicotine and the subsequent risk of addiction could lead to later tobacco use.

CONCLUSIONS: Given the possible association of EC use and later smoking initiation, education in schools may warrant greater emphasis on ECs, the role of nicotine and the risk of addiction associated with experimentation. Young people who deem ECs as a 'safe' option, and may otherwise have never experimented with tobacco, could be at risk of later tobacco use.

The paper is available here.

Format: Abstract

Send to

Public Health. 2018 Jun 2;161:33-35. doi: 10.1016/j.puhe.2018.04.014. [Epub ahead of print]

More than half of adolescent E-Cigarette users had never smoked a cigarette: findings from a study of school children in the UK.

Author information

Abstract

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KEYWORDS:

Adolescents/young people; Electronic cigarettes; Public health; School education; Smoking; Tobacco

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The paper, "Association between smoking and electronic cigarette use in a cohort of young people," published in *Journal of Adolescent Health*, showed that youth who initiated product use with e-cigarettes had 12 times the odds of smoking cigarettes 4 months later than kids who did not use e-cigarettes.

Two strengths of the study are that it is longitudinal (follows the kids forward in time) and controls for a wide range of other risk factors for smoking, including susceptibility to smoking. The fact that, controlling for susceptibility e-cigarettes have such a huge effect, indicates that (like other studies) e-cigarettes are attracting kids at low risk of initiating nicotine use with conventional cigarettes.

Another impressive thing about the results is that any use of e-cigarettes predicts subsequent any conventional cigarette smoking (even a puff). While this doesn't sound like much, another recent paper led by Peter Hajek, "What Proportion of People Who Try One Cigarette Become Daily Smokers," shows that about two-thirds of kids who take even a puff on a cigarette go on to become daily smokers.

This result shows that the gateway of e-cigarettes in Great Britain is about four times as powerful in Great Britain, where health authorities have embraced e-cigarettes, more than in the US (where most health authorities have been skeptical of e-cigarettes), where the odds of youth who initiate with e-cigarettes progressing to smoking are "only" tripled.

In the press release on the study minimizing its significance that was issued by ASH UK, ASH pointed out that there is a "two-way association" between e-cigarettes and cigarettes (and there is), but the odds of taking up e-cigarettes after cigarettes were increased by 3.5, a much smaller effect. While it is true, the direction is dominantly from e-cigarettes to cigarettes. (This result is similar to a study done at Yale showing that movement from e-cigarettes to cigarettes dominated movement in the opposite direction.)

The authors also tried to minimze the impact of their findings by stating (in the Discussionn section) that "only 4% of never smokers initiated e-cigarette use (vs. 32% of ever smokers) This suggests that e-cigarettes are attracting few who have never smoked." This is misleading because there are a lot more never smokers (81.2% of their sample) than ever smokers (19.8% of their sample). Thus, the prevalence of e-cigarette use generated from never smokers is .04 x .812 = 3.5% and the prevalence of e-cigarette use generated from ever smokers is .32 x .198 = 6.4%. This means that, of all kids using e-cigarettes,

0.35/(0.35+0.64) = 29% were kids who had never smoked a cigarette. This is about the same as the fraction of never-smoking kids who were using e-cigarettes that have been found in the other studies. These kids represent an expansion of the nicotine addiction market.

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PURPOSE: Electronic cigarette (e-cigarette) use is associated with smoking initiation among young people; however, it is also possible that smoking is associated with e-cigarette initiation. This study explores these associations among young people in Great Britain.

METHODS: A longitudinal survey of 1,152 11- to 18-year-olds was conducted with baseline in April 2016 and follow-up between August and October 2016. Logistic regression models and causal mediation analyses assessed whether (1) ever e-cigarette use and escalation were associated with smoking initiation (ever smoking at follow-up) among baseline never smokers (n=923), and (2) ever smoking and escalation were associated with e-cigarette initiation (ever e-cigarette use at follow-up) among baseline never e-cigarette users (n=1,020).

RESULTS: At baseline, 19.8% were ever smokers and 11.4% were ever e-cigarette users. Respondents who were ever e-cigarette users (vs. never users, 53% vs. 8%, odds ratio [OR]=11.89, 95% confidence interval [CI]=6.56-39.72) and escalated their e-cigarette use (vs. did not, 41% vs. 8%, OR=7.89, 95% CI=3.06-20.38) were more likely to initiate smoking. Respondents who were ever smokers (vs. never smokers, 32% vs. 4%, OR=3.54, 95% CI=1.68-7.45) and escalated their smoking (vs. did not, 34% vs. 6%, OR=5.79, 95% CI=2.55-13.15) were more likely to initiate e-cigarette use. There was a direct effect of ever e-cigarette use on smoking initiation (OR=1.34, 95% CI=1.05-1.72), and ever smoking on e-cigarette initiation (OR=1.08, 95% CI=1.01-1.17); e-cigarette and smoking escalation, respectively, did not mediate these effects.

CONCLUSIONS: Among young people in Great Britain, ever e-cigarette use is associated with smoking initiation, and ever smoking is associated with e-cigarette initiation.

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Nicotine Tob Res. 2017 Nov 4. doi: 10.1093/ntr/ntx243. [Epub ahead of print]

What proportion of people who try one cigarette become daily smokers? A meta analysis of representative surveys.

Author information

Abstract

Introduction:

The 'conversion rate' from initial experimentation to daily smoking is a potentially important metric of smoking behavior, but estimates of it based on current representative data are lacking.

Methods:

The Global Health Data Exchange was searched for representative surveys conducted in English speaking, developed countries after year 2000 that included questions about ever trying a cigarette and ever smoking daily. The initial search identified 2776 surveys that were further screened for language, location, year, sample size, survey structure and representativeness. 44 surveys that passed the screening process were accessed and their codebooks were examined to see whether the two questions of interest were included. Eight datasets allowed extraction or estimation of relevant information. Survey quality was assessed with regards to response rates, sampling methods and data collection procedures. PRISMA guidelines were followed, with explicit rules for approaching derived variables and skip patterns. Proportions were pooled using random effects meta-analysis.

Results:

The eight surveys used representative samples of the general adult population. Response rates varied from 45% to 88%. Survey methods were on par with the best practice in this field. Altogether 216,314 respondents were included of whom 60.3% (95%CI 51.3-69.3) ever tried a cigarette. Among those, 68.9% (95% CI 60.9-76.9%) progressed to daily smoking.

Conclusions:

Over two thirds of people who try one cigarette become, at least temporarily, daily smokers. The finding provides strong support for the current efforts to reduce cigarette experimentation among adolescents.

Implications:

The transition from trying the first cigarette through occasional to daily smoking usually implies that a recreational activity is turning into a compulsive need that has to be satisfied virtually continuously. The 'conversion rate' from initial experimentation to daily smoking is thus a potentially important metric of smoking behavior, but estimates of it based on representative data are lacking. The present meta analysis addressed this gap. Currently, about two thirds of non-smokers experimenting with cigarettes progress to daily smoking. The finding supports strongly the current efforts to reduce cigarette experimentation among adolescents.

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First evidence linking e-cigs to COPD in the population

The biological and clinical evidence that e-cigarettes are really bad for lungs has been rapidly piling up; now the first evidence linking e-cigarette use with chronic obstructive pulmonary disease (COPD) has been presented. At the American Thoracic Society meeting in May 2018, Mario Perez and colleagues presented an analysis of the NIDA/FDA PATH study and found a strong link between e-cigarette use and COPD.

They compared having been told they were diagnosed with COPD (including COPD, chronic bronchitis, or emphysema) among current (some day or every day) with people who did not use e-cigarettes. They controlled for other tobacco product usage and secondhand smoke exposure using a technique called propensity score matching. Accounting for matched propensities, there were 1321 e-cigarette users and 1321 nonusers. E-cigarette users were about twice as likely to have COPD (odds ratio, 1.86; 95% CI, 1.22-2.83).

Like our earlier paper that showed that daily e-cigarette users are about twice as likely to have had a heart attack, Perez and colleagues' result is based on a cross-sectional analysis, a snapshot in time, that finds an association between e-cigarette use and COPD. PATH is a longitudinal study, so, over time, it will become possible to test for a longitudinal association. But that will likely take years for the necessary new cases to accumulate.

The important thing to do is to interpret this cross-sectional COPD association in the context of all the biological and clinical evidence that would lead you to expect such a link. Since we reviewed the evidence that e-cigarettes trigger inflammatory processes and depress immune function in lungs and are associated with kids having chronic bronchitis, the biological evidence has rapidly accumulated. Two recent animal and human studies (Reinikovaite et al, and Garcia-Arcos et al) have shown that exposure to e-cigarettes produces COPD-like changes to the alveoli (air sacs). You don't have to be a molecular biologist to understand this damage. Just look at the pictures in these papers. There is also evidence of genetic changes in nonsmokers who never used an e-cigarette in one session that explain these effects (Staudt et al). These genetic changes include suppression of the p53 tumor suppressor gene, that suggests that, despite delivering lower levels of carcinogens, e-cigarettes could be increasing the risk of lung cancer.

Viewed from this perspective, Perez' epidemiological findings are exactly what one would expect based on the biology.

In addition, nicotine is directly implicated as causing some of these changes and directly damages lungs. It is time for FDA and e-cigarette enthusiasts to stop ignoring the evidence that nicotine itself has adverse biological effects beyond its addictive properties.

The more we learn about e-cigs the more dangerous they look.

Here is the full citation: Perez MF, Atuegwu N, Mead E, Oncken C, Mortensen EM. E-cigarette use is associated with emphysema, chronic bronchitis and COPD. Presented at: American Thoracic Society 2018 International Conference; May 18-23, 2018; San Diego, CA. Poster 402. The abstract is available here.

Harmful effects of nicotine

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ABSTRACT

With the advent of nicotine replacement therapy, the consumption of the nicotine is on the rise. Nicotine is considered to be a safer alternative of tobacco. The IARC monograph has not included nicotine as a carcinogen. However there are various studies which show otherwise. We undertook this review to specifically evaluate the effects of nicotine on the various organ systems. A computer aided search of the Medline and PubMed database was done using a combination of the keywords. All the animal and human studies investigating only the role of nicotine were included. Nicotine poses several health hazards. There is an increased risk of cardiovascular, respiratory, gastrointestinal disorders. There is decreased immune response and it also poses ill impacts on the reproductive health. It affects the cell proliferation, oxidative stress, apoptosis, DNA mutation by various mechanisms which leads to cancer. It also affects the tumor proliferation and metastasis and causes resistance to chemo and radio therapeutic agents. The use of nicotine needs regulation. The sale of nicotine should be under supervision of trained medical personnel.

Key words: *Addiction, cancer, cardiovascular, gastrointestinal, nicotine, respiratory*

INTRODUCTION

Tobacco is the leading cause of preventable cancers. WHO estimated around 1.27 billion tobacco users world-wide. Tobacco consumption alone accounts for nearly 5.4 million deaths per year and one billion people may die in this century if global tobacco consumption remained at the current levels.[1] An international treaty spearheaded by WHO in 2003 and signed by 170 countries, aims to encourage governments to reduce the production, sales, distribution advertisement and promotion of tobacco products. Despite strong opposition from the Industry, the treaty has been making steady progress in achieving its goal of comprehensive tobacco control around the world.[2] As tobacco consumption is being curbed, there is a growing demand for cessation. Pharmacological treatment of nicotine addiction remains an active area of research. There are many nicotine preparations (nicotine gums, patches, e cigarettes and inhalational agents) that are freely available in most parts of the world. These products are being heavily promoted and marketed as magical remedies. Nicotine gums are available in 2 mg and 4 mg preparation that deliver around 1 mg and 3 mg nicotine to the blood stream respectively. E-cigarette, a sophisticated nicotine delivery device, delivers nicotine in a vapor form and it closely mimics the act of smoking. Currently, these products constitute approximately 1% of total nicotine consumption and are showing an increasing trend in most countries.[3]

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Nicotine is well known to have serious systemic side effects in addition to being highly addictive. It adversely affects the heart, reproductive system, lung, kidney etc. Many studies have consistently demonstrated its carcinogenic potential. [Table 1] The only other known use of nicotine has been as an insecticide since 17th century.[4] After World War II, its use has declined owing to the availability of cheaper, more potent pesticides that are less harmful to mammals. The environment Protection Agency of United States has banned use of nicotine as a pesticide from 1st January 2014.[4] India, one of the largest producer and exporter of nicotine sulphate, has progressively banned its use as agricultural pesticide.[5] We undertook this review to evaluate the systemic adverse effects of nicotine.

MATERIALS AND METHODS

A computer aided search of the Medline and PubMed databases was done using different combination of the keywords "nicotine," "chemical composition," "history," "metabolism," "addiction," "cancer," "toxic," "endocrine system," "cardiovascular system," "respiratory system,"

Table 1: Studies showing nicotine as a carcinogen

Author	Model	System	References
Jensen *et al.*, 2012	Animal	Gastrointestinal	[50]
Schuller *et al.*, 1995	Animal	Lung cancer	[45]
Nakada *et al.* 2012	Human	Tumor promoter in lung cancer	[46]
Al-Wadei *et al.*, 2009	Mice	Pancreatic cancer	[56]
Treviño *et al.*, 2012	Animal	Pancreatic cancer	[58]
Crowley-Weber *et al.*, 2003	Human	Pancreatc cancer	[57]
Chen *et al.*, 2011	Human	Breast cancer	[59]
Wassenaar *et al.*, 2013	Human	Lung	[44]

"lung carcinogenesis, "gastrointestinal system," "immune system," "ocular," " cataract," "central nervous system," "renal system," " reproductive system," "menstrual cycle," "oocytes," "foetus,". Initial search buildup was done using "Nicotine/adverse effects" [Mesh], which showed 3436 articles. Articles were analyzed and 90 relevant articles were included in the review. All the animal and human studies that investigated the role of nicotine on organ systems were analyzed. Studies that evaluated tobacco use and smoking were excluded. All possible physiological effects were considered for this review. We did not exclude studies that reported beneficial effects of nicotine. The objective was to look at the effects of nicotine without confounding effects of other toxins and carcinogens present in tobacco or tobacco smoke.

CHEMICAL PROPERTIES AND METABOLISM

Nicotine was first extracted from tobacco by German physicians Wilhelm Heinrich Posselt and Karl Ludwig Reimann. Nicotine, a strong alkaloid, in its pure form is a clear liquid with a characteristic odour. It turns brown on exposure to air. It is water soluble and separates preferentially from organic solvents. It is an amine composed of pyridine and pyrrolidine rings.

Nicotine is a dibasic compound and the availability and absorption in human body depends upon the pH of the solution.[7] The absorption can occur through oral mucosa, lungs, skin or gut.[6] The increase in pH of a solution causes an increase in concentrations of uncharged lipophilic nicotine, in this form it can actively pass through all biological membranes.[7] The addition of slaked lime and catechu to tobacco increases the absorption of nicotine from the oral cavity.

Nicotine once ingested, is absorbed and metabolized by the liver. The metabolic process can be categorized into two phases. In phase I there is microsomal oxidation of the nicotine via multiple pathways.[8] This leads to formation of various metabolites like cotinine and nornicotine, demethyl cotinine, trans-3-hydroxy-cotinine and d-(3-pyridyl)-g-methylaminobutyric acid.[9,10] Thereafter in phase II there is N'-and O'-glucuronidation of the metabolites and excretion via urine, feces, bile, saliva, sweat etc.[11,12] 5-10% of elimination is by renal excretion of unchanged nicotine, however there is reabsorption from the bladder when the urinary pH is high.[14] There is evidence that nitrosation of nicotine *in vivo* could lead to formation of N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).[13] which are known to be highly carcinogenic. Inflammation in the oral cavity increases risk of endogenous nitrosation.

MECHANISM OF ACTION

Nicotine acts via 3 major mechanisms, producing physiological and pathological effects on a variety of organ systems.[15,16]

1. Ganglionic transmission.
2. Nicotinic acetylcholine receptors (nAChRs) on chromaffin cells via catecholamines.
3. Central nervous system (CNS) stimulation of nAChRs.

Brain imaging studies demonstrate that nicotine acutely increases activity in the prefrontal cortex and visual systems. There is release of a variety of neurotransmitters important in drug-induced reward. Nicotine also causes an increased oxidative stress and neuronal apoptosis, DNA damage, reactive oxygen species and lipid peroxide increase. nAChRs were originally thought to be limited to neuronal cells, however, studies have identified functional nAChRs in tissues outside the nervous system. Actions on nicotinic receptors produce a wide variety of acute and long-term effects on organ systems, cell multiplication and apoptosis, throughout the body.

IMMEDIATE EFFECTS AND TOXICITY

Nicotine on direct application in humans causes irritation and burning sensation in the mouth and throat, increased salivation, nausea, abdominal pain, vomiting and diarrhea.[17] Gastrointestinal effects are less severe but can occur even after cutaneous and respiratory exposure.[18] Predominant immediate effects as seen in animal studies and in humans consist of increase in pulse rate and blood pressure. Nicotine also causes an increase in plasma free fatty acids, hyperglycemia, and an increase in the level of catecholamines in the blood.[19,20] There is reduced coronary blood flow but an increased skeletal muscle blood flow.[20,22] The increased rate of respiration causes hypothermia, a

hypercoagulable state, decreases skin temperature, and increases the blood viscosity.

Nicotine is one of the most toxic of all poisons and has a rapid onset of action. Apart from local actions, the target organs are the peripheral and central nervous systems. In severe poisoning, there are tremors, prostration, cyanosis, dypnoea, convulsion, progression to collapse and coma. Even death may occur from paralysis of respiratory muscles and/or central respiratory failure with a LD50 in adults of around 30-60 mg of nicotine. In children the LD50 is around 10 mg.[23]

GREEN TOBACCO SICKNESS

This is an acute form of nicotine toxicity that is known to occur due to handling of green tobacco leaves, with symptoms lasting from 12 to 24 h. The acute symptoms include headache, nausea, vomiting, giddiness, loss of appetite, fatigue and tachyarrythmias.[24] No significant mortality has been reported due to green tobacco sickness (GTS) but it significantly affects the health of workers in the tobacco industry.[25]

NICOTINE ADDICTION

Nicotine is one of the most addicting agent. The US surgeon general (2010) has concluded nicotine to be as addictive as cocaine or heroin. Nicotine interacts with the nicotinic acetyl choline receptors and stimulates the dopaminergic transmission.[26] This in turn stimulates the reward centre and is responsible for the mood elevation and apparent improvement in cognitive function.[27] With chronic stimulation by nicotine the GABAergic neurons are desensitized and thus lose their inhibitory effect on dopamine.[28] This in turn reinforces the addiction by inducing craving. This effect has been shown to affect the CYP2A6 gene and leads to heritable dependence to nicotine. Studies have shown the nicotine dependence to be transmitted maternally and grand maternally by epigenetic mechanism.[29]

EFFECTS ON METABOLISM

Nicotine causes catecholamine release and stimulates the autonomic system. There is increased glycogen synthesis due to α-adrenoceptor stimulation. This leads to reduction in the fasting blood glucose levels. It also causes lipolysis thus decreasing body weight. Nicotine affects insulin resistance and predisposes to metabolic syndrome. In an animal study prenatal exposure was toxic to pancreatic β-cell and leads to decreased B cell population, thus increasing the risk of diabetes.[30,31]

NICOTINE AND CANCER

The stimulation of nAChRs by nicotine has biologic effects on cells important for initiation and progression of cancer.[26] It activates signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells. In addition, nicotine is a precursor of tobacco specific nitrosamines (TSNAs), through nitrosation in the oral cavity.[32,33] It is shown that nitrosation of nicotine could lead to formation of NNN and NNK. This effect of nicotine may be important because of its high concentration in tobacco and nicotine replacement products.[13] NNN and NNK are strongly carcinogenic.[34]

Nicotine forms arachidonic acid metabolites which cause increased cell division. Binding to Bcl-2 and action on vascular endothelial growth factor and cyclooxygenase-2 (COX-2) causes increased cancer proliferation and survival.[35,36] Promotion of tumor angiogenesis accelerates tumor growth which is mediated by β-adrenergic activation and stimulation of nAChRs.[35,37-39] Nicotine also suppresses apoptosis by phosphorylation mediated extracellular signal regulated kinases of Bcl-2.[40,41] Recent studies show that nicotine, activates nuclear factor kappa B (NF-kB)-dependent survival of cancer cell and proliferation.[42]

In normal cells, nicotine can stimulate properties consistent with cell transformation and the early stages of cancer formation, such as increased cell proliferation, decreased cellular dependence on the extracellular matrix for survival, and decreased contact inhibition. Thus, the induced activation of nAChRs in lung and other tissues by nicotine can promote carcinogenesis by causing DNA mutations[26] Through its tumor promoter effects, it acts synergistically with other carcinogens from automobile exhausts or wood burning and potentially shorten the induction period of cancers[43] [Table 2].

LUNG CARCINOGENESIS

A study relates lung carcinogenesis by nicotine due to genetic variation in CYP2B6.[44] Its simultaneous exposure with hyperoxia has been found to induce cancer in hamsters.[45] Cotinine has been found to promote lung tumorigenesis by inhibiting anti-apoptotic pathway.[46] Nuclear translocation of ARB1 gene by nicotine has found in proliferation and progression of nonsmall-cell lung cancer. Several Studies have shown that nicotine has significant role in tumor progression and metastasis via CXCR4 and increased angiogenesis.[36,47] Carriers of the lung-cancer-susceptibility loci in their DNA extract more nicotine. Smokers carrying the gene CHRNA3 and CHRNA5 were found to extract more nicotine and cells

Table 2: Studies showing the role of nicotine as tumor promoter

Author	System	References
Chu *et al.*, 2013	Gastrointestinal tumor growth	[71]
Improgo *et al.*, 2013	Lung	[47]
Heusch and Maneckjee, 1998	Lung	[40]
Mai *et al.*, 2003	Lung	[41]
Shin *et al.*, 2005	Gastric	[36]
Heeschen *et al.*, 2001	Tumor growth and angiogenesis	[35]
Zhu *et al.*, 2003	Tumor angiogenesis and growth	[39]
Heusch and Maneckjee, 1998	Lung	[40]
Le Marchand *et al.*, 2008	Lung	[48]
Perez-Sayans *et al.*, 2010	GIT	[51]
Zhang *et al.*, 2010	GIT	[49]
Petros *et al.*, 2012	Chemoresistance	[53]
Trevino *et al.*, 2012	Tumor growth and chemoresistance	[90]

GIT – Gastrointestinal tract

were thus exposed to a higher internal dose of carcinogenic nicotine-derived nitrosamines.[48] Additionally modulation of the mitochondrial signaling pathway leads to resistance to the chemotherapeutic agents.[49]

GASTRO INTESTINAL CARCINOGENESIS

The carcinogenic role may be mediated by the MAPK/COX-2 pathways, α-7 nAchR and β-adrenergic receptor expression, and mi RNAs α-BTX anatagonist.[50] Nicotine forms adducts with liver DNA which enhances its mutagenic potential.[49,51,52] activation of cell-surface receptors by nicotine stimulates downstream kinases that can mediate resistance to chemotherapy. It has been shown by the finding that smokers who continue to smoke during chemotherapy have a worse prognosis. Moreover they also have increased toxicity and lower efficacy of chemo therapeutic drugs.[53] Nicotine affects the periostin gene, α-7-nAChR and e-cadherin suppression which explains the mechanism of gastric cancer growth, invasion and metastasis.[54,55] Nicotine negatively impacts tumor biology by promoting angiogenesis, tumor invasion and increased risk of metastasis.[53]

PANCREATIC CANCER

Nicotine has been found to induce pancreatic adenocarcinoma in mice model, by stimulating the stress neurotransmitters.[56,57] In another study nicotine promoted the growth of nonsmall cell lung cancer and pancreatic cancer in a receptor dependent fashion. It also increased tumor metastasis, and resistance to gemcitabine induced apoptosis, causing chemoresistance.[58] The MUC-4 upregulation, NF-kB and GRP78 activation and Id1 expression by Src dependent manner are the probable mechanism leading to tumor growth, metastasis and chemotherapeutic drug resistance.[57,58]

BREAST CANCER

Nicotine causes α9-nAChR-mediated cyclin D3 overexpression which might cause transformation of normal breast epithelial cells and induce cancer. Nicotine and cotinine has been found to be present in the breast fluid of lactating women.[59] Several studies have found that α9-nAChR mediated mechanism leads to increased tumor growth, metastasis and tumor cells resistant to chemotherapeutic drugs in breast cancer.[59,60]

CARDIOVASCULAR SYSTEM

The acute hemodynamic effects of cigarette smoking or smokeless tobacco are mediated primarily by the sympathomimetic action. The intensity of its hemodynamic effect is greater with rapid nicotine delivery.[61] Nicotine causes catecholamine release both locally and systemically leading to an increase in heart rate, blood pressure and cardiac contractility. It reduces blood flow in cutaneous and coronary vessels; and increases blood flow in the skeletal muscles. Due to restricted myocardial oxygen delivery there is reduced cardiac work. In a study, chewing a low dose (4 mg) of nicotine gum by healthy nonsmokers blunted the increase in coronary blood flow that occurs with increased heart rate produced by cardiac pacing.[21] Thus, persistent stimulation by nicotine can contribute to Coronary Vascular Disease by producing acute myocardial ischemia. In the presence of coronary disease, myocardial dysfunction can be worsened. In a placebo-controlled experiment that produced transient ischemia in anesthetized dogs myocardial dysfunction was produced at doses, that did not alter heart rate, blood pressure, or blood flow or myocyte necrosis.[62]

Nicotine alters the structural and functional characteristics of vascular smooth muscle and endothelial cells.[63] It enhances release of the basic fibroblast growth factor and inhibits production of transforming growth factor-β1.[64] These effects lead to increased DNA synthesis, mitogenic activity, endothelial proliferation and increases atherosclerotic plaque formation.[65] Neovascularization stimulated by nicotine can help progression of atherosclerotic plaques.[66] These effects lead to myointimal thickening and atherogenic and ischemic changes, increasing the incidence of hypertension and cardiovascular disorders. A study on

dogs demonstrated the deleterious effects of nicotine on the heart.[67]

Nicotinic acetylcholine receptor's actions on vascular smooth muscle proliferation and plaque neovascularization increases the risk of peripheral arterial disorders. In a murine model of hind limb ischemia, short-term exposure to nicotine paradoxically increased capillary density and improved regional blood flow in the ischemic hind limb.[35] However, long-term exposure to nicotine for 16 weeks (about one-third of the life span of a mouse) before induction of ischemia obliterated angiogenic response to nicotine.[68]

RESPIRATORY SYSTEM

The effects of nicotine on respiratory system are twofold. One, directly by a local exposure of lungs to nicotine through smoking or inhaled nicotine, and second via a central nervous system mechanism. Nicotine plays a role in the development of emphysema in smokers, by decreasing elastin in the lung parenchyma and increasing the alveolar volume. Nicotine stimulates vagal reflex and parasympathetic ganglia and causes an increased airway resistance by causing bronchoconstriction.[69] Nicotine alters respiration through its effects on the CNS. The simultaneous effect of bronchoconstriction and apnea increases the tracheal tension and causes several respiratory disorders. In a study microinjection of nicotine were administered to the prebotzinger complex and adjacent nuclei in the brain. The firing pattern of the brain signals and breathing pattern were monitored. There was an increased frequency of bursts and decreased amplitude and a shallow and rapid rhythm of respiration.[70]

GASTROINTESTINAL SYSTEM

Nicotine use has been associated with Gastro Esophageal Reflux Disorder (GERD) and peptic ulcer disease (PUD).[36,71] This effect is mediated by increased gastric acid, pepsinogen secretion and stimulatory effects on vasopressin. The action on the cyclo-oxygenase pathway also increases the risk of GERD and PUD.[72] Nicotine causes smooth muscle relaxation by action of endogenous nitric oxide as a nonadrenergic noncholinergic neurotransmitter.[73] The decrease in tone of the colon and gastric motility and reduced lower esophageal sphincteric pressure might be the reason of increased incidence of GERD.[74]

There is an increased incidence of treatment resistant *Helicobacter pylori* infection in smokers. It potentiates the effects of toxins of *H. pylori* by its action on the gastric parietal cells.[75] This effect could be due to histamine mediated response of nicotine.

IMMUNOLOGICAL SYSTEM

Nicotine has been known to be immunosuppressive through central and peripheral mechanisms. It impairs antigen and receptor mediated signal transduction in the lymphoid system leading to decreased immunological response. The T-cell population is reduced due to arrest of cell cycle. Even the macrophage response, which forms the first line defense against tuberculosis becomes dysfunctional and causes increased incidence of tuberculosis.[76] The migration of fibroblasts and inflammatory cells to the inflamed site is reduced. There is decreased epithelialization and cell adhesion and thus there is a delayed wound healing as well as increased risk of infection in nicotine exposed individuals.

The action on the hypothalamo-pituitary adrenal axis and autonomic nervous system stimulation via sympathetic and parasympathetic pathways affects the immune system. The adrenocorticotropic hormone (ACTH) secretion pathway and corticotrophin release is affected and this causes immunosuppression.[77]

OCULAR SYSTEM

Nicotine promotes pathologic angiogenesis and retinal neovascularization in murine models. It causes age-related macular degeneration in mice.[78] In a clinical study, the most virulent form of age-related maculopathy was associated with retinal neovascularization that contributed to visual deterioration. Tobacco smokers are known to be at greater risk of age-related macular degeneration than are nonsmokers.[79] In animal model, spraguely Dawley rats with type 1 diabetes treated with nicotine, developed cataract.[80] Thus the syngergistic relationship between nicotine and glucose metabolism exaggerating diabetes might cause accelerated cataract formation. There is synergistic relationship between nicotine and glucose metabolism which increases the risk of diabetes mellitus. This might cause accelerated cataract formation.

RENAL SYSTEM

Risk of chronic kidney disease in smokers is high. Cigarette smoking has been found to increase albumin excretion in urine, decrease glomerular filtration rate, causes increased incidence of renal artery stenosis and is associated with an increased mortality in patients with end-stage renal disease. The pathogenesis of renal effects is due to the action of nicotine via COX-2 isoform induction. The COX-2

isoforms causes increased glomerular inflammation, acute glomerulonephritis and ureteral obstruction.[81] There is impaired response of kidneys to the increased systemic blood pressure in smokers. This loss of renoprotective mechanism in smokers also leads to pathogenetic effects of nicotine on the renal system.[82]

REPRODUCTIVE SYSTEM – MALES

Nitrous oxide liberated from parasympathetico-nergic nerves plays a pivotal role in generating immediate penile vasodilatation and corpus cavernosum relaxation, and NO derived from endothelial cells contributes to maintaining penile erection. Nicotine causes impairment of NO synthesis. This may lead to loss of penile erections and erectile dysfunction.[83]

Various animal studies suggest that nicotine causes seminiferous tubules degeneration, disrupts the spermatogenesis and at cellular level, affect germ cell structure and function in males.[84] It decreases testosterone levels which is secondary to decreased production of StAR.[85] StAR is the protein which plays an important role in testosterone biosynthesis.

REPRODUCTIVE SYSTEM – FEMALE

Menstrual cycle

Nicotine by inhibiting the 21 hydoxylase causes hypoestrogenic state. It shunts the metabolites to formation of androgen. This leads to chronic anovulation and irregular menstrual cycles. Nicotine can predispose the endometrium to inappropriate cytokine production and irregular bleeding.[86] There is consistent evidence that increase in follicle-stimulating hormone levels and decreases in estrogen and progesterone that are associated with cigarette smoking in women, is atleast in part due to effects of nicotine on the endocrine system.[26]

Effect on oocytes

Nicotine affects the ovaries and alters the production of oocytes in various animal studies. Nicotine-treated oocytes appeared nonspherical with rough surface and torn and irregular zona-pellucida. Nicotine also caused disturbed oocyte maturation. There is a decreased blood flow to the oviducts and thus impaired fertilization.[87]

Peri-natal effects

Maternal smoking has always been known to have deleterious effects on the fetal outcome. There is an increased incidence of intrauterine growth restriction, still birth, miscarriages and mental retardation.[88] Various animal studies show retarded fetal growth and lower birth weight when treated perinatally with nicotine. The lower levels of ACTH and cortisol due to nicotine are probable reasons for the incidence of lower birth weight in the newborns.[89]

Maternal as well as grand maternal smoking has been found to increase risk of pediatric asthma. Another serious and important effect is the transgenic transmission of the addictive pattern.[29]

CONCLUSION

Nicotine is the fundamental cause of addiction among tobacco users. Nicotine adversely affects many organs as shown in human and animal studies. Its biological effects are widespread and extend to all systems of the body including cardiovascular, respiratory, renal and reproductive systems. Nicotine has also been found to be carcinogenic in several studies. It promotes tumorigenesis by affecting cell proliferation, angiogenesis and apoptotic pathways. It causes resistance to the chemotherapeutic agents. Nicotine replacement therapy (NRT) is an effective adjunct in management of withdrawal symptoms and improves the success of cessation programs. Any substantive beneficial effect of nicotine on human body is yet to be proven. Nicotine should be used only under supervision of trained cessation personnel therefore its sale needs to be strictly regulated. Needless to say, that research for safer alternative to nicotine must be taken on priority.

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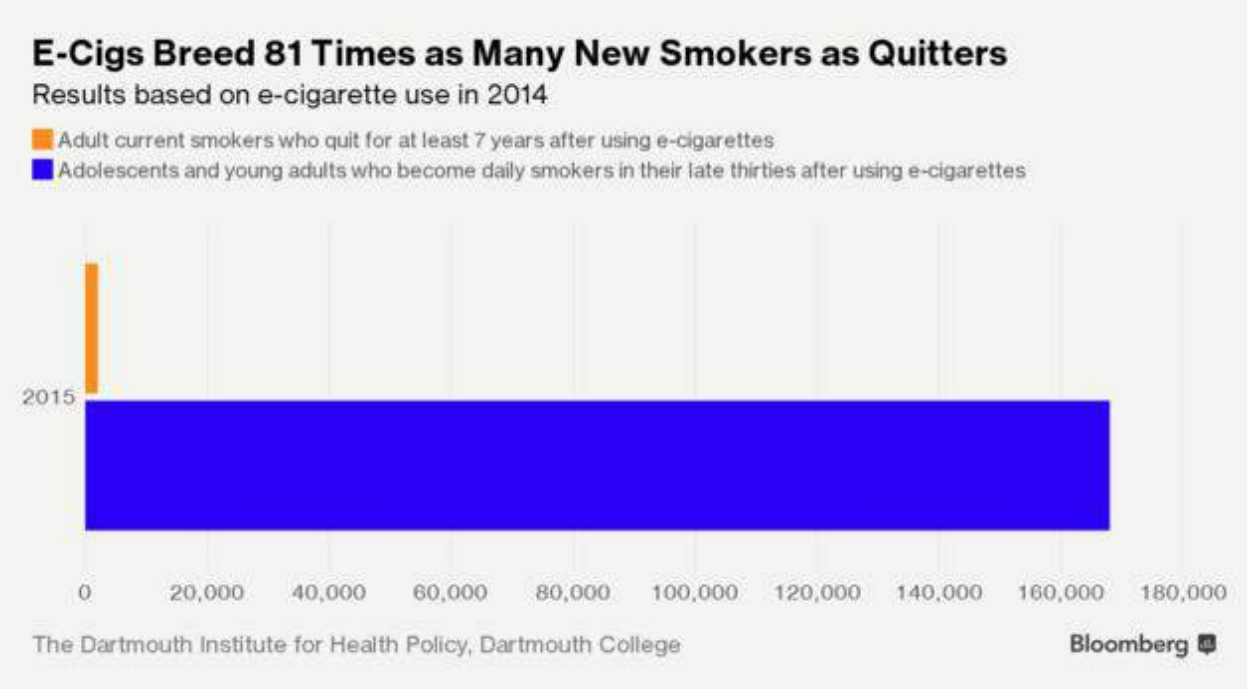

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E-Cigarette Study Says They Lead to More Smokers Than They Stop

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Janine Wolf

(Bloomberg) -- Electronic cigarettes have long been touted not only as a safer alternative to cigarettes but as a potential avenue by which existing smokers might quit. The industry, now worth $11.4 billion, hasn't been hurt by this one-two pitch of safety and good public policy.

New research shows, however, that e-cigarettes are hurting a lot more than they help.

Researchers at Dartmouth College's Norris Cotton Cancer Center said vaping has led more people to start a real smoking habit, rather than avoid tobacco or quit in favor of e-cigarettes, according to a study published Wednesday.

Using 2014 census data, published literature and surveys on e-cigarette usage to build a model, the scientists were able to estimate that about 2,070 cigarette-smoking adults in America quit in 2015 with the help of the electronic devices. However—and perhaps more alarming—the model estimated that, at the same time, an additional 168,000 adolescents and young adults who had never smoked cigarettes began smoking and eventually became daily cigarette smokers after first using e-cigarettes.

The model estimates that e-cigarette use in 2014 would eventually lead to about 1,510,000 years of life lost—a figure based on an optimistic 95 percent relative harm reduction of using e-cigarettes compared to traditional cigarettes.

Samir Soneji, an associate professor of health policy at Dartmouth's Geisel School of Medicine and the paper's lead author, said that advertising e-cigarettes as a means to quit or reduce smoking has done damage, mostly to young people. E-cigarettes use cartridges of chemicals, including nicotine, that are transformed into vapor. Despite a federal requirement that purchasers be at least 18 years of age, use of the product in popular culture, combined with its fruity flavors, have proved a strong draw to younger, would-be vapers. These characteristics have been at the core of keeping youths interested in the devices, Soneji said, and should be the focus of restriction efforts by the U.S. Food and Drug Administration.

"The harms of e-cigarette use among adolescents and young adults are serious," he said. "Kids who vape are more likely to start smoking cigarettes—notably kids who were otherwise not at a high risk of starting to smoke." Currently, Soneji said, the risk of initiating cigarette smoking is three times as high for adolescents who vape than for those who do not.

In 2015, 68 percent of Americans who smoked wanted to quit, with about55.4 percent of them doing so successfully for at least one day, according to the Centers for Disease Control and Prevention. That same year, 45.5 percent of high school-aged cigarette

smokers said they had tried to stop smoking over the previous 12 months. After first regulating the devices in 2016, the FDA embraced vaping as a way for smokers to quit.

Last July, a study published in the British Medical Journal found that e-cigarette users were indeed more likely than non-users to attempt to quit smoking—and be more successful at doing so. However, at around the same time the survey was conducted, e-cigarette use among high school students was jumping from 1.5 percent in 2011 to 16 percent in 2015, making the products the most commonly used tobacco product by young people in the U.S.

“E-cigarettes could, indeed, provide more population benefit if they were more effective as a cessation tool.”

Current research already points toward e-cigarettes being a public health risk because of the chemicals they use, making the new research even more problematic for the industry. However, the Dartmouth researchers point out that a future in which e-cigarettes do help people quit isn’t impossible—as long as they’re kept out of the hands of young people.

“E-cigarettes could indeed provide more population benefit if they were more effective as a cessation tool,” Soneji said. “For example, if smokers who used e-cigarettes to help quit were twice as likely to actually quit compared to smokers who used nicotine-replacement therapy, then the benefits of e-cigarette use would approximately balance the harms of e-cigarette use.”

Representatives from Reynolds American Inc., which owns market-leading e-cigarette Vuse, and competitor Altria Group Inc., maker of MarkTen and APEX, didn’t immediately respond to requests for comment.

Alex Clark, executive director of Consumer Advocates for Smoke-Free Alternatives Association, an e-cigarette industry lobby group, called the study’s results “surprising,” given government studies showing an overall decline in smoking. (A recent CDC study shows that while smoking has declined, vaping has increased.) Clark said his organization prefers that e-cigarette makers be truthful in advertisements by marketing products as “less risky alternatives” to smoking that have the ability to help smokers quit.

The government has made some effort to dissuade young adopters, with a new requirement for product warnings set to take effect this summer. In October, the FDA addressed youth use of e-cigarettes and other electronic nicotine-delivery systems (ENDS) through its “The Real Cost” campaign. Commissioner Scott Gottlieb said in a statement that vaping devices are by far the most common source of experimentation with tobacco products among children.

“While we continue to encourage innovation of potentially less harmful forms of nicotine delivery for currently addicted adult smokers, we can all agree no child should be using any nicotine-containing product,” he said.

Michael Bloomberg, the majority owner of Bloomberg LP, parent of Bloomberg News, provides philanthropic support to anti-smoking campaigns and other health initiatives.

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RESEARCH ARTICLE

Quantifying population-level health benefits and harms of e-cigarette use in the United States

Samir S. Soneji Hai-Yen Sung, Brian A. Primack, John P. Pierce, James D. Sargent
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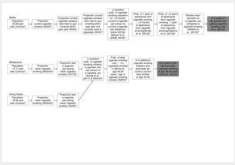
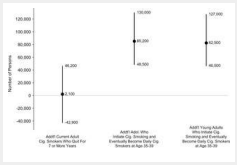
Figures





Abstract

Background

Electronic cigarettes (e-cigarettes) may help cigarette smokers quit smoking, yet they may also facilitate cigarette smoking for never-smokers. We quantify the balance of health benefits and harms associated with e-cigarette use at the population level.

Methods and findings

Monte Carlo stochastic simulation model. Model parameters were drawn from census counts, national health and tobacco use surveys, and published literature. We calculate the expected years of life gained or lost from the impact of e-cigarette use on smoking cessation among current smokers and transition to long-term cigarette smoking among never smokers for the 2014 US population cohort.

Results

The model estimated that 2,070 additional current cigarette smoking adults aged 25–69 (95% CI: -42,900 to 46,200) would quit smoking in 2015 and remain continually abstinent from smoking for ≥7 years through the use of e-cigarettes in 2014. The model also estimated 168,000 additional never-cigarette smoking adolescents aged 12–17 and young adults aged 18–29 (95% CI: 114,000 to 229,000), would initiate cigarette smoking in 2015 and eventually become daily cigarette smokers at age 35–39 through the use of e-cigarettes in 2014. Overall, the model estimated that e-cigarette use in 2014 would lead to 1,510,000 years of life lost (95% CI: 920,000 to 2,160,000), assuming an optimistic 95% relative harm reduction of e-cigarette use compared to cigarette smoking. As the relative harm reduction decreased, the model estimated a greater number of years of life lost. For example, the model estimated-1,550,000 years of life lost (95% CI: -2,200,000 to -980,000) assuming an approximately 75% relative harm reduction and -

1,600,000 years of life lost (95% CI: -2,290,000 to -1,030,000) assuming an approximately 50% relative harm reduction.

Conclusions

Based on the existing scientific evidence related to e-cigarettes and optimistic assumptions about the relative harm of e-cigarette use compared to cigarette smoking, e-cigarette use currently represents more population-level harm than benefit. Effective national, state, and local efforts are needed to reduce e-cigarette use among youth and young adults if e-cigarettes are to confer a net population-level benefit in the future.

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Introduction

The use of electronic cigarettes (e-cigarettes) has become intensely controversial since their introduction to the US in 2007 [1–7]. E-cigarettes might help the 40 million current adult cigarette smokers quit—the vast majority of whom want to stop smoking completely—by delivering nicotine with the same sensory experience as combustible, or traditional, cigarettes but without inhalation of as many toxicants [8–12]. Conversely, e-cigarettes might facilitate the transition to traditional cigarette smoking among never-smoking adolescents and young adults [13–21]. This harm is potentially substantial because youth e-cigarette use has risen rapidly over time [6,22,23]. For example, past 30-day use of e-cigarettes increased from 1.5% in 2011 to 11.3% in 2016 among high school students and exceeded their level of past 30-day use of traditional cigarettes (8.0% in 2016) [24].

The controversy over e-cigarettes persists because we do not yet know if e-cigarette use results in more benefit than harm at the population level [25–27]. This uncertainty creates a quandary for the US Food and Drug Administration (FDA), which recently asserted its regulatory authority over e-cigarettes and developed regulations to promote their safety and limit youth appeal [28]. Quantifying the balance of benefits and harms of e-cigarette use requires simultaneous accounting of the additional number of (1) current cigarette smokers who will quit through the use of e-cigarettes and (2) never-cigarette smokers who will initiate cigarette smoking through the use of e-cigarettes, a substantial proportion of whom may become long-term daily cigarette smokers. A recent study concluded a net population-level health benefit under a scenario in which e-cigarette use increases in the future only among cigarette smokers interested in quitting, and net harm under a scenario in which e-cigarette use increases in the future only among youth who would have never smoked [29]. A second study modeled future cigarette and e-cigarette use patterns over the next decade for young adults aged 18–24 years and concluded that e-cigarette use would have a limited impact on the prevalence of current cigarette smoking [30]. However, this study did not assess the effect of e-cigarette use among adolescents or adults aged ≥25 years. A third study estimated the population impact of e-cigarettes on smoking cessation and found e-cigarettes could increase the number of smokers who successfully quit for one year. However, this study also did not assess the effect of e-cigarette use among adolescents [31]. Thus, these last two studies could not determine the balance of benefits and harms of e-cigarette use at the population level.

In this study, we developed a Monte Carlo stochastic simulation model that extends

prior research in two ways. First, we simultaneously consider multiple population subgroups including current cigarette smokers and never cigarette smokers. Second, we quantify the net population benefits (or harms) of e-cigarette use in terms of the total number of years of life gained among additional current cigarette smokers who quit smoking and years of life lost among additional cigarette smoking initiators who become long-term daily cigarette smokers, both through the use of e-cigarettes. We base our calculations on 2014 US census data, national health or tobacco use surveys on e-cigarette use, and published randomized trials and cohort studies on the e-cigarette associated transition probabilities of cigarette smoking cessation and initiation.

Methods

Analytic model

Our analytic approach consists of two main steps (Fig 1). The first step estimates the number of years of life gained among the additional number of current cigarette smokers who quit smoking through the use of e-cigarettes as a cessation tool, compared to those who did not use e-cigarettes as a cessation tool, and remain continually abstinent from smoking for ≥7 years. We set the threshold for continual abstinence at 7 years because cohort studies found that relapse beyond this point is rare [32,33]. Additionally, the risk of death among former cigarette smokers who quit for this long begins to approximate the risk of death among never cigarette smokers [34]. We began with the US adult population of 25–69 year olds in 2014 (in five-year age groups) and multiplied these counts by the: (1) age-group-specific prevalence of current cigarette smoking, (2) age-group-specific prevalence of trying to quit smoking within the past year among current cigarette smokers, (3) age-group-specific prevalence of current e-cigarette use among current cigarette smokers who tried quitting within the past year, (4) difference in the transition probability of ≥6-month cigarette smoking cessation between current smokers who used e-cigarettes as a cessation tool and current smokers who did not use e-cigarettes as a cessation tool, (5) probability of 1 year of cigarette smoking abstinence from cigarette smoking given ≥6 months of cigarette smoking abstinence, (6) probability of ≥6 years of abstinence from cigarette smoking given 1 year of cigarette smoking abstinence, and (7) age-group-specific number of years of life gained from quitting cigarette smoking. We assumed 95% relative harm reduction of e-cigarette use, compared to cigarette smoking, among current cigarette smokers who used e-cigarettes as a cessation tool and quit smoking [35]. As described below, we vary the relative harm of e-cigarette use, compared to cigarette smoking, to include the levels of relative harm inferred from in vitro and mouse model studies [36,37].

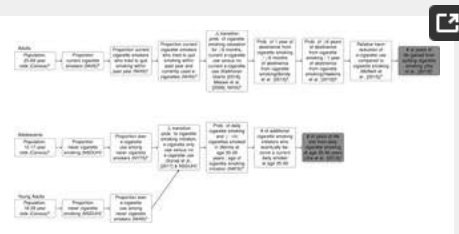

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Fig 1. Population-level model to quantify benefits and harms of E-cigarette use.
Superscripted letters refer to the columns in Tables A and B in S3 Appendix for age- and age-group-specific parameter point estimates and 95% confidence intervals. Note: Δ = Change in; | = Conditional On; NATS = National Adult Tobacco Survey; NHIS = National Health Interview Survey; NSDUH = National Survey on Drug Use and Health; NYTS = National Youth Tobacco Survey; and Prob. = Probability.
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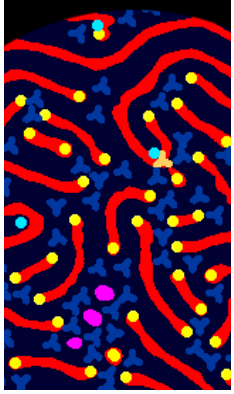
The second step estimates the number of years of life lost among the additional number of never-cigarette smoking adolescents and young adults who eventually become current daily cigarette smokers (and also smoked ≥100 cigarettes in lifetime) at age 35–39 through the use of e-cigarettes. We began with the US adolescent and young adult population of 12–29 year olds in 2014 (by single year of age) and multiplied these counts by the: (1) age-specific prevalence of never cigarette smoking, (2) age-specific prevalence of ever having tried e-cigarettes among never cigarette smokers, (3) the difference in the transition probability of cigarette smoking initiation among never cigarette smoking adolescents and young adults who had ever used e-cigarettes, compared to the corresponding probability among those who had never used e-cigarettes, (4) probability of becoming a current daily cigarette smoker at age 35–39 based on the age of cigarette smoking initiation, and (5) age-specific number of years of life lost from current daily cigarette smoking at age 35–39.

We assessed three outcomes of interest: (1) the additional number of current cigarette smokers who will quit smoking through the current use of e-cigarettes and abstain from smoking for ≥7 years, compared to those who do not currently



use e-cigarettes and (2) the additional number of adolescents and young adults who will initiate cigarette smoking through the ever use of e-cigarettes and eventually become daily cigarette smokers at age 35–39, compared to those who never used e-cigarettes; and (3) the total number of expected years of life gained or lost across all these population subgroups.

Table 1 describes the data source of each model parameter. S1 Appendix describes how the difference in transition probabilities of ≥6-month cigarette smoking cessation between current e-cigarette users and non-current e-cigarette users was estimated based on various parameters such as the proportion of current cigarette smokers who used pharmaceutical aids during quit attempt and the pooled odds ratio of quitting smoking among smokers interested in quitting reported by the meta-analysis of Kalkhoran & Glantz [38]. S2 Appendix describes the estimation of the difference in transition probabilities of cigarette smoking initiation between never cigarette smokers who ever used e-cigarettes compared to those who never used e-cigarettes based on the pooled odds ratio of cigarette smoking initiation reported by the meta-analysis of Soneji et al. [19]. Tables A and B in S3 Appendix show the value of each model parameter.

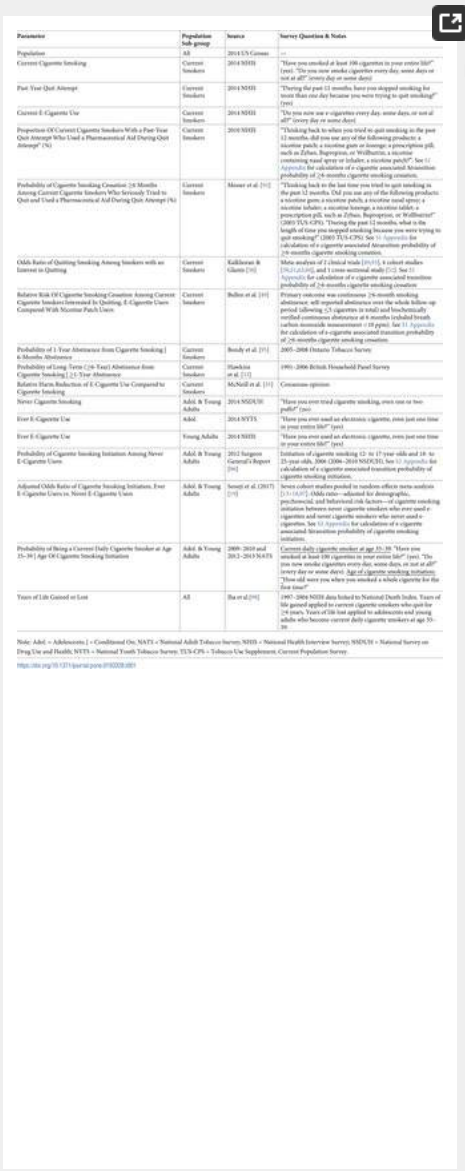


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Table 1. Data Sources of model parameters.
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Validation of model

We validated the model against one-year intermediate outcomes (e.g., the number of adolescents and young adult cigarette smoking initiators). For current adult smokers, we applied the model to 2013 National Health Interview Survey (NHIS) data to predict the number of current cigarette smoking adults (both current and non-current e-cigarette users) who would quit in 2014 and remain continually abstinent from smoking for ≥6 months. We then compared this predicted number with the observed number in 2014, estimated from 2014 NHIS data, by identifying new ≥6-month quitters as respondents who answered six months to one year to the question: “How long has it been since you quit smoking cigarettes?”. For adolescent and young adult never smokers, we applied the model to 2013 National Survey on

Drug Use and Health (NSDUH) data to predict the number of cigarette smoking initiators in 2014 (both ever and never e-cigarette users). We then compared this predicted number with the observed number of initiators in 2014, estimated from 2014 NSDUH data, by identifying respondents who answered "yes" to the question: "Have you smoked part or all of a cigarette?" and whose current age was ≤1 year less than the age at which they first smoked a cigarette ("How old were you the first time you smoked part or all of a cigarette?").

Analytic considerations and sensitivity analyses

To account for uncertainty in the prevalence and transition probability parameters, we utilized Monte Carlo simulation and independently drew from normal distributions with the means and standard deviations equal to the parameters' means and standard errors shown in Tables A and B in S3 Appendix. We repeated this process 100,000 times to create a distribution of each outcome of interest.

We conducted a sensitivity analysis by varying the level of four key parameters: (1) the adjusted odds ratio of smoking cessation, (2) the adjusted odds ratio of cigarette smoking initiation, (3) age-group-specific prevalence of current e-cigarette use among current cigarette smokers who tried quitting within the past year, and (4) age-specific prevalence of ever having tried e-cigarettes among never cigarette smokers. We also calculated the probability of positive total years of life gained across a wide range of possible values for these four parameters. For example, we supposed the adjusted odds ratio of smoking cessation equaled 2.5 times the baseline estimate (2.15 = 2.5 x 0.86) and recalculated the years of life gained, drawing all other parameters from their baseline distributions. The probability of a positive total years of life gained under this supposition equaled the ratio of the (1) number of simulations that yielded a positive value and (2) total number of simulations (100,000). Finally, we varied from 0% to 100% the relative harm of e-cigarette use, compared to cigarette smoking, in terms of the number of years of life gained from quitting cigarette smoking. We used R, Version 3.2.3 for all analyses. Results of years of life gained were determined to be statistical significant if their 95% confidence intervals do not contain zero.

Results

Additional quitters and initiators

In 2014, 3,490,000 current adult cigarette smokers who had attempted to quit smoking in the past year had also currently used e-cigarettes. Additionally, 3,640,000 never-cigarette smoking adolescents and young adults had ever used e-cigarettes.

The model estimated that 2,070 additional current cigarette smoking adults (95% CI: -42,900 to 46,200) who currently used e-cigarettes in 2014 would quit smoking in 2015 and remain continually abstinent from smoking for ≥7 years using e-cigarettes, compared to those who did not currently use e-cigarettes (Fig 2). The model also estimated that an additional 168,000 never-cigarette smoking adolescents and young adults in 2014 (95% CI: 114,000 to 229,000) who had ever used e-cigarettes would initiate cigarette smoking in 2015 and eventually become daily cigarette smokers at age 35–39, compared to those who had never used e-cigarettes.

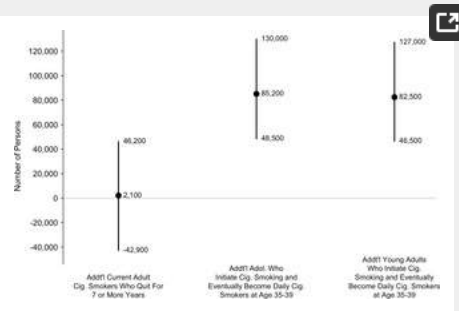

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Fig 2. Number of additional adult current cigarette smokers who quit for ≥7 years and additional adolescents and young adults who initiate cigarette smoking and eventually become daily cigarette smokers at age 35–39, all through the use of E-cigarettes.
The mean of the distribution is shown as a solid circle and the 95% confidence interval is shown as a vertical line. Source: stochastic simulation (100,000 iterations). Note: Addt'l = Additional; Cig. = Cigarette. Estimates reported as text in the figure rounded to 3 significant digits.
https://doi.org/10.1371/journal.pone.0193328.g002

Years of life gained

The model estimated that the 2,070 additional long-term quitters would gain -3,000 years of life (95% CI: -351,000 to 325,000). The model also estimated the

additional 168,000 adolescent and young adult cigarette smoking initiators who eventually become daily cigarette smokers at age 35–39 will lose 1,510,000 years of life (95% CI: 1,030,000 to 2,060,000). Thus, considering all population subgroups, the model estimated that e-cigarette use in 2014 would lead to 1,510,000 years of life lost (95% CI: 920,000 to 2,160,000; Fig 3) assuming an approximate 95% relative harm reduction of e-cigarette use compared to cigarette smoking.

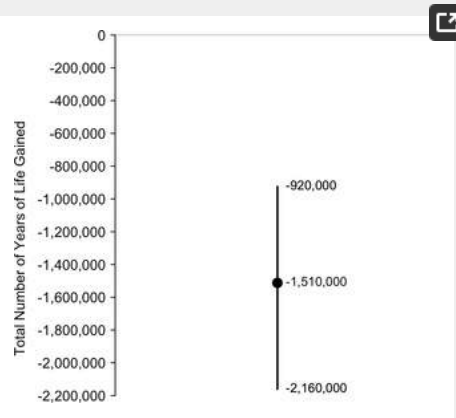

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Fig 3. Total number of years of life gained.
Negative years of life gained represent years of life lost. The mean of the distribution is shown as a solid circle and the 95% confidence interval is shown as a vertical line. Source: stochastic simulation (100,000 iterations). Estimates reported as text in the figure rounded to 3 significant digits.
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Sensitivity analysis

Our results were sensitive to the adjusted odds ratios of cigarette smoking cessation and cigarette smoking initiation (Table 2). The model estimated that e-cigarette use in 2014 would lead to 1,150,000 years of life lost (95% CI: 2,130,000 to 242,000) under the relative risk of smoking cessation estimated by Bullen et al. (transformed to an odds ratio). The model estimated that e-cigarette use in 2014 would lead to 1,330,000 years of life lost (95% CI: 1,950,000 to 780,000) and 1,150,000 years of life lost (95% CI: 1,730,000 to 620,000) if the adjusted odds ratio of cigarette smoking initiation decreased by 10% and 20%, respectively. Our results were also sensitive to the prevalence of current e-cigarette use among current cigarette smokers who tried quitting within the past year and ever e-cigarette use and never cigarette smokers. Finally, we varied the health risks of e-cigarette use as a percentage of the risk associated with cigarette smoking. The total number of years of life lost increased as the relative harm of e-cigarette use, compared to cigarette smoking, grew (Fig 4). The model estimated that e-cigarette use in 2014 would lead to 1,530,000 years of life lost (95% CI: 2,180,000 to 960,000) and 1,580,000 years of life lost (95% CI: 2,250,000 to 1,020,000) if the health risks of e-cigarette use were 10%-20% (i.e., 80%-90% safer) and 40%-50% (i.e., 50%-60% safer) of the risks of cigarette smoking, respectively.

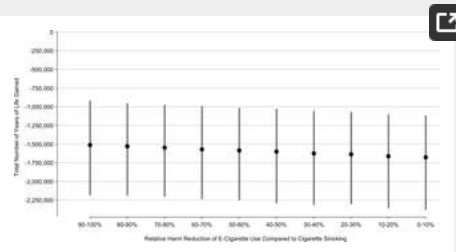

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Fig 4. Total number of years of life gained by relative harm of E-cigarette use compared to cigarette smoking.
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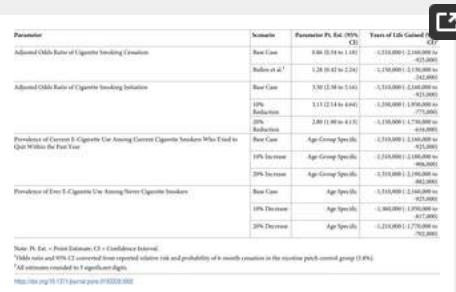

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Table 2. Results of sensitivity analysis.
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The probability of a positive total number of years of life gained increased with the relative risk of smoking cessation: 6.7%, 44.6%, and 83.3% as the relative risk increased to 2.0, 2.5, and 3.0, respectively (Fig 5, Panel A). The probability also increased with higher prevalence of current e-cigarette use among current cigarette smokers (Fig 5, Panel B). Conversely, the probability increased to 0.0%, 0.0%, and 47.6% as the adjusted odds ratio decreased to 3.0, 2.0, and 1.0, respectively (Fig 5, Panel C). Finally, the probability increased with lower prevalence of ever e-cigarette use among never cigarette smokers (Fig 5, Panel D).

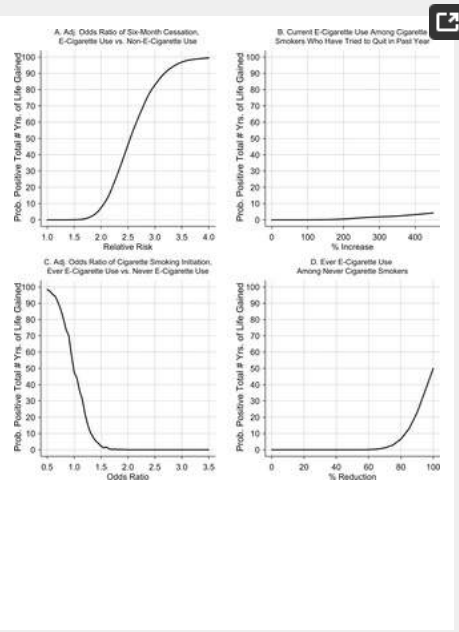

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Fig 5. Probability of a positive total number of years of life gained varying the level of four key model parameters.
Note: vs. = versus; Adj. = Adjusted.
https://doi.org/10.1371/journal.pone.0193328.g005

Model validation

Based on 2013 NHIS data, we predicted 1.2 million current cigarette smoking adults would have quit and remained continually abstinent from smoking for ≥6 months in 2014 (95% CI, 1.0 to 1.4 million), which was not statistically different ($p = 0.57$) from the estimated number from the 2014 NHIS data (1.1 million, 95% CI: 0.9 to 1.3 million). Based on 2013 NSDUH data, we predicted that 5.5 million adolescents and young adults would have initiated cigarette smoking in 2014 (95% CI: 4.0 to 6.9 million), which was not statistically different ($p = 0.53$) from the observed number from 2014 NSDUH data (5.0 million, 95% CI: 4.1 to 5.9 million).

Discussion

Our study developed a Monte Carlo stochastic simulation model to assess the balance of health benefits and harms of e-cigarette use at the population level. Based on the most up-to-date published evidence, our model estimated that e-cigarette use in 2014 represents a population-level harm of about 1.6 million years of life lost over the lifetime of all adolescent and young adult never-cigarette smokers and adult current cigarette smokers in the 2014 US population. Our model also estimated even greater population-level harm if e-cigarette use confers long-term health risks.

Our study is consistent with Kalkhoran & Glantz (2015), who estimated the effects of e-cigarette use on cessation among smokers and on cigarette smoking initiation by never-smokers under various scenarios [29]. For example, their study found the largest relative health costs occurred in the scenario under which e-cigarette use increased among never-smokers because of the resulting increase in cigarette smoking initiation and the dual use of cigarettes and e-cigarettes, while e-cigarette use remained unchanged among established smokers. Our study also supports the conclusion of Cherng et al. (2016) on the relative effects of e-cigarettes on smoking initiation and cessation [39]. Our model indicates that the odds of smoking initiation among e-cigarette users would need to decrease more than the odds of smoking cessation would need to increase to achieve the same change in the total number of years of life gained.

Our conclusions differ from those of Levy et al. (2016), Levy et al. (2017), and Hill & Camacho (2017)—a tobacco industry-funded study [40–42]. Hill & Camacho found

the use of e-cigarettes would result in a decrease in smoking-related mortality in the UK from 8.4% to 8.1% in 2050 [40]. Levy et al. found that the use of vaporized nicotine products (VNPs; e.g., e-cigarettes) would lead to years of life gained for the US birth cohort of 1997 as it ages over time [41]. Hill & Camacho estimated an "overall beneficial effect from launching e-cigarettes", in part, because they explicitly assumed the transition probability of cigarette smoking initiation among never cigarette smokers who used e-cigarettes equaled 5% [40]. Levy et al. (2016) estimated a "positive public health impact" from VNP use, in part, because they implicitly assumed the odds of cigarette smoking initiation was only marginally higher for ever e-cigarette users than never e-cigarette users (odds ratio≈1.16) among adolescents and young adults who would not have become a cigarette smoker in the absence of VNPs. Yet, both of these assumptions are substantially different from empirical estimates of these parameters from thirteen published cohort studies with a combined sample size of over 44,000 respondents [13–18,20,21,43–47]. Levy et al. (2017) estimates a substantial number of years of life gained from e-cigarette use, in part, because they explicitly assumed e-cigarette use among never cigarette smokers does not increase the rate of cigarette smoking initiation, which—again—contrasts with growing scientific evidence to the contrary. Nevertheless, these models provide useful conceptual frameworks to assess the net benefits of e-cigarette use and would likely yield substantively different conclusions under alternative—and empirically based—assumptions of e-cigarette use and cigarette smoking initiation.

E-cigarettes could, indeed, confer a positive population benefit if they were more effective as a smoking cessation device. For example, if current smokers who used e-cigarettes as a smoking cessation tool achieved six-month smoking abstinence at a rate of approximately 2.55 times greater than their counterparts who did not use e-cigarettes, then our model estimated that the probability of a positive total number of years of life gained would approach 50%. However, the estimated effectiveness of e-cigarettes for smoking cessation from all published randomized trials and nearly all cohort studies fall well below this threshold including some studies that concluded cigarette smokers who used e-cigarettes were less—not more—likely to quit than those who used standard clinic-based smoking cessation treatments [11,38,48–65]. Three cohort studies of current cigarette smokers did, indeed, estimate relative risks of smoking cessation above this threshold among intensive e-cigarette users (daily use for at least one month), daily tank e-cigarette users, and long-term (i.e., ≥2-year) e-cigarette users [59,66,67]. However, the prevalence of intensive e-cigarette use, daily e-cigarette tank use, and long-term e-cigarette use were low in these studies: only 34% of e-cigarette users were intensive users, 12% of e-cigarette users were daily e-cigarette tank users, and 14% of e-cigarette users were long-term users [59,66,67].

A decline in public acceptability of cigarette smoking has been accompanied by proscriptions on where smoking is allowed [68,69]. Nearly two-thirds of e-cigarette users reported using them when and where cigarette smoking was not allowed [70,71]. Further, an analysis of e-cigarette tweets highlighted that e-cigarette vaping was considered social acceptable by many, as opposed to cigarette smoking [72]. However, the lower level of sensation and satisfaction experienced with e-cigarettes, compared to cigarettes, may explain why some individuals who initiate with e-cigarettes then transition to cigarettes even thought this transition is associated with higher nicotine ingestion [73–75].

E-cigarette use among former cigarette smokers may confer health risks. For example, e-cigarette aerosols carry high levels of aldehydes (e.g., formaldehyde) that affect cardiovascular function and high levels of fine particles that accelerate heart disease [76,77]. E-cigarette users experience equivalent reductions in vascular function (e.g., vitamin E levels and flow-mediation dilatation) as cigarette smokers. Furthermore, e-cigarette use suppresses immune and inflammatory-response genes in nasal epithelial cells and injures lung epithelial cells [78,79].

Our study has some potential limitations. First, we do not know if e-cigarette use causes cigarette-smoking initiation in adolescents and young adults. Published cohort studies have found consistent evidence of an increased risk of cigarette smoking initiation among non-smoking youth who had ever used e-cigarettes after accounting for known demographic, psychosocial, and behavioral risk factors [13–18,20,21]. We varied this longitudinal association between e-cigarette use and cigarette smoking initiation and reach similar conclusions. Perhaps more concerning that cigarette smoking initiation, e-cigarette use was independently associated with progression to heaving patterns of cigarette smoking among US adolescents [80]. Second, we do not know the type of e-cigarette currently used by cigarette-smoking adults. Second generation e-cigarettes (e.g., tank-style systems) deliver nicotine more efficiently than the first generation e-cigarettes used in Bullen et al. trial [49,81]. Third generation e-cigarettes (e.g., advanced personal vaporizers) deliver nicotine at approximately the same level and speed as traditional cigarettes [82]. However, we do not yet know the national prevalence of second and third generation e-cigarette use among current cigarette smokers who are trying to quit, and no published trials or cohort studies estimate cessation efficacy or effectiveness of third-generation e-cigarettes.

Third, in our calculation of benefit, we did not consider the possibility that e-cigarette use among current cigarette smokers leads to a reduction in the intensity of cigarettes smoked per day. A trial conducted by Caponnetto et al. found e-cigarette reduced the median number of cigarettes smoked per day among 300

Italian smokers not intending to quit [83]. Yet, similar reductions in the number of cigarettes smoked per day has not been observed in the US between dual users of e-cigarettes and cigarettes and exclusive cigarette smokers [65].

Fourth, we did not consider the potential population-level health benefit or harm of e-cigarette use among former cigarette smokers because no published trials or cohort studies assessed whether e-cigarette use among former cigarette smokers led to higher or lower rates of relapse to cigarette smoking. A recent cross-sectional study suggested long-term former cigarette smokers who use e-cigarettes may not experience any higher rate of relapse to smoking than their counterparts who do not use e-cigarettes [84].

Current public health models may yield substantively different conclusions about the net harm or benefit of e-cigarette use because there is insufficient data on the effect of e-cigarette use on cigarette smoking-related transitions and tobacco-related diseases. Conclusions may also differ because of decisions—both implicit and explicit—about the framework and underlying assumptions inherent in the model. The host of decisions required to develop a model produce structural uncertainty that may exceed parameter uncertainty [85,86]. Sensitivity analysis will not capture structural uncertainty because the model, itself, remains constant. Future work could incorporate Bayesian model averaging to account structural, or model-based, uncertainty [87]. Future work could also grade the quality of models based on published best practices [86,88].

In conclusion, based on currently available evidence on the e-cigarette associated transition probabilities of cigarette smoking cessation and initiation, our study suggests that e-cigarettes pose more harm than they confer benefit at the population level. If e-cigarettes are to confer a net population-level benefit in the future, the effectiveness of e-cigarettes as a smoking cessation tool will need to be much higher than it currently is. The US Preventive Services Task Force concludes the existing scientific evidence is insufficient to clinically recommend e-cigarettes as a smoking cessation tool [89]. In the United Kingdom, the National Institute of Clinical Excellence also notes limited evidence on the long-term health effects of e-cigarette use and does not clinically recommend e-cigarettes for smoking cessation, in contrast to Public Health England and the Royal College of Physicians [35,90,91]. Additionally, comprehensive tobacco control efforts are needed to reduce the appeal of e-cigarettes to youth.

Supporting information

S1 Appendix. E-vigarette-associated Δ transition probability of cigarette smoking cessation.

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(DOCX)

S2 Appendix. E-cigarette-associated Δ transition probability of cigarette smoking initiation.

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(DOCX)

S3 Appendix. Model parameters.

S3 Appendix including Tables A and B. Table A shows model parameters for current adult cigarette smokers. Table B shows model parameters for adolescents and young adults.
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(DOCX)

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View Article • PubMed/NCBI • Google Scholar

THIS REPORT DATA SHOWS 59% OF US ADULTS ARE DUAL USERS OF CIGARETTES AND E-CIGARETTES

Epidemiology of E-Cigarette Use

United States of America

BRIAN A. KING, PHD, MPH
DEPUTY DIRECTOR FOR RESEARCH TRANSLATION
CDC OFFICE ON SMOKING AND HEALTH

Technical Meeting on Testing and Regulating
Electronic Cigarettes and Novel Tobacco Products
Hong Kong ~ December 1, 2017

1

Background

2

Patterns of Use: Adults

3

Patterns of Use: Youth

1

Background

2

Patterns of Use: Adults

3

Patterns of Use: Youth

Electronic Nicotine Delivery Systems (ENDS)

E-Cigarettes

Hookah Pens

E-Cigars

Vape Pens

E-Pipes

E-Hookahs

At Least 450 Brands

New Regulatory Framework

- ✓ Further limits youth access
- ✓ Bans tobacco company sponsorship of sporting and entertainment events
- ✓ Prohibits the sale of tobacco-branded merchandise such as clothing and jewelry
- ✓ Prohibits false and misleading advertising and labels, such as “light” and “mild”

Family Smoking Prevention and Tobacco Control Act (2009)

Two U.S. Regulatory Pathways for ENDS

Tobacco Products

Cessation Devices

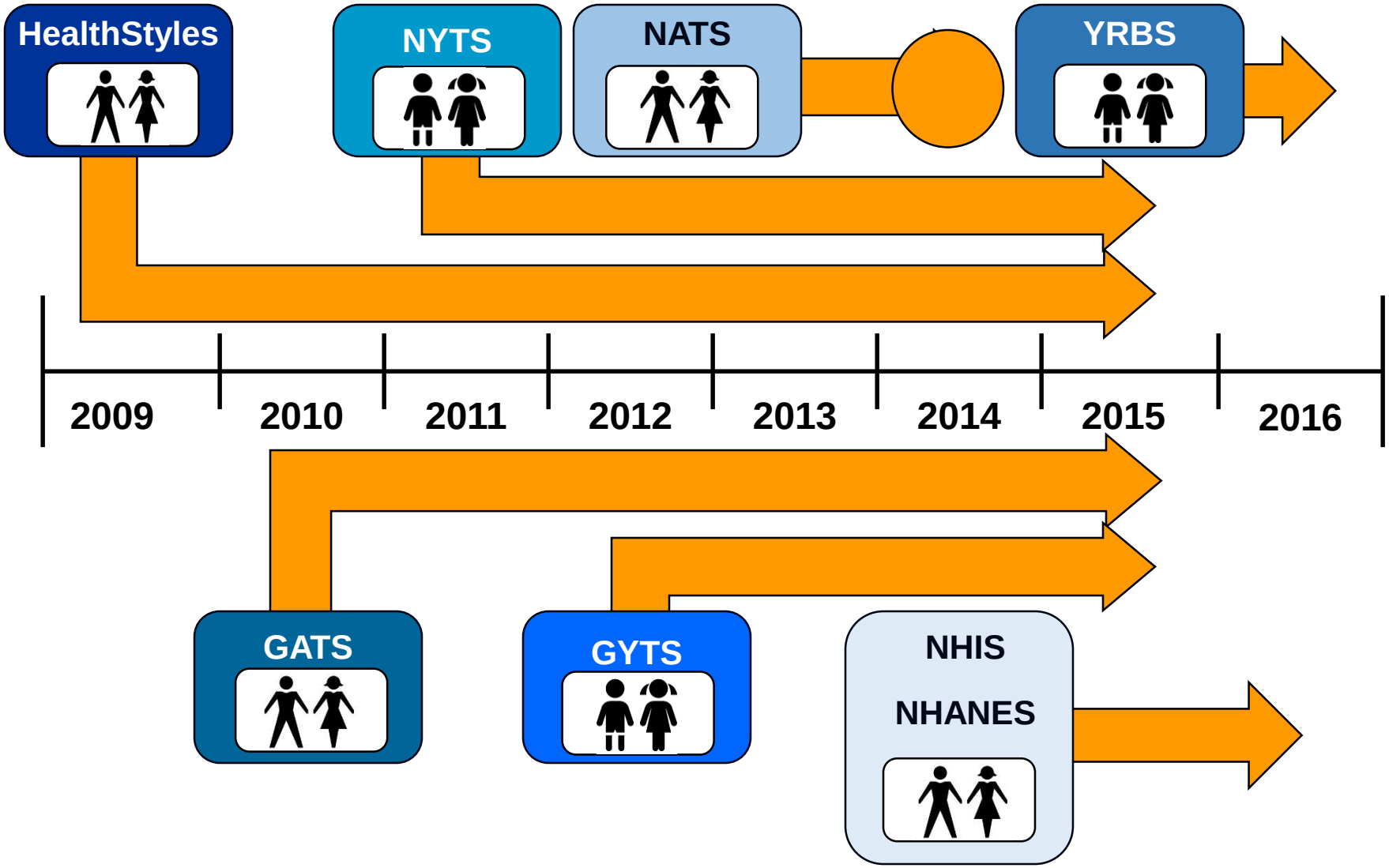
U.S. Food and Drug Administration Center for Tobacco Products

U.S. Food and Drug Administration Center for Drug Evaluation and Research

CDC Surveillance Systems with ENDS Measures

	HealthStyles (Styles)	Global Adult Tobacco Survey (GATS)	Global Youth Tobacco Survey (GYTS)	National Adult Tobacco Survey (NATS)	National Health and Nutrition Examination Survey (NHANES)	National Health Interview Survey (NHIS)	National Youth Tobacco Survey (NYTS)	Youth Risk Behavior Survey (YRBS)
Mode								
Periodicity	Annual	Varies by Country	Varies by Country	2009-2010 2012-2013 2013-2014	Annual	Annual	Annual	Biennial
Scope	National	International	International	National	National	National	National	National & Select States
Population	Adults ≥18 Years	Adults ≥15 Years	Students 13-15 Years	Adults ≥18 Years	Population ≥ 2 Months	Adults ≥18 Years	Middle & High School Students	High School Students
Sample	~4,000	~8,000	~2,000	~60,000	~5,000	~35,000	~18,000	~14,000
Response Rate	~65%	~70%-90%	~80%-90%	~45%	~70%	~60%	~70%	~70%

Timeline of CDC ENDS Surveillance Activities



1

Background

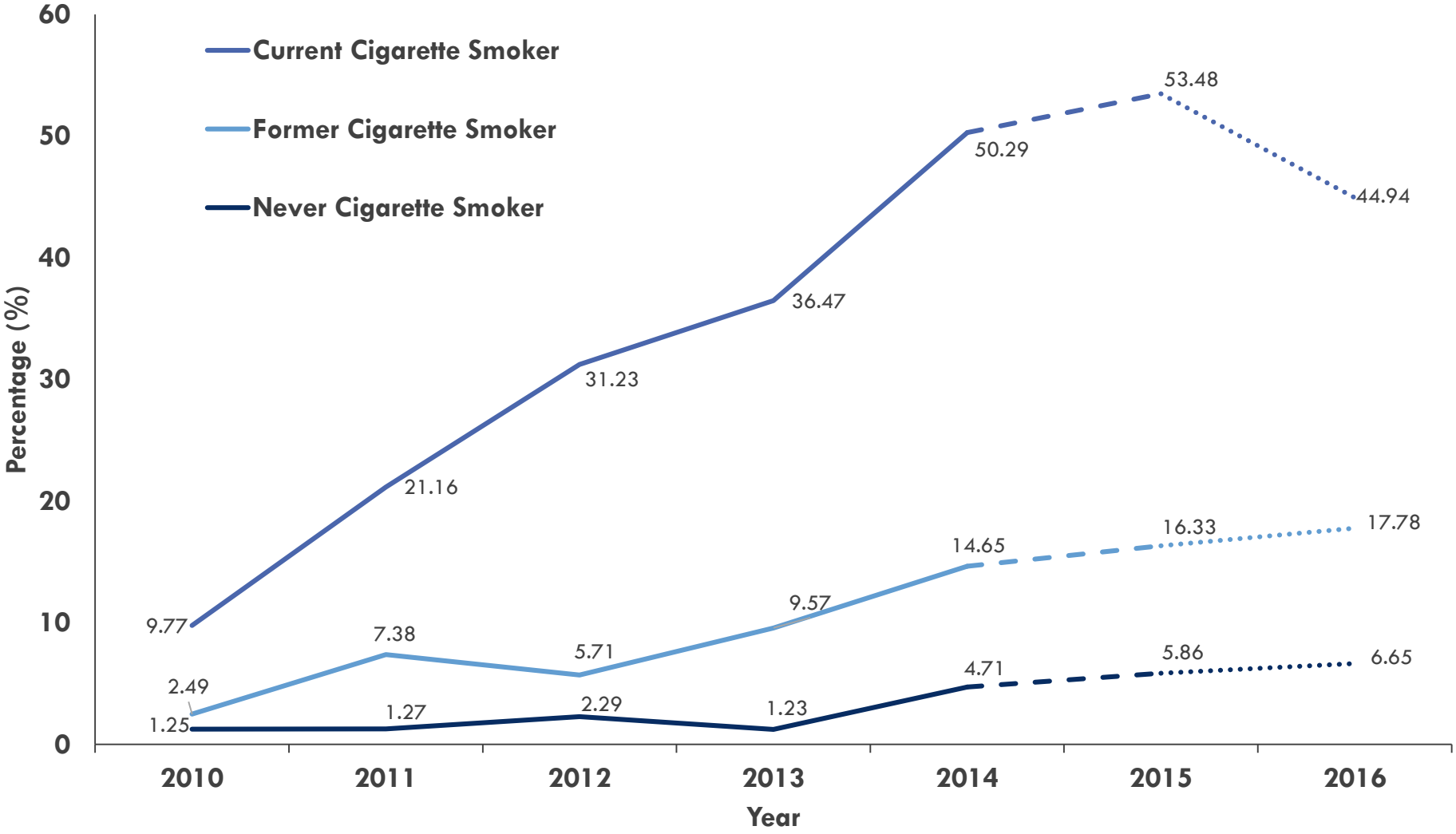
2

Patterns of Use: Adults

3

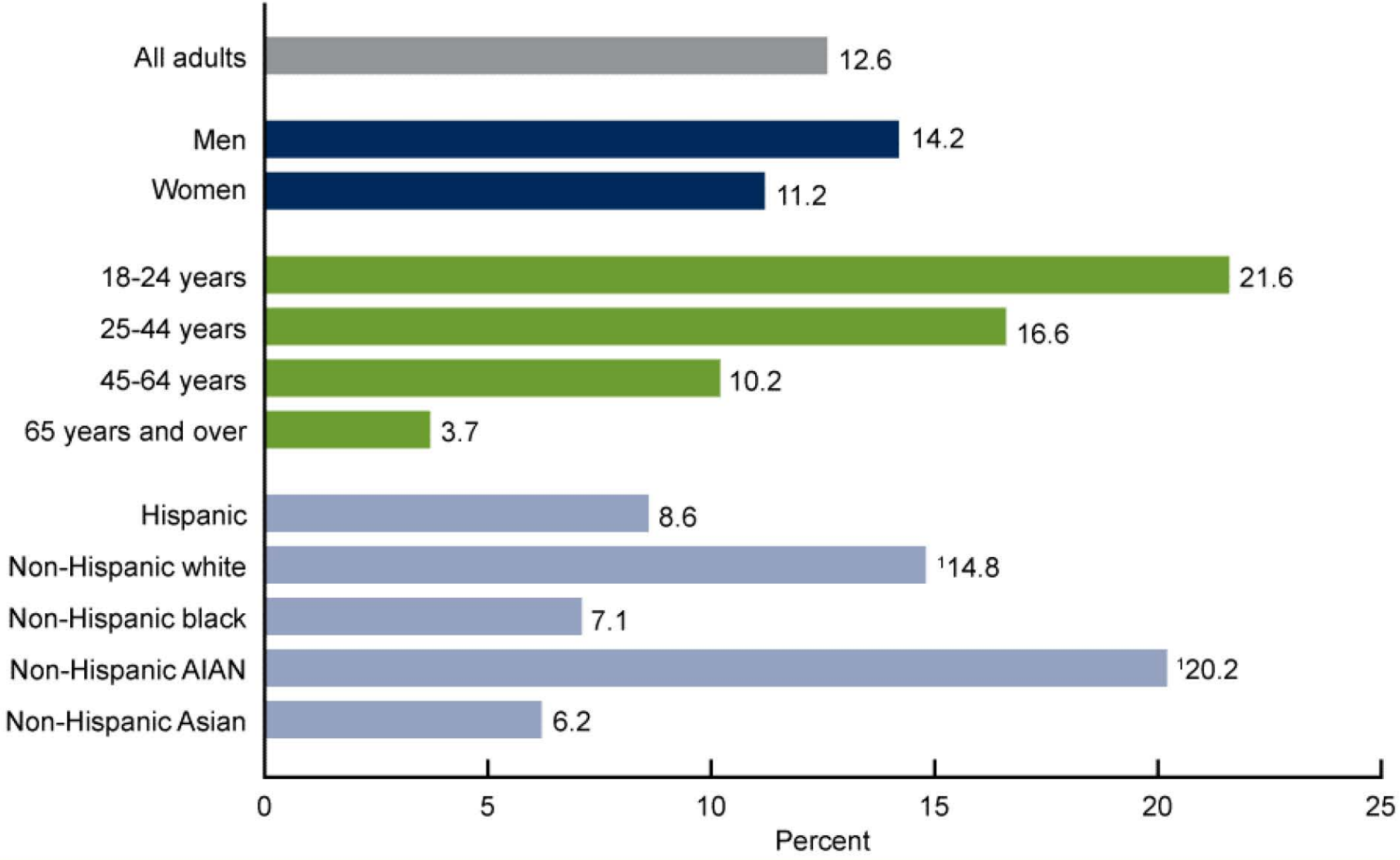
Patterns of Use: Youth

Ever use of e-cigarettes among adults, by cigarette smoking status—U.S., 2010-2016



Source: CDC. Styles Survey. 2010-2016

Percentage of U.S. adults who ever tried an e-cigarette, by sex, age, and race/ethnicity, 2014

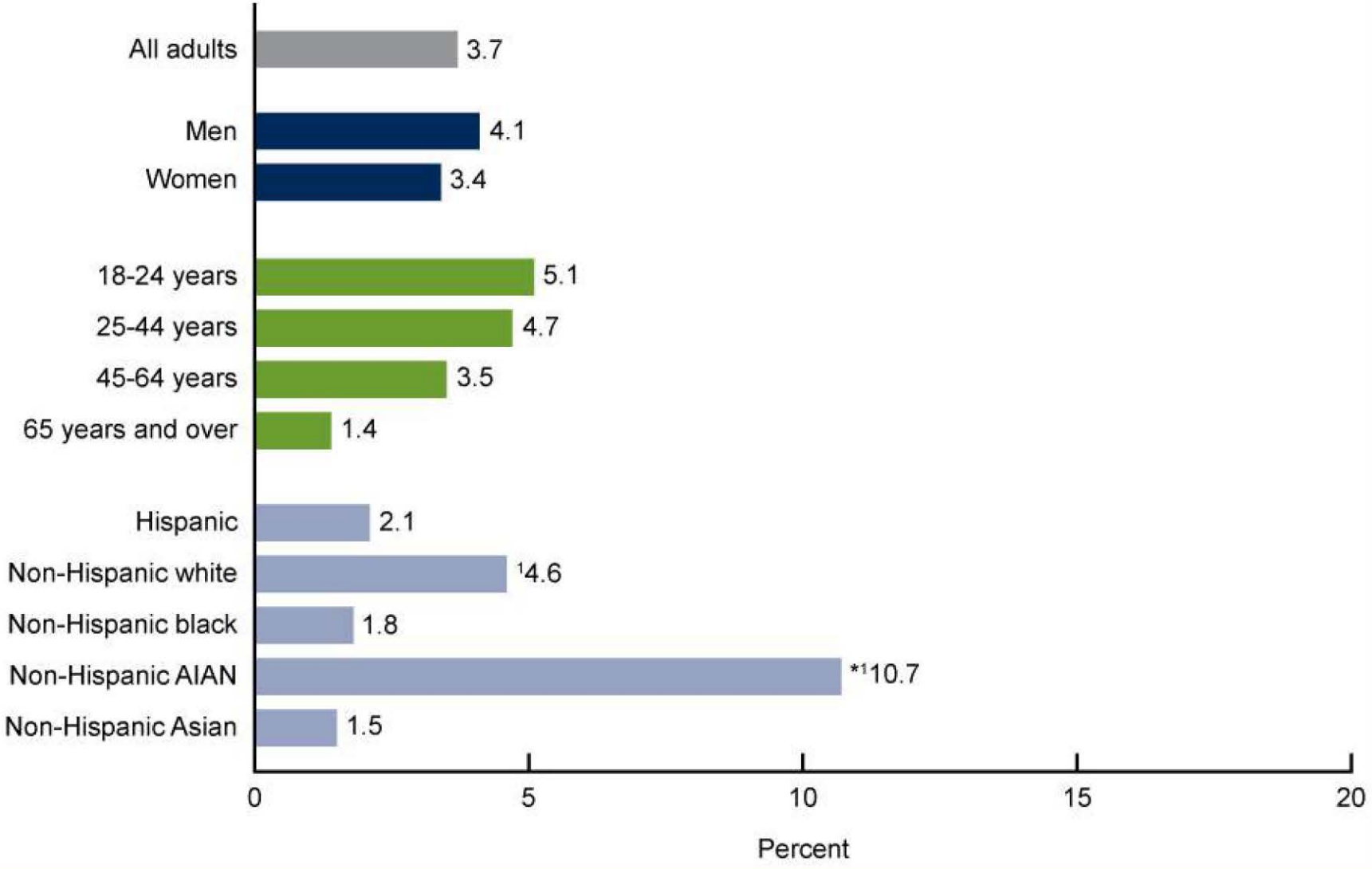


Source: CDC/NCHS, National Health Interview Survey, 2014. http://www.cdc.gov/nchs/data/databriefs/db217.htm

[1] Significantly different from Hispanic, non-Hispanic black, and non-Hispanic Asian subgroups.

NOTES: AIAN is American Indian or Alaska Native. Within sex and age groups, all subgroups are significantly different from each other. There is a significant linear trend by age group.

Percentage of U.S. adults who currently use e-cigarettes, by sex, age, and race/ethnicity, 2014



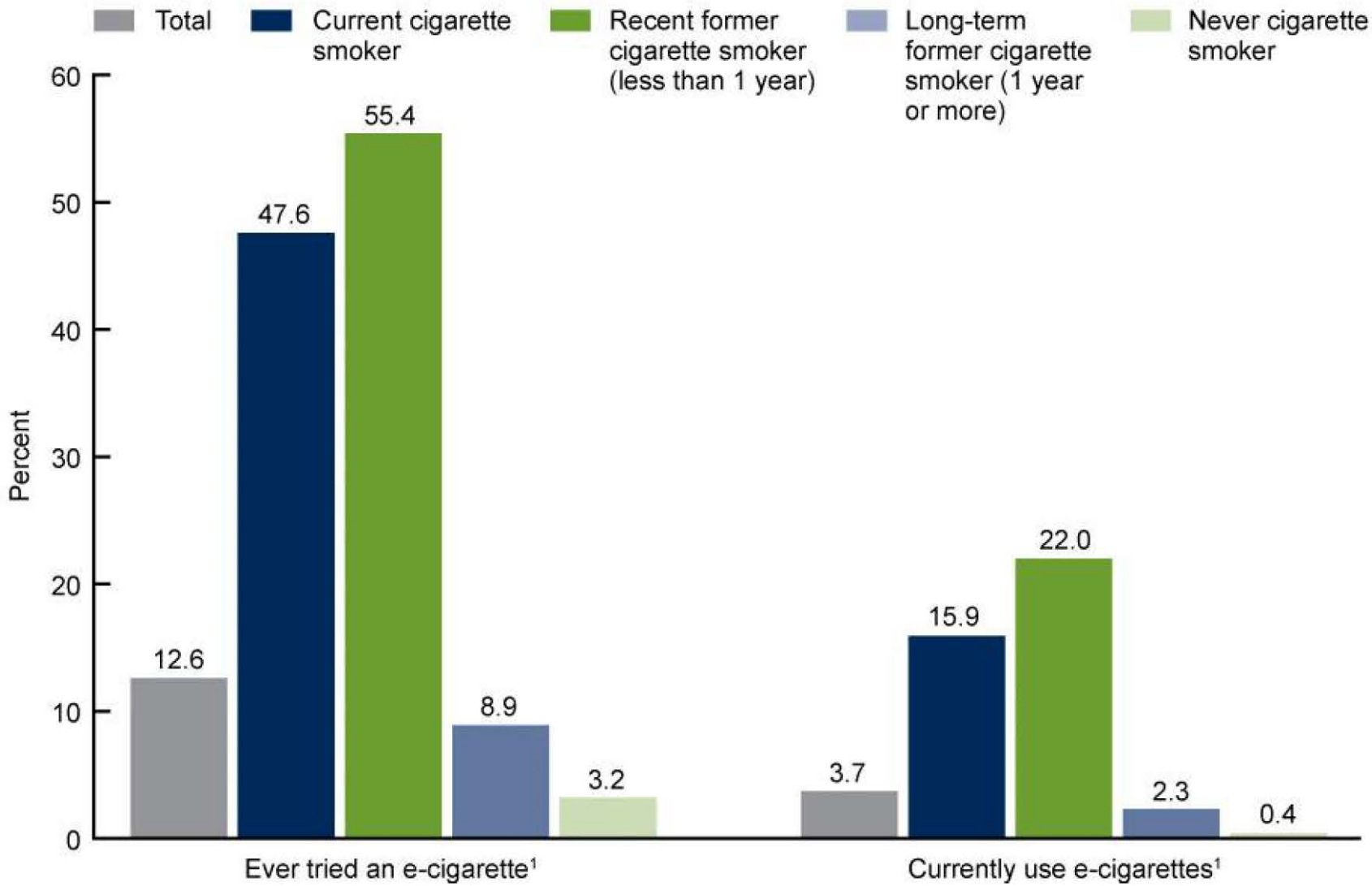
Source: CDC/NCHS, National Health Interview Survey, 2014. http://www.cdc.gov/nchs/data/databriefs/db217.htm

* Estimate has a relative standard error greater than 30% but less than 50% and does not meet standards of reliability or precision. The 95% confidence interval is 5.3–20.4.

[1] Significantly different from Hispanic, non-Hispanic black, and non-Hispanic Asian subgroups.

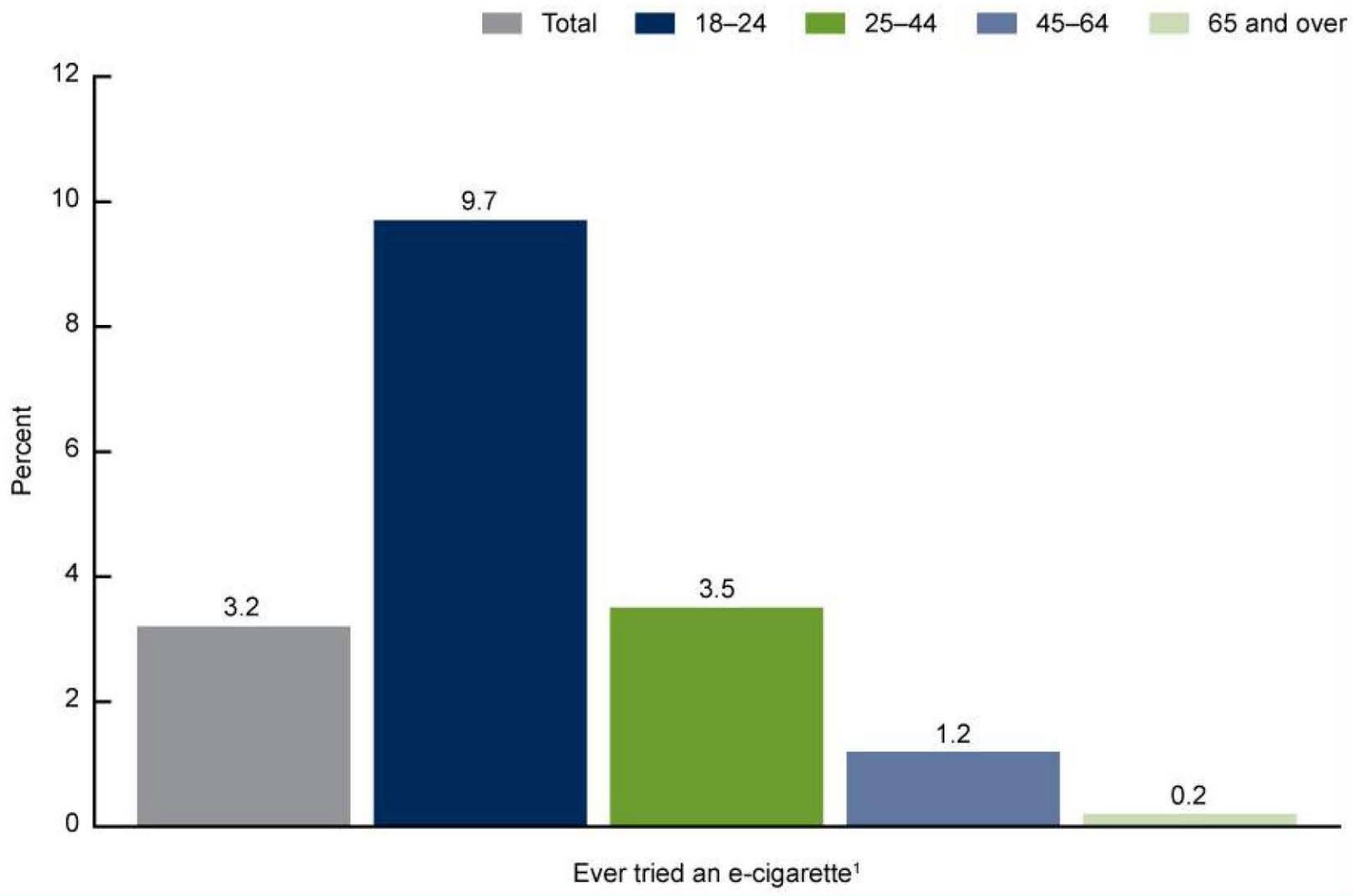
NOTE: AIAN is American Indian or Alaska Native.

Percentage of U.S. adults who ever tried and currently use e-cigarettes, by cigarette smoking status, 2014



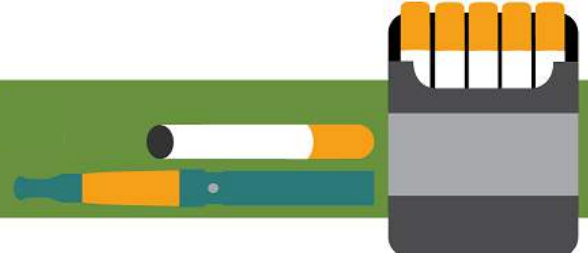
Source: CDC/NCHS, National Health Interview Survey, 2014. http://www.cdc.gov/nchs/data/databriefs/db217.htm

Percentage of U.S. adults who never smoked cigarettes and who ever tried an e-cigarette, by age, 2014

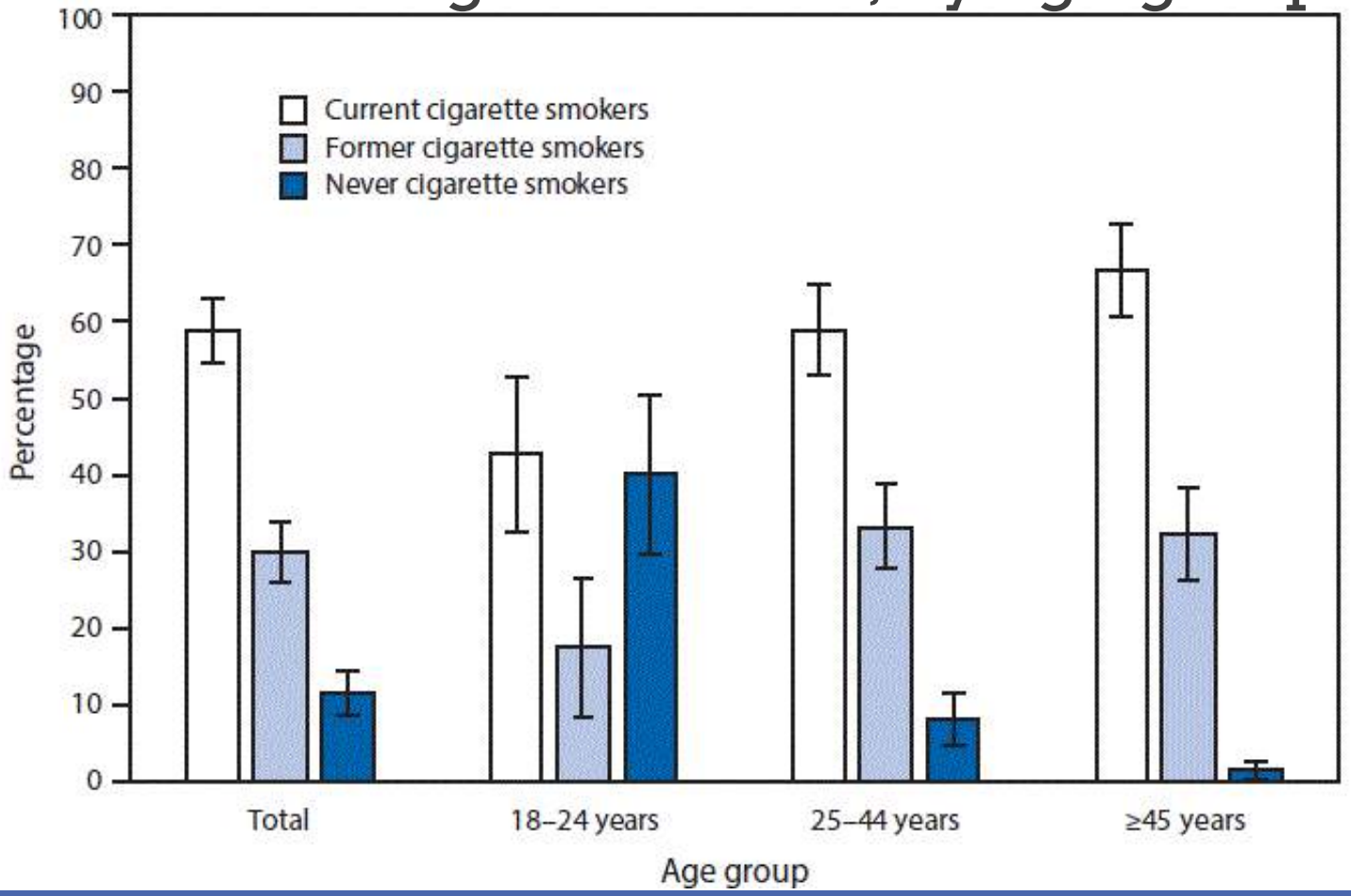


Source: CDC/NCHS, National Health Interview Survey, 2014. http://www.cdc.gov/nchs/data/databriefs/db217.htm

A majority of adult e-cigarette users also smoke conventional cigarettes: "dual use."



Cigarette smoking status among current adult e-cigarette users, by age group



Source: *QuickStats:* Cigarette Smoking Status Among Current Adult E-cigarette Users, by Age Group — National Health Interview Survey, United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1177. DOI: http://dx.doi.org/10.15585/mmwr.mm6542a7

E-Cigarette Use As a Smoking Cessation Tool in Adults

"The long-term safety of e-cigarettes is unknown."

"There is evidence from two trials that e-cigarettes help smokers to stop smoking in the long term compared with placebo e-cigarettes.

However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated 'low' by GRADE standards."

"Overall, the USPSTF found the evidence on the use of ENDS as a smoking cessation tool in adults, including pregnant women, and adolescents to be insufficient."

Source: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1

1

Background

2

Patterns of Use: Adults

3

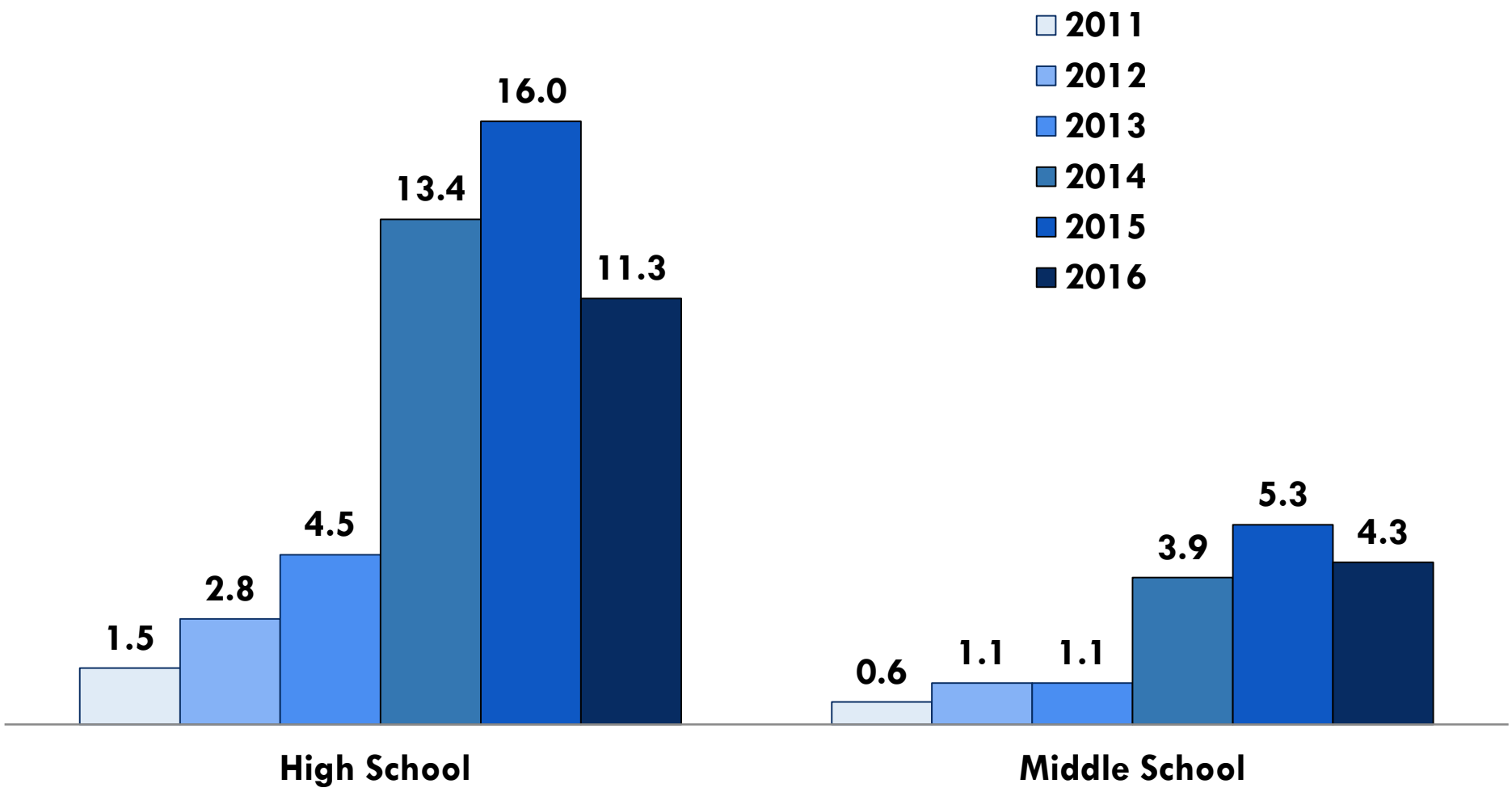
Patterns of Use: Youth

Surgeon General Report

E-cigarette Use Among Youth and Young Adults

December 8, 2016
Washington, D.C.

Current (past 30 day) use of e-cigarettes among U.S. middle and high school students, 2011-2016



Source: Centers for Disease Control and Prevention & U.S. Food and Drug Administration. National Youth Tobacco Survey.

Among youth, e-cigarette use may lead to conventional cigarette use

- Never smoking high school students who reported **ever using e-cigarettes** at baseline:
  - Were **2.7 times more likely** to report initiation of combustible tobacco use after 1 year compared with **never users of e-cigarettes**

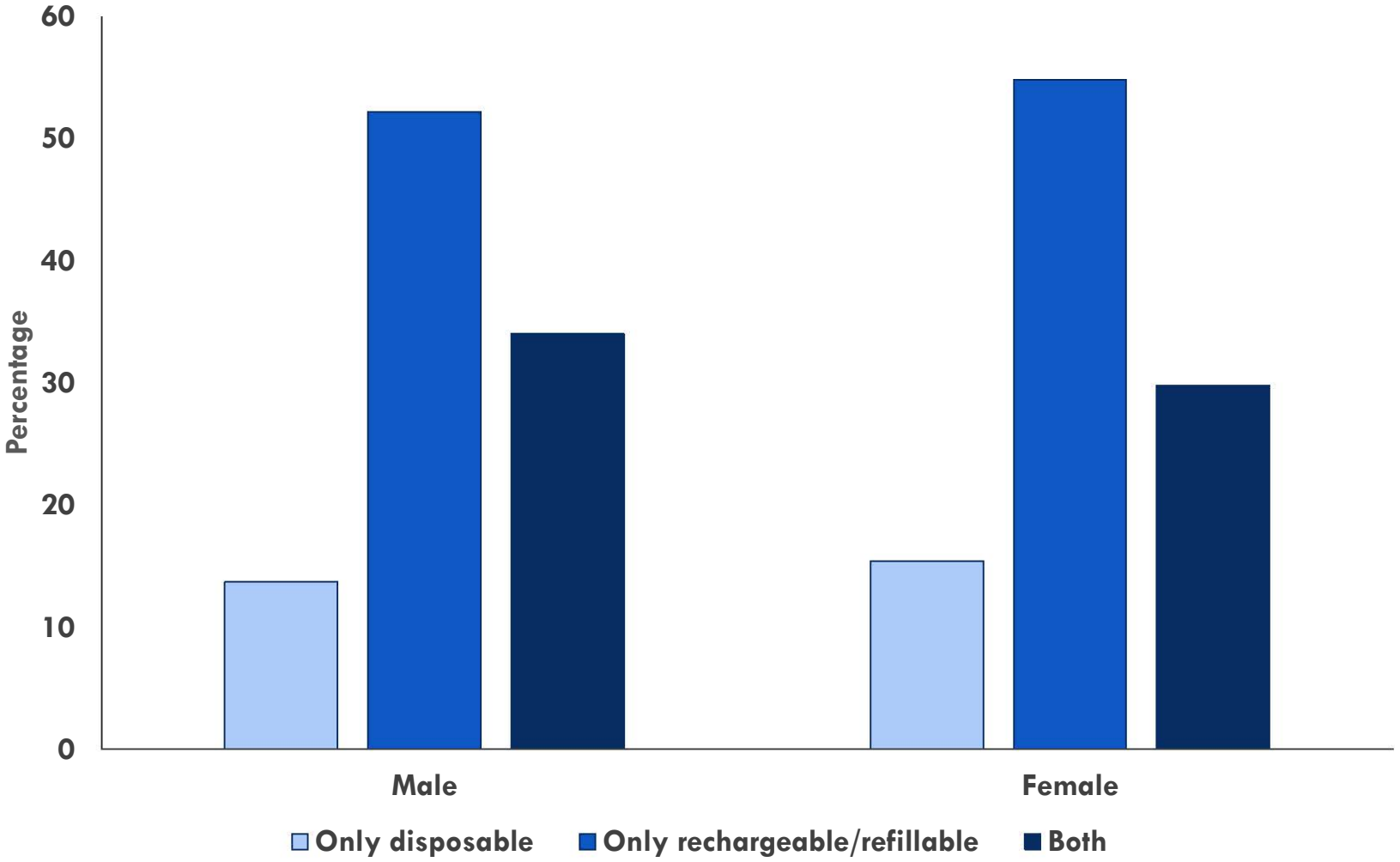
JAMA study

- Never smoking U.S. adolescent and young adult **e-cigarette users** at baseline:
  - Were **8.3 times more likely** to progress to cigarette smoking after 1 year than **non-users of e-cigarettes**

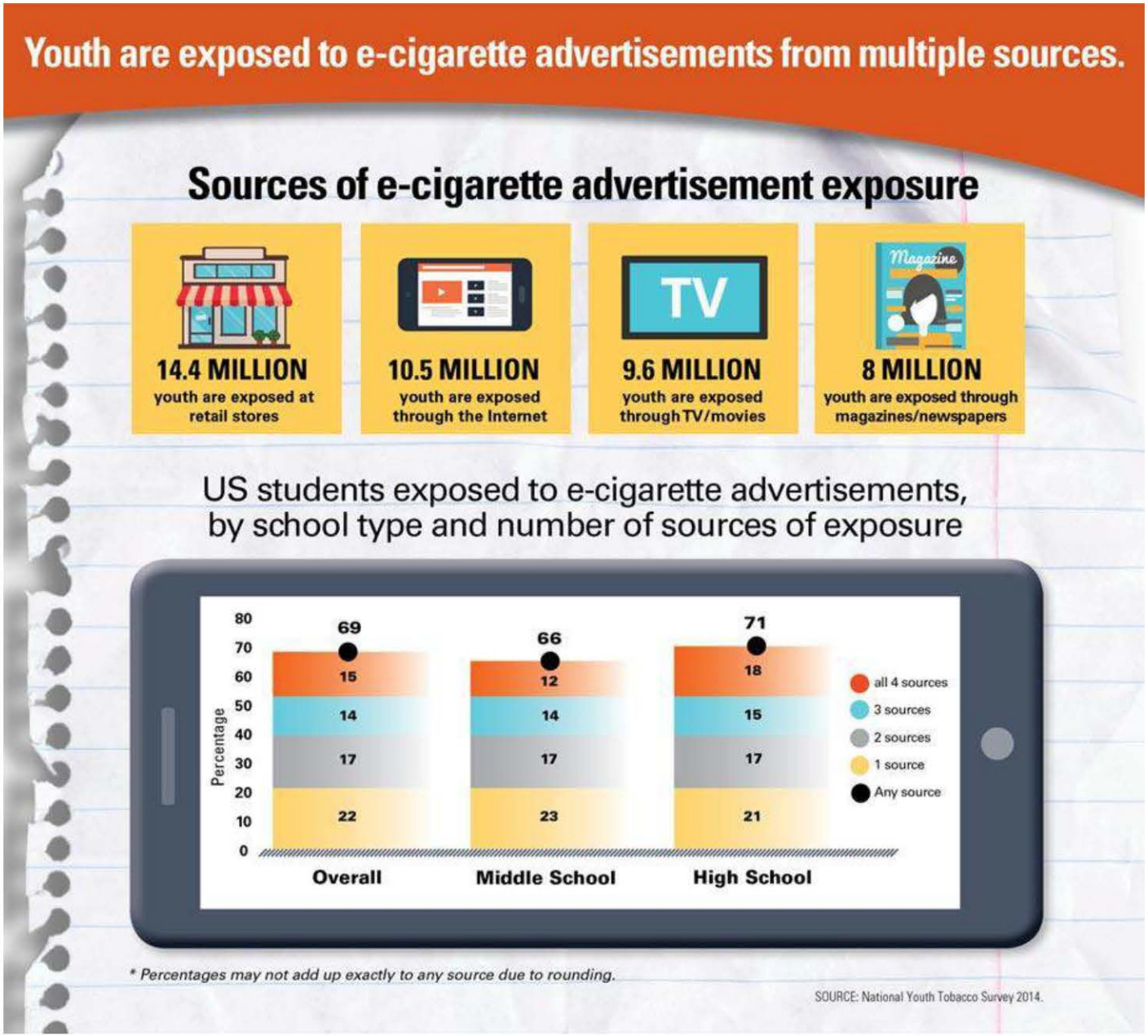
JAMA Pediatrics study

Sources: Leventhal, Adam, Strong, David, et al, Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence, JAMA, 2015.
Primack, Brian, Soneji, Samir, et al, Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults, JAMA, 2015

Percentages of middle and high school students who reported ever using an e-cigarette, by type and sex

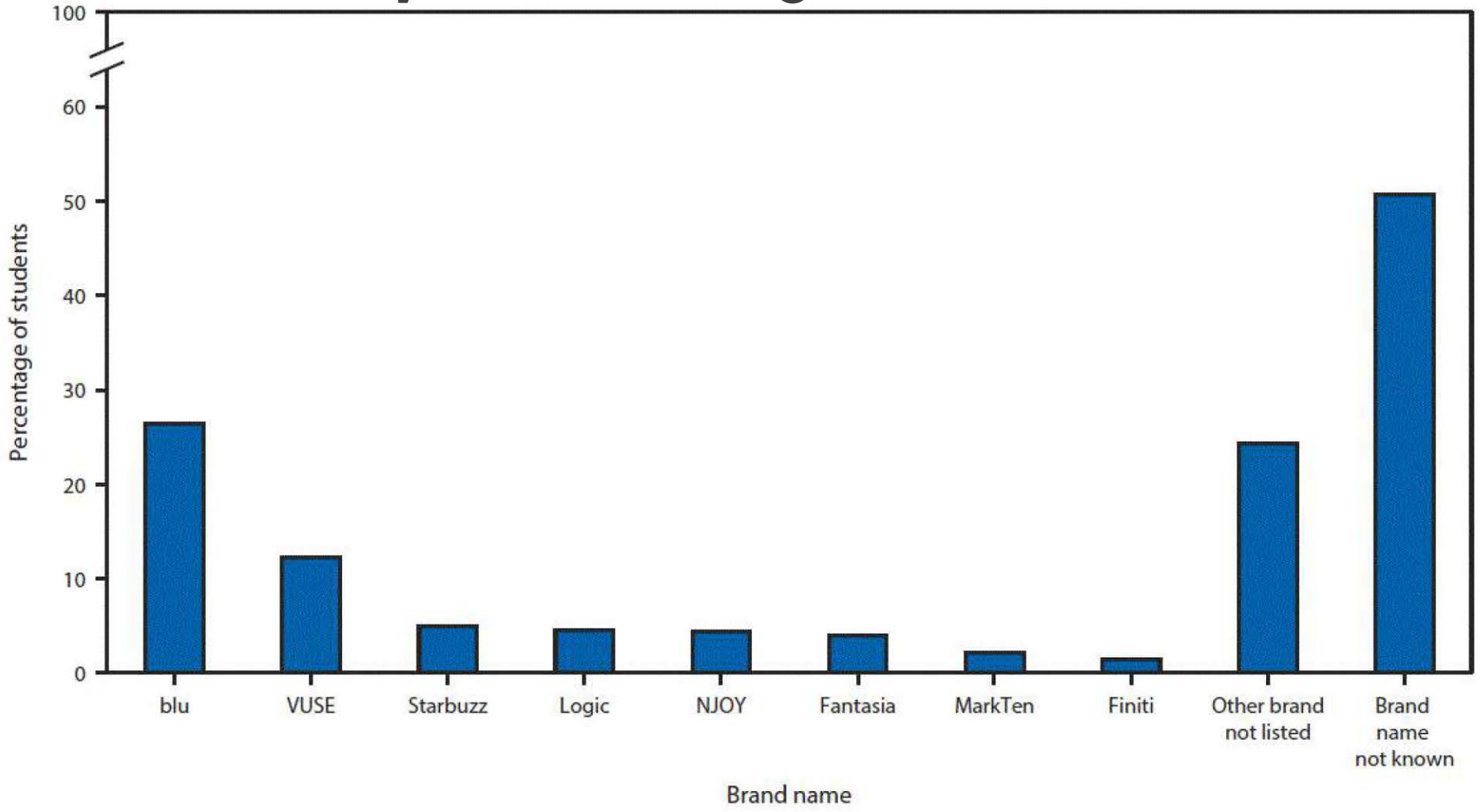


Source: Singh T, Kennedy S, Marynak K, Persoskie A, Melstrom P, King BA. Characteristics of Electronic Cigarette Use Among Middle and High School Students — United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1425–1429. DOI: http://dx.doi.org/10.15585/mmwr.mm655051a2



Source: Singh et al. Vital Signs: Exposure to Electronic Cigarette Advertising Among Middle School and High School Students — United States, 2014. MMWR. 2016.

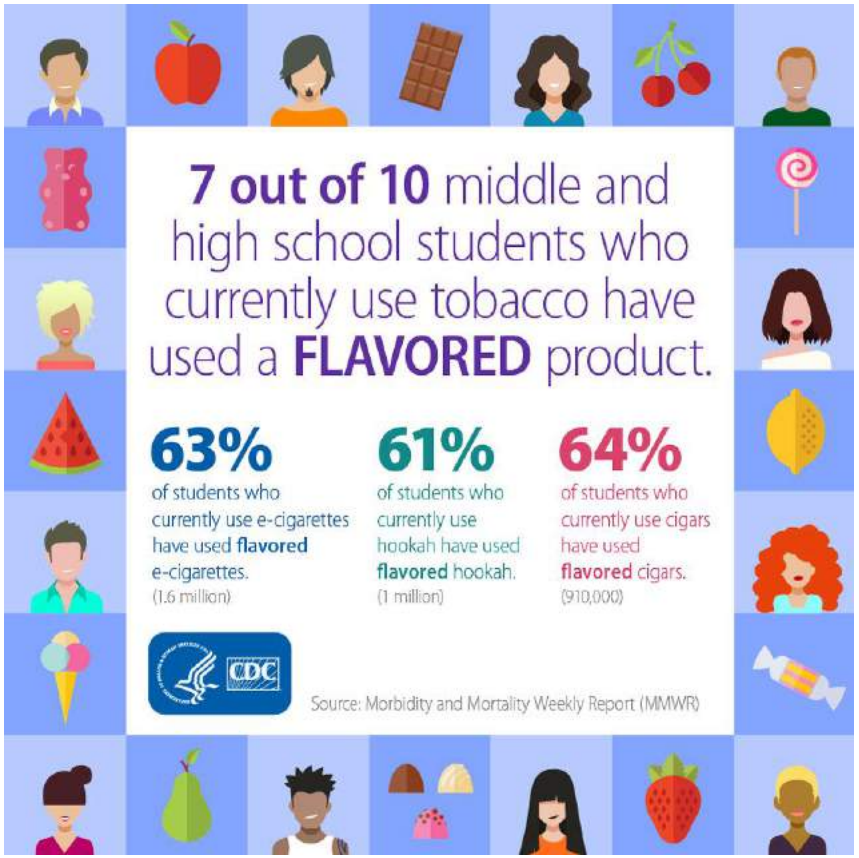
Percentages of middle and high school students who reported ever using e-cigarettes, by brand of e-cigarette used*



* Categories are not mutually exclusive.

Source: Singh T, Kennedy S, Marynak K, Persoskie A, Melstrom P, King BA. Characteristics of Electronic Cigarette Use Among Middle and High School Students — United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1425–1429. DOI: http://dx.doi.org/10.15585/mmwr.mm655051a2

A majority of current youth e-cigarette users report using flavored e-cigarettes



In 2014, among U.S. middle and high school students who used an e-cigarette in the past 30 days,

63.3% (1.58 million)

had used a

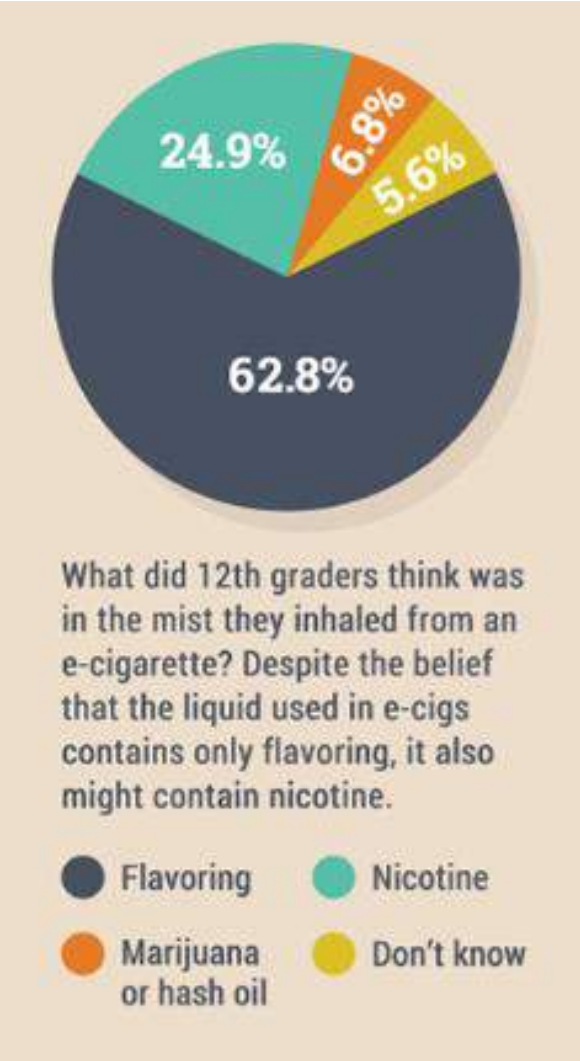
flavored e-cigarette.

Source: Corey et al. Flavored Tobacco Product Use Among Middle and High School Students—United States, 2014. MMWR October 2, 2015 / 64(38);1066-1070

Are youth using e-cigarettes for nicotine?

Self-reported nicotine consumption among youth may be subject to bias:

- Youth may not know what nicotine is, let alone whether it is in their e-cigarette.
- Youth who access e-cigarettes from peers may not see packaging.
- Some e-cigarette labels obscure nicotine content.
- Question asked respondents to choose only one response option.



Source for infographic: https://www.drugabuse.gov/related-topics/trends-statistics/infographics/monitoring-future-2016-survey-results

Sales data tell another story…

Percentage of products that contained nicotine

- 99.6% of disposable e-cigarette sales
- 100% of rechargeable sales
- 99.5% of refill sales

Percentage that contained nicotine by product type

- 99.6% of all e-cigarette products sold
- 99.4% of flavored e-cigarette products
- 99.9% of non-flavored e-cigarette products

RESEARCH AND PRACTICE

Sales of Nicotine-Containing Electronic Cigarette Products: United States, 2015

Kristy L. Marynak, MPP, Doris G. Gammon, MS, Todd Rogers, PhD, Ellen M. Coats, MS, Tushar Singh, MD, PhD, and Brian A. King, PhD, MPH

Objectives. To assess the proportion of electronic cigarette (e-cigarette) products sold in the United States that contain nicotine according to retail scanner data.

Methods. We obtained unit sales data from January 11, 2015, to December 12, 2015, from The Nielsen Company for convenience stores; supermarkets; mass merchandisers; drug, club, and dollar stores; and Department of Defense commissaries. The data did not include purchases from tobacco specialty shops, "vape shops," or online sources. Nicotine content was assessed by product type (disposables, rechargeables, and refills), region, and flavor status based on nicotine strength listed in the Universal Product Codes. For the 36.7% of entries lacking nicotine content information, we conducted Internet searches by brand, product, and flavor.

Results. In 2015, 99.0% of e-cigarette products sold contained nicotine, including 99.8% of disposables, 99.7% of rechargeables, and 98.8% of refills. Overall, 98.7% of flavored e-cigarette products and 99.4% of nonflavored e-cigarette products contained nicotine.

Conclusions. In 2015, almost all e-cigarette products sold in US convenience stores and other assessed channels contained nicotine.

Public Health Implications. Findings reinforce the importance of warning labels for nicotine-containing products, ingredient reporting, and restrictions on sales to minors. (*Am J Public Health.* Published online ahead of print March 21, 2017: e1–e4. doi:10.2105/AJPH.2017.303660)

Electronic cigarettes (e-cigarettes) are devices capable of delivering aerosolized nicotine, flavorings, and other substances to the user. E-cigarettes were the most commonly used tobacco product among US youths in 2015 and are more commonly used among high school students and young adults aged 18 to 24 years than among adults older than 25 years.[1–4] Youth use of e-cigarettes is a public health concern because nicotine (e-liquid) flavors and nicotine concentrations, including zero nicotine.

Demand for nicotine-containing e-cigarette products relative to zero-nicotine products is currently unknown but of public health importance given the consequences of nicotine exposure for young people.[1,5] More than 80% of 266 e-cigarette brands analyzed in 2014 offered zero-nicotine varieties,[6] and studies of self-reported use of e-cigarettes self-reported information on nicotine content may be susceptible to bias, especially among youths. To address this gap, we used retail sales data from 2015 to assess unit sales of nicotine-containing e-cigarettes.

METHODS

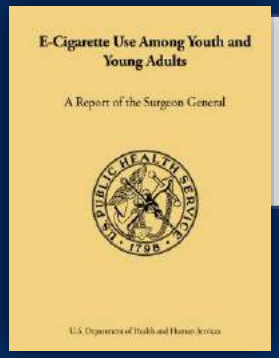
In 4-week aggregate periods from January 11, 2015, to December 12, 2015, we acquired nationally representative Universal Product Code (UPC) data on unit sales of e-cigarettes from The Nielsen Company (Nielsen) for convenience stores; supermarkets; mass merchandisers; club, drug, and dollar stores; and Department of Defense commissaries. Nielsen collects information when a product's UPC is scanned at checkout, which includes detailed characteristics of text on the product packaging, such as brand, subbrand, flavor, nicotine content (if any), type of device, and quantity per package.

We categorized e-cigarette products into 3 mutually exclusive types: (1) disposables, (2) starter kits or rechargeable devices ("rechargeables"), and (3) refills, including prefilled cartridges and cartomizers, and e-liquid bottles ("e-liquids"). The analysis excluded accessories that do not contain e-liquid.

Nicotine Content

Each product was classified into 3 mutually

Source: Marynak, K.L.; Gammon, D.G.; Rogers, T.; Coats, E.M.; Singh, T.; King, B.A., "Sales of nicotine-containing electronic cigarette products: United States, 2015," American Journal of Public Health 107(5): 702-705, May 2017.



Major Conclusion

#7

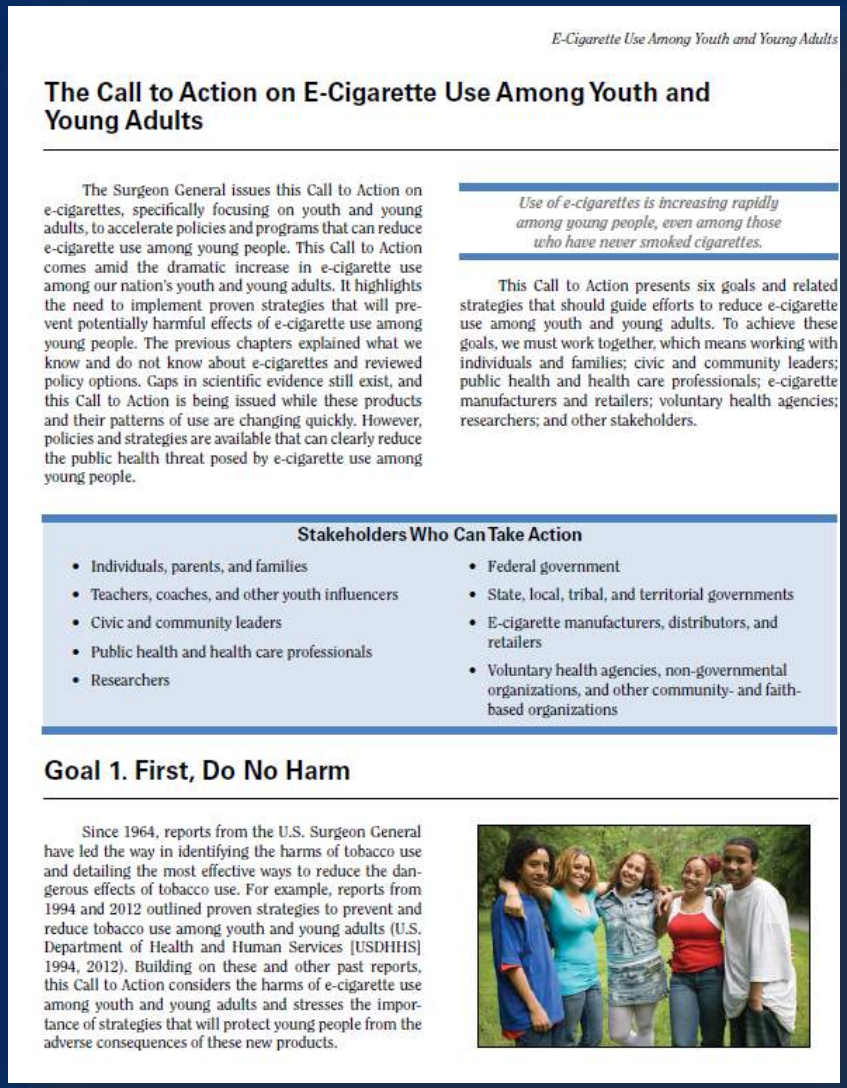
"Action can be taken at the national, state, local, tribal, and territorial levels to address e-cigarette use among youth and young adults. Actions could include incorporating e-cigarettes into smoke-free policies, preventing access to e-cigarettes by youth, price and tax policies, retail licensure, regulation of e-cigarette marketing likely to attract youth, and educational initiatives targeting youth and young adults."

Source: U.S Department of Health and Human Services. *E-cigarette Use Among Youth and Young Adults.* Office of the Surgeon General, HHS, CDC Office on Smoking and Health. 2016.

Call to Action

The Surgeon General issues this Call to Action on e-cigarettes, specifically focusing on youth and young adults, to accelerate policies and programs that can reduce e-cigarette use among young people.

It highlights the need to implement proven strategies that will prevent potentially harmful effects of e-cigarette use among young people.



E-Cigarette Use Among Youth and Young Adults

The Call to Action on E-Cigarette Use Among Youth and Young Adults

The Surgeon General issues this Call to Action on e-cigarettes, specifically focusing on youth and young adults, to accelerate policies and programs that can reduce e-cigarette use among young people. This Call to Action comes amid the dramatic increase in e-cigarette use among our nation's youth and young adults. It highlights the need to implement proven strategies that will prevent potentially harmful effects of e-cigarette use among young people. The previous chapters explained what we know and do not know about e-cigarettes and reviewed policy options. Gaps in scientific evidence still exist, and this Call to Action is being issued while these products and their patterns of use are changing quickly. However, policies and strategies are available that can clearly reduce the public health threat posed by e-cigarette use among young people.

Use of e-cigarettes is increasing rapidly among young people, even among those who have never smoked cigarettes.

This Call to Action presents six goals and related strategies that should guide efforts to reduce e-cigarette use among youth and young adults. To achieve these goals, we must work together, which means working with individuals and families; civic and community leaders; public health and health care professionals; e-cigarette manufacturers and retailers; voluntary health agencies; researchers; and other stakeholders.

Stakeholders Who Can Take Action

- Individuals, parents, and families
- Teachers, coaches, and other youth influencers
- Civic and community leaders
- Public health and health care professionals
- Researchers
- Federal government
- State, local, tribal, and territorial governments
- E-cigarette manufacturers, distributors, and retailers
- Voluntary health agencies, non-governmental organizations, and other community- and faith-based organizations

Goal 1. First, Do No Harm

Since 1964, reports from the U.S. Surgeon General have led the way in identifying the harms of tobacco use and detailing the most effective ways to reduce the dangerous effects of tobacco use. For example, reports from 1994 and 2012 outlined proven strategies to prevent and reduce tobacco use among youth and young adults (U.S. Department of Health and Human Services [USDHHS] 1994, 2012). Building on these and other past reports, this Call to Action considers the harms of e-cigarette use among youth and young adults and stresses the importance of strategies that will protect young people from the adverse consequences of these new products.

Source: U.S Department of Health and Human Services. *E-cigarette Use Among Youth and Young Adults.* Office of the Surgeon General, HHS, CDC Office on Smoking and Health. 2016.

Takeaways

1. E-cigarettes are now the most commonly used tobacco product among U.S. youth.
2. There is a growing body of science showing that e-cigarette use may lead to future cigarette smoking among youth.
3. Adult e-cigarette use increased from 2011 to 2014, primarily among current and former smokers, before plateauing since 2015.
4. Science on the efficacy of e-cigarettes for long-term cessation from conventional cigarettes is inconclusive.
5. The tobacco product landscape continues to diversify. It's critical to modernize tobacco control interventions and surveillance efforts to adapt to these changes.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells

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Significance

E-cigarette smoke (ECS) delivers nicotine through aerosols without burning tobacco. ECS is promoted as noncarcinogenic. We found that ECS induces DNA damage in mouse lung, bladder, and heart and reduces DNA-repair functions and proteins in lung. Nicotine and its nitrosation product 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone can cause the same effects as ECS and enhance mutations and tumorigenic cell transformation in cultured human lung and bladder cells. These results indicate that nicotine nitrosation occurs in the lung, bladder, and heart, and that its products are further metabolized into DNA damaging agents. We propose that ECS, through damaging DNA and inhibiting DNA repair, might contribute to human lung and bladder cancer as well as to heart disease, although further studies are required to substantiate this proposal.

Abstract

E-cigarette smoke delivers stimulant nicotine as aerosol without tobacco or the burning process. It contains neither carcinogenic incomplete combustion byproducts nor tobacco nitrosamines, the nicotine nitrosation products. E-cigarettes are promoted as safe and have gained significant popularity. In this study, instead of detecting nitrosamines, we directly measured DNA damage induced by nitrosamines in different organs of E-cigarette smoke-exposed mice. We found mutagenic O^6-methyldeoxyguanosines and γ-hydroxy-1,N^2-propano-deoxyguanosines in the lung, bladder, and heart. DNA-repair activity and repair proteins XPC and OGG1/2 are significantly reduced in the lung. We found that nicotine and its metabolite, nicotine-derived nitrosamine ketone, can induce the same effects and enhance mutational susceptibility and tumorigenic transformation of cultured human bronchial epithelial and urothelial cells. These results indicate that nicotine nitrosation occurs in vivo in mice and that E-cigarette smoke is carcinogenic to the murine lung and bladder and harmful to the murine heart. It is therefore possible that E-cigarette smoke may contribute to lung and bladder cancer, as well as heart disease, in humans.

E-cigarettes (E-cigs) are designed to deliver the stimulant nicotine, similar to conventional cigarettes, through an aerosol state. In E-cigs, nicotine is dissolved in relatively harmless organic solvents, such as glycerol and propylene glycol, then aerosolized with the solvents by controlled electric heating. Hence, E-cig smoke (ECS) contains mostly nicotine and the gas phase of the solvents (1⇓⇓–4). In contrast, conventional tobacco smoke (TS), in addition to nicotine and its nitrosamine derivatives, contains numerous (>7,000) incomplete combustion byproducts, such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines, aldehydes, and benzene, many of which are human carcinogens, irritants, and allergens (5, 6). TS also has a strong scent. Therefore, TS is both harmful and carcinogenic

to smokers, as well as being unpleasant and harmful to bystanders (7). Because of these effects, TS has become an unwelcome social habit and is no longer acceptable in many social settings and public domains (8). E-cigs have been promoted as an alternative to cigarettes that can deliver a TS "high" without TS's ill and unpleasant effects. Since it appears that ECS contains neither carcinogens, allergens, nor odors that result from incomplete combustion, as a result of these claims, E-cigs have become increasingly popular, particularly with young people (9). However, the question as to whether ECS is as harmful as TS, particularly with regard to carcinogenicity, remains a serious public health issue that deserves careful examination.

It is well established that most chemical carcinogens, either directly or via metabolic activation, can induce damage in genomic DNA, that unrepaired DNA damage can induce mutations, and that multiple mutations can lead to cancer (10). Many chemical carcinogens can also impair DNA-repair activity (11⇓–13). Therefore, in this study, as a step to understanding the carcinogenicity of ECS, we determined whether ECS can induce DNA damage in different organs of a mouse model and whether ECS can affect DNA-repair activity. We then characterized the chemical nature of ECS-induced DNA damage and how ECS affects DNA repair. Last, we determined the effect of ECS metabolites on the susceptibility to mutations and tumorigenic transformation of cultured human cells.

Results

ECS Induces O^6-Methyl-Deoxuguanosine in the Lung, Bladder, and Heart.

Nicotine is the major component of ECS (3). The majority (80%) of inhaled nicotine in smoke is quickly metabolized into cotinine, which is excreted into the bloodstream and subsequently into urine (14). Cotinine is generally believed to be nontoxic and noncarcinogenic (15); however, a small portion (<10%) of inhaled nicotine is believed to be metabolized into nitrosamines in vivo (16⇓–18). Nitrosamines induce tumors in different organs in animal models (6, 19). Inhaled nitrosamines are metabolized into *N*-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK). It has been proposed that NNK can be further metabolized and spontaneously degraded into methyldiazohydroxide (MDOH), pyridyl-butyl derivatives (PBDs), and formaldehyde, and that NNN degrade into hydroxyl or keto PBDs (20). While nicotine cannot bind to DNA directly, MDOH can methylate deoxyguanosines and thymidines in DNA (21). Although the fate of nitrosamine-induced formaldehyde and PBDs in vivo is less clear, both are capable of inducing DNA damage in vitro (22⇓⇓–25). Therefore, if ECS in fact is a carcinogen, it is likely that its carcinogenicity is derived from nitrosamines that are derived from the nitrosation of nicotine (5, 19, 21). Nitrosamines are potent carcinogens and it is generally believed that their carcinogenicity is via induction of methylation DNA damage (26, 27). As a step in examining the carcinogenicity of ECS, we determined whether ECS can induce O^6-methyl-deoxuguanosine (O^6-medG) adducts in lung, heart, liver, and bladder tissues of mice. Mice were exposed to ECS (10 mg/mL, 3 h/d, 5 d/wk) for 12 wk; the dose and duration equivalent in human terms to light E-cig smoking for 10 y. The results in Fig. 1 *A* and *B*, Fig. S1, and Table S1 show that ECS induced significant amounts of O^6-medG adducts in the lung, bladder, and heart and that the level of O^6-medG adducts in lung was three- to eightfold higher than in the bladder and heart. These results are consistent with

the explanation that nicotine is metabolized into MDOH, which can methylate DNA (16, 20).

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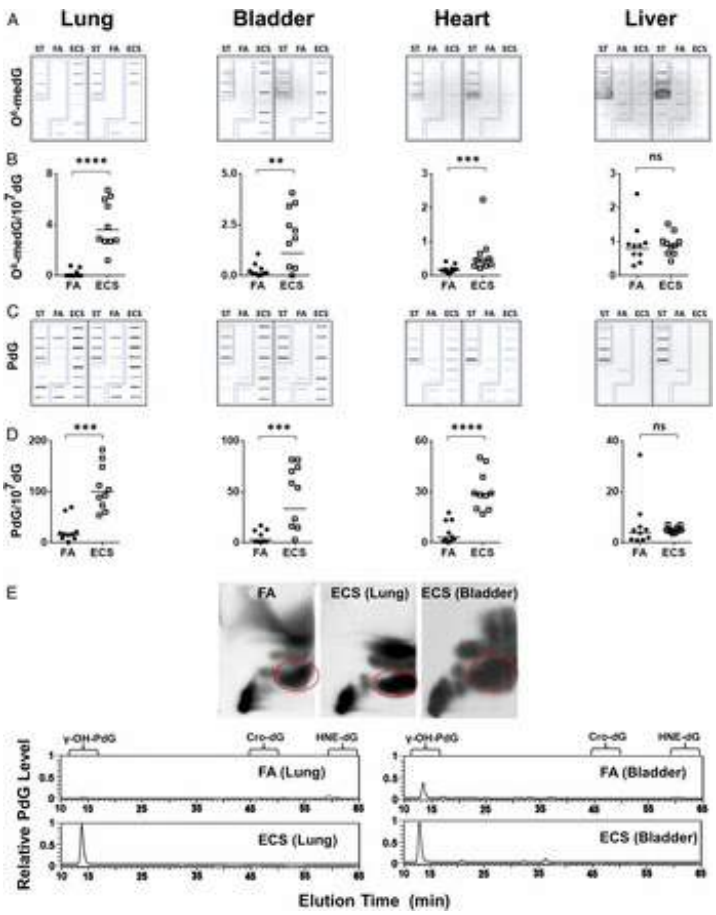

Fig. 1.
ECS induces γ-OH-PdG and O^6-medG adducts in the lung, bladder and heart. Genomic DNA were isolated from different organs of mice exposed to FA or ECS as described in text. (*A*–*D*) O^6-medG and PdG formed in the genomic DNA were detected by immunochemical methods (28). (*A* and *C*) Slot blot. (*B* and *D*) Quantification results. The bar represents the mean value. (*E*) Identification of γ-OH-PdG adducts formed in the genomic DNA of lung and bladder by the 2D-TLC (*Upper*) and then HPLC (*Lower*) (28). ST, PdG, or O^6-medG standard DNA. ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$.

ECS Induces γ-OH-PdG in the Lung, Bladder, and Heart.

Recently, we found that aldehyde-derived cyclic 1,N^2-propano-dG (PdG), including γ-OH-1,N^2-PdG (γ-OH-PdG) and α-methyl-γ-OH-1,N^2-PdG adducts, are the major DNA adducts in mouse models (28) induced by TS, which contains abundant nitrosamines and aldehydes (20). We therefore determined the extent of PdG formation in different organs of ECS-exposed mice using a PdG-specific antibody (28⇓–30).

The results in Fig. 1 *C* and *D* show that ECS induced PdG adducts in the lung, bladder, and heart, and that the level of PdG in the lung is two- to threefold higher than in the bladder and heart. Moreover, the level of PdG is 25- to 60-fold higher than the level of O^6-medG in lung, bladder, and heart tissues, indicating that induction of PdG is more efficient than induction of O^6-medG by nicotine metabolic products and/or that O^6-medG is more efficiently repaired in these organs. ECS, however, did not induce either O^6-medG or PdG in liver DNA.

Due to the relatively minute amount of genomic DNA that is possible to isolate from mouse organs, in this case, specifically from bladder mucosa, which is only able to yield up to 2 μg of genomic DNA from each mouse, we used the sensitive ^{32}P-postlabeling thin layer chromatography (TLC)/HPLC method to identify the species of the PdG formed in lung and

bladder tissues (13, 28, 31). The results in Fig. 1*E* show that the majority of PdG (>95%) formed in these tissues coelute with γ-OH-PdG adduct standards with a minor portion that coelute with α-OH-PdG standards.

Relationship of ECS-Induced PdG and O^6-medG Formation in Different Organs of Each Animal.

We then determined the relationship of PdG and O^6-medG formation in different organs of each animal. The results in Fig. 2*A* show that the levels of PdG and O^6-medG in the same organs are positively related to each other. Thus, a lung tissue sample that had a high level of PdG also had a high level of O^6-medG. The same relationship between PdG and O^6-medG formation was found in the bladder and heart (Fig. 2*A* and Table S1). The results in Fig. 2*B* show that in the same mouse, the levels of PdG and O^6-medG formation in different organs also have a positive correlation: Mice with a high level of PdG and O^6-medG formation in the lung also had a high level of these DNA adducts in the bladder and heart (Fig. 2*B* and Table S1). Together, these results indicate that the formation of PdG and O^6-medG DNA adducts in the lung, bladder, and heart tissue are the result of DNA damaging agents derived from ECS exposure, and raising the possibility that the ability for nicotine absorption and metabolism and DNA-repair activity of different organs determine their susceptibility to ECS-induced DNA adduct formation.

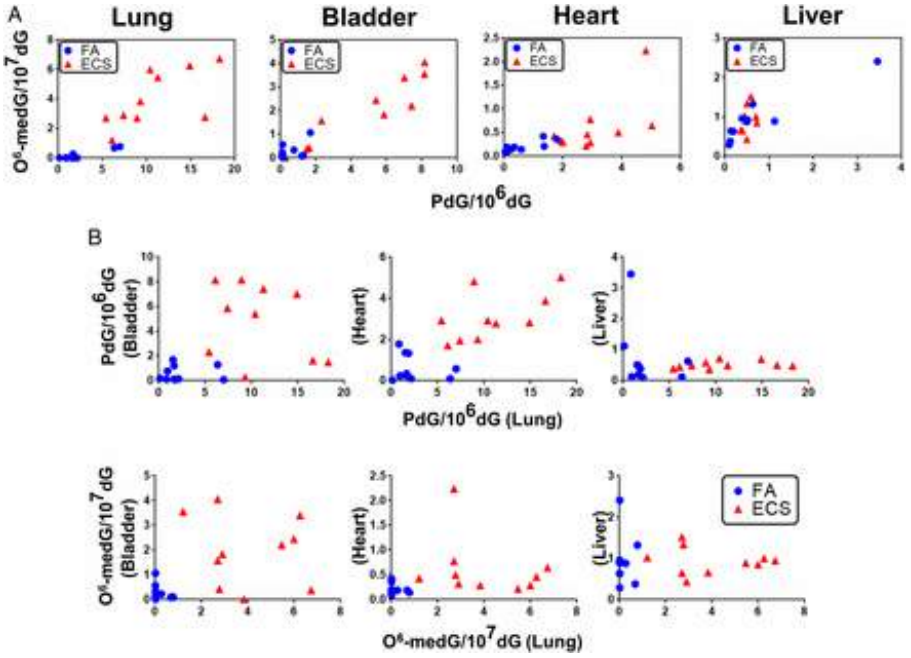

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Fig. 2.
Relationship of ECS-induced PdG versus O^6-medG formation in different organs of mice. The levels of PdG and O^6-medG detected in different organs from mice exposed to FA and ECS were determined in Fig. 1. In *A*, O^6-medG formation is plotted against PdG formation in each organ in mice exposed to ECS (red triangles) and FA (blue dots). In *B*, formation of PdG and O^6-medG in the bladder, heart, and liver is plotted against PdG and O^6-medG formation, respectively, in the lung of mice exposed to ECS and FA. Each symbol represents each individual mouse.

ECS Reduces DNA-Repair Activity in the Lung.

Recently, we have found that lung tissues of mice exposed to TS have lower DNA-repair activity and lower levels of DNA-repair proteins XPC and OGG1/2 and that aldehydes, such as acrolein, acetaldehyde, crotonaldehyde, and 4-hydroxy-2-nonenal, can modify DNA-repair proteins, causing the degradation of these repair proteins and impairing DNA-repair function (11, 12, 28). These findings raise the possibility that, via induction of aldehydes, ECS can impair DNA-repair functions. To test this possibility, we determined the effect of ECS on the activity of the two major DNA-repair mechanisms in mouse lung tissues: nucleotide excision repair (NER) and base excision repair (BER) (32). We adopted a well-established in vitro DNA damage-dependent repair synthesis assay, which requires only 10 μg of freshly prepared cell lysates (11, 13, 28). Since the amount of bladder mucosa collected from individual mice was minute, we were only able to determine DNA-repair activity in lung tissues (28). We used UV-irradiated DNA, which contains cyclobutane pyrimidine dimers as well as <6-4> photoproducts; Acr-modified DNA, which contains γ-OH-PdG; and H_2O_2-modified DNA, which contains 8-oxo-dG, as substrates (13, 28). It is well established that NER is the major mechanism that repairs cyclobutane pyrimidine dimers, <6-4> photoproducts, and γ-OH-PdG, and that BER is the major mechanism that repairs 8-oxo-dG (32, 33). Therefore, these two types of substrates allow us to determine the NER and BER activity in the cell lysates (11, 13). The results in Fig. 3 *A* and *B* and Fig. S2 show that both NER and BER activity in lung tissue of ECS-exposed mice are significantly lower than in lung tissue of filtered air (FA)-exposed mice.

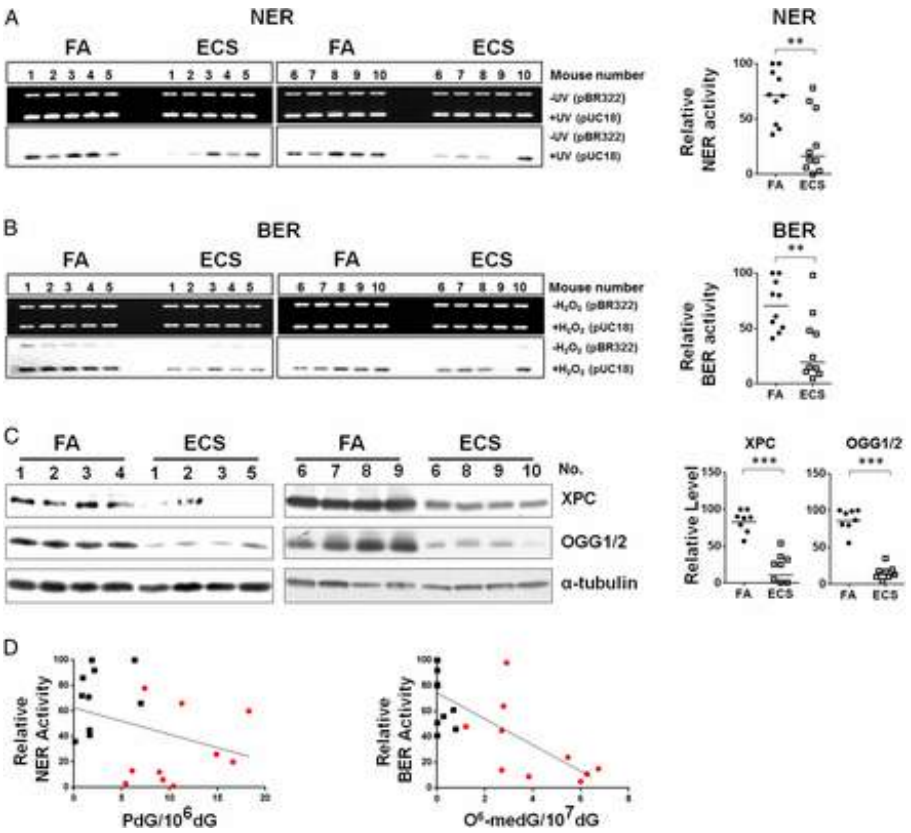

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Fig. 3.
ECS reduces DNA-repair activity and XPC and OGG1/2 in the lung. Cell lysates were isolated from lung tissues of mice exposed to FA (*n* = 10) or to ECS (*n* = 10) the same as in Fig. 1. The NER and the BER activity in the cell lysates were determined by the in vitro DNA damage-dependent repair synthesis assay as described (13, 28). (*A* and *B*) Ethidium bromide-stained gels (*Upper*) and autoradiograms (*Lower*) are shown in *Left*. In *Right*, the radioactive counts in the autoradiograms were normalized to input DNA. The relative repair activity was calculated using the highest band as 100%. (*C*) Detection of XPC and OGG1/2 protein in lung tissues (*n* = 8) by Western blot (*Left*). *Right* graphs are quantifications of ECS effect on the abundance of XPC and OGG1/2. The bar represents the mean value. (*D*) The relationship between the level of PdG and O^6-medG adduct and the NER and BER activity in lung tissues of FA- (black square) and ECS (red dot)-exposed mice.

ECS Causes a Reduction of Repair Protein XPC and OGG1/2.

We then determined the level of XPC and OGG1/2, the two crucial proteins, respectively, for NER and BER (34, 35). The results in Fig. 3*C* show that the level of XPC and OGG1/2 in lung tissues of ECS-exposed mice was significantly lower than in control mice. We further determined the relationship between DNA adduct formation and DNA-repair activity in lung tissues of FA- and ECS-exposed mice. Since NER is the major repair mechanism for bulky DNA damage such as γ-OH-PdG and photodimers (11, 33) and BER is a major repair mechanism for base damage (32), we compared BER activity with the level of O^6-medG adducts and NER activity with the level of γ-OH-PdG adducts. The results in Fig. 3*D* show that NER and BER activity in lung tissue of different mice is inversely related to the level of γ-OH-PdG and O^6-medG adducts, respectively. These results indicate that in lung tissue, NER and BER activities are crucial factors in determining the level of ECS-induced γ-OH-PdG and O^6-medG DNA damage; mice that are more sensitive to ECS-induced DNA-repair inhibition accumulate more ECS-induced DNA damage in their lung and, perhaps, bladder and heart. It should be noted that in human cells, repair of O^6-medG adducts is mainly carried out by *O*^{6}-methylguanine DNA methyltransferase (MGMT) (36, 37). The positive relationship between BER activity and the O^6-medG level in lung tissues of mice implies that ECS impairs BER enzymes as well as MGMT, and/or O^6-medG is repaired by a BER mechanism in mice.

Nicotine Induces DNA Damage in Human Cells.

Many tobacco-specific nitrosamines that result from the nitrosation of nicotine, such as NNN and NNK, are potent carcinogens and can induce cancer in different organs, including the lung (20, 21, 27). While NNK and NNN cannot covalently bind with DNA directly, it has been proposed that one of NNK's metabolic products, MDOH, can interact with DNA to induce mutagenic O^6-medG adducts (20, 21, 27). These results raise the possibility that ECS-induced O^6-medG is due to the nitrosation of nicotine, and that NNK resulting from nicotine nitrosation then further transforms into MDOH in lung and bladder tissue (20). To test this possibility, we determined the DNA adducts induced by nicotine and NNK in cultured human bronchial epithelial and urothelial cells, and the effect of nicotine and NNK treatments on DNA repair, using the same methods indicated in Fig. 1. The results in Fig. 4 show that both nicotine and NNK can induce the same type of γ-OH-PdG adducts, and O^6-

medG adducts. Since it is well established that many aldehydes can induce cyclic PdG in cells (38⇓–40), these results suggest that aldehydes as well as MDOH are NNK metabolites, which induce γ-OH-PdG and O^6-medG.

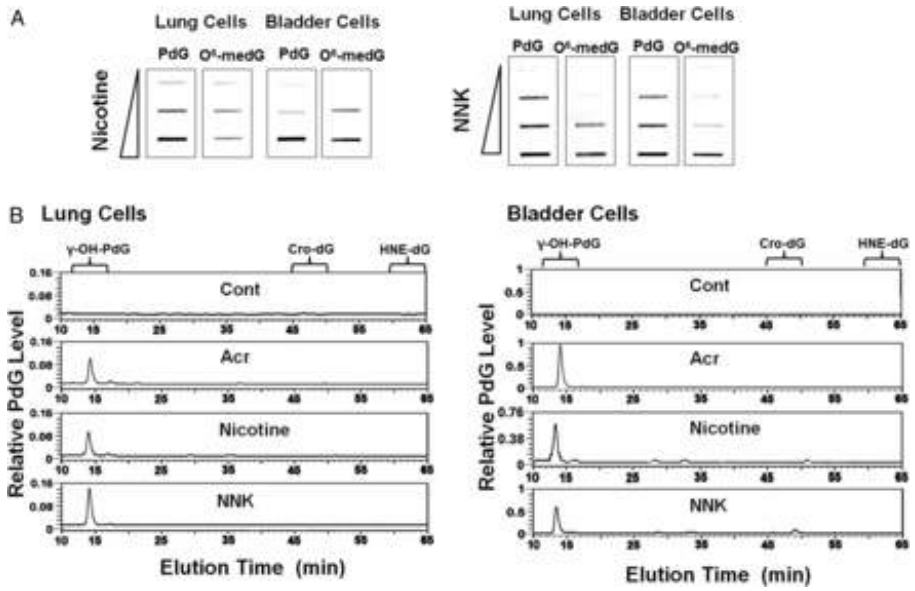

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Fig. 4.
Nicotine and NNK induce γ-OH-PdG and O^6-medG in cultured human lung and bladder epithelial cells. Human lung epithelial (BEAS-2B) cells and urothelial (UROtsa) cells were treated with different concentrations of nicotine and NNK as described in text. O^6-medG and PdG formed in the genomic DNA were determined as described in Fig. 1. (*A*) The DNA adducts were detected by immunochemical methods (13, 28). (*B*) The PdG adducts formed in the genomic DNA were further identified as γ-OH-PdG adducts by the ^{32}P postlabeling followed by 2D-TLC/HPLC method (13, 28).

Nicotine Reduces DNA Repair in Human Cells.

We next determined the effects of nicotine and NNK treatment on DNA-repair activity and repair protein levels in human lung and bladder epithelial cells using the method described in Fig. 3. The results in Fig. 5 show that nicotine and NNK treatments not only inhibit NER and BER activities, they also reduce the protein levels of XPC and hOGG1/2. We found that these reductions of XPC and hOGG1/2 induced by nicotine and NNK can be prevented or attenuated by the proteasome and autophagosome inhibitors MG132, 3-methyladenine (3-MA), and lactacystin (Fig. S3) (13, 41⇓–43). These results indicate that metabolites of nicotine and NNK can modify DNA-repair proteins and cause proteosomal and autophagosomal degradation of these proteins and that ECS's effect on the inhibition of DNA-repair activity is via modifications and degradation of DNA-repair proteins by its metabolites.

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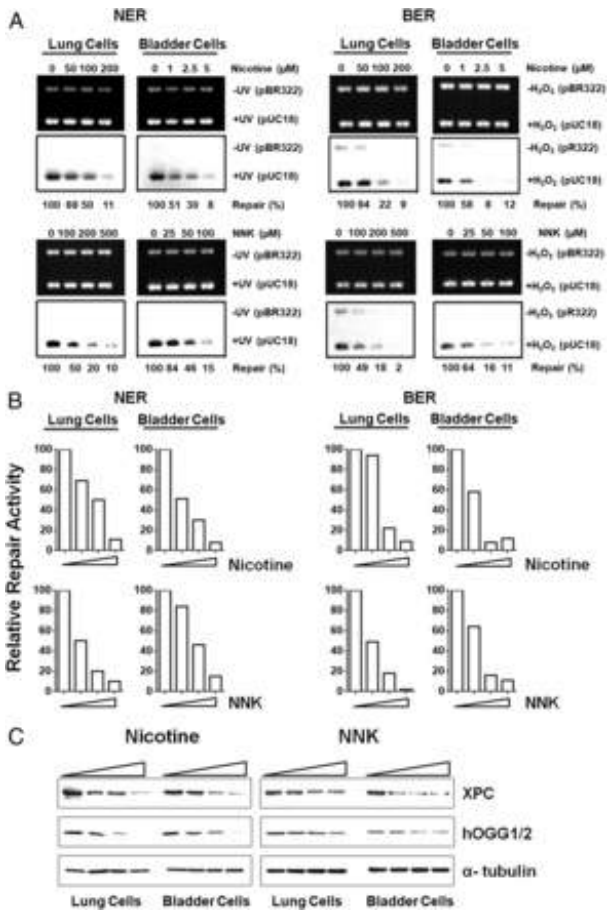

Fig. 5.
Nicotine and NNK reduce DNA-repair activity and the level of repair proteins XPC and hOGG1/2 in cultured human lung and bladder epithelial cells. Cell-free cell lysates were isolated from human lung (BEAS-2B) and bladder epithelial (UROtsa) cells treated with different concentrations of nicotine and NNK 1 h at 37 °C. The NER and the BER activity in the cell lysates were determined by the in vitro DNA damage-dependent repair synthesis assay as described in Fig. 3. (*A*) Ethidium bromide-stained gels (*Upper*) and autoradiograms (*Lower*) are shown. (*B*) Quantifications results. The radioactive counts in the autoradiograms were normalized to input DNA. The relative repair activity was calculated using the control band as 100%. (*C*) The effect of nicotine and NNK treatment on abundance of XPC and hOGG1/2 in human lung and bladder urothelial cells were determined as described in Fig. 3.

Together, these results indicate that human bronchial epithelial and urothelial cells as well as lung, heart, and bladder tissues in the mouse are able to nitrosate nicotine and metabolize nitrosated nicotine into NNK and then MDOH and aldehydes. Furthermore, whereas MDOH induces O^6-medG adducts, aldehydes not only can induce γ-OH-PdG, they also can inhibit DNA repair and cause repair protein degradation.

Nicotine Enhances Mutations and Cell Transformation.

The aforementioned results demonstrate that ECS's major component nicotine, via its metabolites, MDOH, and aldehydes, not only can induce mutagenic DNA adducts, but that they also can inhibit DNA repair in human lung and bladder epithelial cells. These results raise the possibility that ECS and its metabolites can function not only as mutagens but also as comutagens to enhance DNA damage-induced mutagenesis. To test this possibility, we determined the effect of these agents on cell mutation susceptibility on UV- and H_2O_2-induced DNA damage using the well-established *supF* mutation system (13). The results in Fig. 6*A* show that nicotine and NNK treatment in both human lung and bladder epithelial cells enhances the spontaneous mutation frequency as well as UV- and H_2O_2-induced mutation frequency by two- to fourfold. These results indicate that nicotine and NNK treatment sensitize these human cells to the extent that they are more susceptible to mutagenesis. We further tested the effect of these agents on induction of tumorigenic transformation using the anchorage-independent soft-agar growth assay (44, 45). The

results in Fig. 6 *B* and *C* show that nicotine and NNK greatly induce soft-agar anchorage-independent growth of human lung and bladder cells, a necessary ability for tumorigenic cells (46⇓⇓–49).

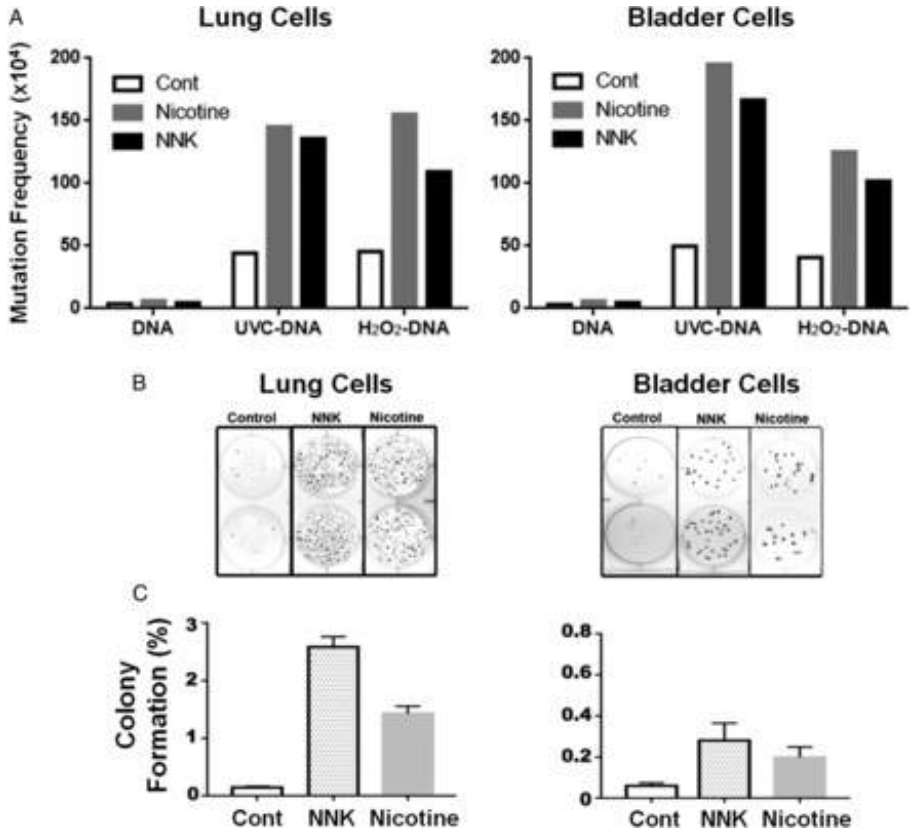

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Fig. 6.

Nicotine and NNK treatments enhance mutational susceptibility and cell transformation. Human lung and bladder epithelial cells (BEAS-2B and UROtsa) were treated with NNK (0.5 mM) and nicotine (25 mM for BEAS-2B cells, and 5 mM for UROtsa cells) for 1 h at 37 °C; these treatments render 50% cell killing. (*A*) UVC-irradiated (1,500 J/m^2) or H_2O_2 modified (100 mM, 1 h at 37 °C) plasmid DNAs containing the *supF* gene were transfected into these cells, and the mutations in control, and nicotine- and NNK- treated cells were detected and quantified as previously described (13, 28). (*B*) Detection of anchorage-independent soft-agar growth. A total of 5,000 treated cells were seeded in a soft-agar plate. The method for anchorage-independent soft-agar growth is the same as previously described (28). Typical soft-agar growth plates stained with crystal violet were shown. (*C*) Quantifications of percent of control, nicotine, and NNK-treated cells formed colonies in soft-agar plates.

Discussion

The major purpose of E-cig smoking as well as tobacco smoking is to deliver the stimulant nicotine via aerosols, which allow smokers to obtain instant gratification. Unlike TS, which contains nitrosamines and numerous carcinogenic chemicals resulted from burning, ECS contains nicotine and relatively harmless organic solvents. Therefore, E-cig has been

promoted as noncarcinogenic and a safer substitute for tobacco. In fact, recent studies show that E-cig smokers, similar to individuals on nicotine replacement therapy, have 97% less 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), an isoform form of NNK, a tobacco nitrosamine and lung carcinogen, in their body fluid than tobacco smokers (50). Based on these results, ECS has been recommended as a substitute for TS (50). However, E-cig smoking is gaining popularity rapidly particularly in young individuals and it is important to note that many of these E-cig smokers have taken up E-cig smoking habit are not necessary doing it for the purpose of quitting TS, rather, it is because they are assuming that E-cig smoking is safe. Currently, there are 18 million E-cig smokers in the United States and 16% of high school students smoke E-cig (51, 52). Understanding the carcinogenicity of ECS is an urgent public health issue. Since it takes decades for carcinogen exposure to induce cancer in humans, for decades to come there will be no meaningful epidemiological study to address the carcinogenicity of ECS. Therefore, animal models and cell culture models are the reasonable alternatives to address this question.

Nicotine has not been shown to be carcinogenic in animal models (7). However, during tobacco curing, substantial amounts of nicotine are transformed into tobacco-specific nitrosamines (TSA) via nitrosation, and many of these TSA, such as NNK and NNN, are carcinogenic in animal models (19, 53⇓–55). Because of these findings, the occurrence and the level of nitrosamines in blood fluid have been used as the gold standard for determination of the potential carcinogenicity of smoking (56). While the NNAL level in E-cig smokers is 97% lower than in tobacco smokers, nonetheless, it is significant higher than in nonsmokers (50). This finding indicates that nitrosation of nicotine occurs in the human body and that ECS is potentially carcinogenic.

It is well established that cytochrome p450 enzymes in human and animal cells can metabolize and transform NNK, NNAL, and NNN into different products, which can modify DNA as well as proteins (20, 57, 58). This finding raises the possibility that the level of these nitrosamines detected in the blood stream of E-cig smokers at any given time may grossly underestimate the level of nicotine nitrosation. We undertake the approach of detecting DNA damage induced by nicotine rather than detecting nitrosamine level to address the potential mutagenic and carcinogenic effect of ECS. It should be noted that in vivo DNA damage can remain in genomic DNA for many hours and even days (13, 59, 60). Therefore, this approach not only is direct but also more sensitive in determining the carcinogenicity of ECS.

The level of γ-OH-PdG adducts induced by E-cig smoke in mice and by nicotine and NNK in cultured human cells is 10-fold higher than O^6-medG (Fig. 1). We have shown that γ-OH-PdG adducts are as mutagenic as BPDE-dG and UV photoproducts and induce G to T and G to A mutations similar to the mutations in the p53 gene in tobacco smoker lung cancer patients (11). Together, these results suggest that γ-OH-PdG adducts are the major cause of nitrosamine lung carcinogenicity.

The current understanding of NNK and NNN metabolism indicates that NNK metabolites are further transformed into PBDs, formaldehyde, and MDOH (20, 21, 61), while NNN metabolites are hydroxyl and keto forms of PBD (20, 21, 61). While MDOH can induce O^6-medG adducts, it is unclear what metabolites induce γ-OH-PdG adducts. It is well established that acrolein–DNA interaction generates γ-OH-PdG adducts (11, 13, 30) and

that formaldehyde induces hydroxymethylated nucleotides, mainly dG, in animal models (62). It has been found that in vitro formaldehyde combined with acetaldehyde can induce γ-OH-PdG (63). Therefore, it possible that ECS, nicotine, and NNK induce γ-OH-PdG via their metabolite formaldehyde, which triggers lipid peroxidation and produces acrolein and acetaldehyde byproducts; consequently, these byproducts induce γ-OH-PdG.

In summary, we found that ECS induces mutagenic γ-OH-PdG and O^6-medG adducts in lung, bladder, and heart tissues of exposed mice. ECS also causes reduction of DNA-repair activity and repair proteins XPC and OGG1/2 in lung tissue. Furthermore, nicotine and NNK induce the same effects in human lung and bladder epithelial cells. We propose that nicotine can be nitrosated, metabolized, and further transformed into aldehydes and MDOH in lung, bladder, and heart tissues of humans and mice. Whereas MDOH induced O^6-medG, aldehydes not only induce γ-OH-PdG, but also inhibit DNA repair and reduce XPC and OGG1 proteins (Fig. S3). We also found that nicotine and NNK can enhance mutational susceptibility and induced tumorigenic transformation of human lung and bladder epithelial cells. Based on these results, we propose that ECS is carcinogenic and that E-cig smokers have a higher risk than nonsmokers to develop lung and bladder cancer and heart diseases.

Materials and Methods

Materials.

Acr-dG monoclonal antibodies and plasmid pSP189 were prepared, as described (13, 41). Acr-dG antibodies are specific for PdG adducts including Acr-, HNE-, and crotonaldehyde (Cro)-dG (29). Antibodies for XPC, hOGG1/2 (cross reacts with mouse OGG1/2), α-tubulin, and mouse/rabbit IgG; enzymes, T4 kinase, protease K, nuclease P, and RNase A; and chemicals, acrolein, nicotine, and NNK were commercially available. Immortalized human lung (BEAS-2B) and bladder epithelial (UROtsa) cells were obtained from American Type Culture Collection and J.R. Masters, University College London, London. All animal procedures were approved by the Institutional Animal Care and Use Committee, New York University School of Medicine.

ECS Generation and Mice Exposure.

Twenty FVBN (Jackson Laboratory, Charles River) male mice were randomized into two groups, 10 each. Mice were exposed to ECS (10 mg/mL), 3 h/d, 5 d/wk, for 12 wk. ECS was generated by an E-cig machine, as previously described (64). An automated three-port E-cigarette aerosol generator (e∼Aerosols) was used to produce E-cigarette aerosols from NJOY top fill tanks (NJOY, Inc.) filled with 1.6 mL of e-juice with 10 mg/mL nicotine in a propylene glycol/vegetable glycerin mixture (50/50 by volume; MtBakerVapor MESA). Each day the tanks were filled with fresh e-juice from a stock mixture, and the voltage was adjusted to produce a consistent wattage (∼1.96 A at 4.2 V) for each tank. The puff aerosols were generated with charcoal and high-efficiency particulate filtered air using a rotorless and brushless diaphragm pump and a puff regime consisting of 35-mL puff volumes of 4-s duration at 30-s intervals. Each puff was mixed with filtered air before entering the exposure chamber (1 m^3). Tanks were refilled with fresh e-juice at 1.5 h into

the exposure period during the pause between puffs. Mass concentrations of the exposure atmospheres were monitored in real time using a DataRam4 (Thermo Fisher Scientific) and also determined gravimetrically by collecting particles on Teflon filters (Teflo, 2 mm pore size; Pall) weighed before and after sample collection using an electrobalance (MT-5; Metler).

Cell Cultures and Treatments of Nicotine and NNK.

Exponentially growing BEAS-2B and UROtsa were treated with different concentrations of nicotine (BEAS-2B: 0, 100, 200 μM; UROtsa: 0, 1, 2.5 μM), and NNK (BEAS-2B: 0, 100, 300, 1,000 μM; UROtsa: 0, 50, 100, 200 μM) for determination of DNA adduct and DNA-repair activity. For XPC and hOGG1/2 detection, BEAS-2B were treated with nicotine (0, 50, 100, 200 μM), and NNK (0, 500, 750, 1,000 μM) and UROtsa were treated with nicotine (0, 1, 2.5, 5 μM) and NNK (0, 100, 200, 400 μM) for 1 h at 37 °C. Genomic DNA and cell lysate isolation from these cells was the same as described (28).

PdG and O^6-medG Adduct Detection.

Cyclic PdG and O^6-medG adducts formed in the genomic DNA were determined by the immunochemical slot blot hybridization method using Acr-dG and O^6-medG antibodies and quantum dot labeled second antibody, as described (13, 28). PdG adducts formed in cultured human cells, and mouse lung tissue were further analyzed by the ^{32}P postlabeling-2D-TLC/HPLC method, as previously described (28).

In Vitro DNA-Damage-Dependent Repair Synthesis Assay.

The DNA-repair activity was assessed by an in vitro DNA damage-dependent repair synthesis assay, as previously described (13).

DNA Repairs Proteins Detection.

The levels of XPC and OGG1/2 proteins in lung tissues of mice with and without ECS exposure, and in BEAS-2B and UROtsa cells treated with nicotine and NNK, were determined, as described (13).

Mutation Susceptibility Determination.

Shuttle vector pSP189 plasmids, which contain the tyrosine suppressor tRNA coding gene the *supF*, were UV (1,500 J/m^2) irradiated or modified with H_2O_2 (100 mM, 1 h at 37 °C), then transfected into cells with and without pretreated with nicotine and NNK for 1 h at 37 °C. Mutations in the *supF* mutations were detected, as previously described (13).

Anchorage-Independent Soft-Agar Growth.

Lung (BEAS-2B) and bladder (UROtsa) epithelial cells were treated with NNK (0.5 mM) and nicotine (25 and 5 mM) for 1 h at 37 °C; these treatments rendered 50% cell killing. The method for anchorage-independent soft-agar growth is the same as previously described (28).

Statistical Analysis.

Statistical analysis and graphs were performed with Prism 6 (GraphPad) software. Two group comparisons were conducted with the unpaired, two-tailed Mann–Whitney *u* test or the unpaired, two-tailed *t* test with Welsh's correction for unequal variances. A *P* value <0.05 was considered to be significant.

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Footnotes

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- Author contributions: H.-W.L., S.-H.P., M.-w.W., H.-T.W., L.-C.C., and M.-s.T. designed research; H.-W.L., S.-H.P., M.-w.W., H.-T.W., and M.-s.T. performed research; M.-s.T. contributed new reagents/analytic tools; H.-W.L., S.-H.P., M.-w.W., W.C.H., H.L., X.-R.W., and M.-s.T. analyzed data; and H.-W.L., S.-H.P., M.-w.W., H.-T.W., W.C.H., H.L., X.-R.W., L.-C.C., and M.-s.T. wrote the paper.
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View Abstract

Scientists Help ID New Cancer-Causing Agent in Tobacco Smoke

Lilo H. Stainton | June 22, 2018
http://www.njspotlight.com/stories/18/06/21/rutgers-scientist-helps-id-new-cancer-causing-agent-in-tobacco-smoke/

Organic compounds known as 'aldehydes' are primary source of damage to DNA and also suppress its ability to repair that damage

When it comes to cancer caused by cigarette smoke, **experts may have misplaced the bulk of the blame.**

According to a new study, scientists at NYU School of Medicine and Rutgers University have found that **chemicals called aldehydes — present in tobacco smoke in high quantities — are the primary cause of damage to DNA and suppress its ability to repair damage.** And ongoing, related work at Rutgers suggests consumption of certain healthy foods may help reduce the impact of these aldehydes.

Breakdown in a person's DNA, or genetic code, is a major cause of cancer, according to the study; tobacco smoke has been linked to more than 80 percent of lung cancers and half of bladder cancers.

While smoking rates have declined to less than 14 percent of Garden State adults, each year roughly 2,500 residents are diagnosed with bladder cancer and nearly 6,000 with lung cancer, according to federal data.

Shifting scientific focus

In the past, researchers had focused on certain **hydrocarbons and nitrosamines** — organic compounds that are known carcinogens — present in cigarette smoke as the link to cancer. But the study suggests that **while these chemicals are carcinogenic, they did not result in the same level of DNA harm as the aldehydes**, which are also present in some foods in far lower levels.

The study by Moon-shong Tang, an environmental medicine and pathology professor at NYU, and co-author Chung S. Yang, a distinguished professor of pharmacy at Rutgers University and director of the university's Center for Cancer Prevention Research, was published online Tuesday in the Proceedings of the National Academy of Sciences.

The findings suggest that instead of focusing only on hydrocarbons and nitrosamines, **researchers must also consider the impact of aldehydes**. "Our findings provide the correct targets for both therapy and prevention of tobacco smoke-induced cancer," Tang said.

The scientists hope their work will help generate better methods to assess cancer risks, as well as ways to reduce the damage caused by tobacco smoke. That's where work by Yang and his Rutgers colleagues comes in. They are looking at how green tea and other beverages, fruits and some vegetables, can reduce these aldehydes from the body, cutting the risk for cancer and other diseases.

"In theory, this may help reduce the aldehydes generated through cigarette smoking," Yang said, "and a lot of other compounds from our diet could do the same."

'Practical implications' for preventing disease

The ability to reduce the impact of reactive aldehydes could have a "large practical implication in the prevention of disease," Yang added, but he stressed that nothing is more effective in reducing cancer risk than quitting smoking.

The research echoes findings published two years ago in JAMA Oncology by scientists at the M.D. Anderson Cancer Center at Cooper, in Camden. They found that nearly half of all cancers could be prevented in the United States if people quit smoking, reduced their alcohol intake, lost weight, got more exercise, and ate healthier food — factors they found reduced the rate of cell mutations caused by breakdowns in DNA.

The organic compounds known as aldehydes can also be found in trace amounts in certain baked or fried foods, Yang said, since they are a common result of the chemical reactions that take place when fats or meat gristle is heated to a certain point. In fact, he said studies in China have shown higher levels of aldehydes in individuals who frequently cook over a wok, which heats oil to an extremely high temperature, especially in poorly ventilated homes.

“Aldehydes exist in many places in small quantities,” Yang said. “It’s the quantity that counts,” he added, saying that the level in food does not present much of a concern, “whereas in cigarette (smoke), it’s a very high concentration.”

While the study focused on cigarettes, Yang said in theory the process of heating oils — generally infused with tobacco or other substances — in a smokeless device, or vape pen, could also generate aldehydes, but he has not seen data on this.

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Aldehydes are the predominant forces inducing DNA damage and inhibiting DNA repair in tobacco smoke carcinogenesis

Weng, Mao-Wen; Lee, Hyun-Wook; Park, Sung-Hyun; Hu, Yu; Wang, Hsing-Tsui; Chen, Lung-Chi; Rom, William N; Huang, William C; Lepor, Herbert; Wu, Xue-Ru; Yang, Chung S; Tang, Moon-Shong

Tobacco smoke (TS) contains numerous cancer-causing agents, with polycyclic aromatic hydrocarbons (PAHs) and nitrosamines being most frequently cited as the major TS human cancer agents. Many lines of evidence seriously question this conclusion. To resolve this issue, we determined DNA adducts induced by the three major TS carcinogens: benzo(*a*)pyrene (BP), 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanoe (NNK), and **aldehydes** in humans and mice. In mice, TS induces abundant aldehyde-induced Î³-hydroxy-propano-deoxyguanosine (Î³-OH-PdG) and Î±-methyl-Î³-OH-PdG adducts in the lung and bladder, but not in the heart and liver. TS does not induce the BP- and NNK-DNA adducts in lung, heart, liver, and bladder. TS also reduces DNA repair activity and the abundance of repair proteins, XPC and OGG1/2, in lung tissues. These TS effects were greatly reduced by diet with polyphenols. We found that Î³-OH-PdG and Î±-methyl-Î³-OH-PdG are the major adducts formed in tobacco smokers' buccal cells as well as the normal lung tissues of tobacco-smoking lung cancer patients, but not in lung tissues of nonsmokers. However, the levels of BP- and NNK-DNA adducts are the same in lung tissues of smokers and nonsmokers. We found that while BP and NNK can induce BPDE-dG and O^6-methyl-dG adducts in human lung and bladder epithelial cells, these inductions can be inhibited by **acrolein. Acrolein also can reduce DNA repair activity and repair proteins.** We propose a TS carcinogenesis paradigm. **Aldehydes are major TS carcinogens exerting dominant effect: Aldehydes induce mutagenic PdG adducts, impair DNA repair functions, and inhibit many procarcinogens in TS from becoming DNA-damaging agents.**

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E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells

Lee, Hyun-Wook; Park, Sung-Hyun; Weng, Mao-Wen; Wang, Hsiang-Tsui; Huang, William C; Lepor, Herbert; Wu, Xue-Ru; Chen, Lung-Chi; Tang, Moon-Shong
E-cigarette smoke delivers stimulant nicotine as aerosol without tobacco or the burning process. It contains neither carcinogenic incomplete combustion byproducts nor tobacco nitrosamines, the nicotine nitrosation products. E-cigarettes are promoted as safe and have gained significant popularity. In this study, instead of detecting nitrosamines, we directly measured DNA damage induced by nitrosamines in different organs of E-cigarette smoke-exposed mice. We found mutagenic O6-methyldeoxyguanosines and Î³-hydroxy-1,N2 -propano-deoxyguanosines in the lung, bladder, and heart. DNA-repair activity and repair proteins XPC and OGG1/2 are significantly reduced in the lung. **We found that nicotine and its metabolite, nicotine-derived nitrosamine ketone, can induce the same effects and enhance mutational susceptibility and tumorigenic transformation of cultured human bronchial epithelial and urothelial cells**. These results indicate that nicotine nitrosation occurs in vivo in mice and that E-cigarette smoke is carcinogenic to the murine lung and bladder and harmful to the murine heart**. It is therefore possible that E-cigarette smoke may contribute to lung and bladder cancer, as well as heart disease, in humans.**
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Acrolein induces mtDNA damages, mitochondrial fission and mitophagy in human lung cells

Wang, Hsiang-Tsui; Lin, Jing-Heng; Yang, Chun-Hsiang; Haung, Chun-Hao; Weng, Ching-Wen; Maan-Yuh Lin, Anya; Lo, Yu-Li; Chen, Wei-Shen; Tang, Moon-Shong
Acrolein (Acr), a highly reactive unsaturated aldehyde, can cause various lung diseases including asthma, chronic obstructive pulmonary disease (COPD), and lung cancer. We have found that Acr can damage not only genomic DNA but also DNA repair proteins causing repair dysfunction and enhancing cells' mutational susceptibility. While these effects may account for Acr lung carcinogenicity, the mechanisms by which Acr induces lung diseases other than cancer are unclear. In this study, we found that Acr induces damages in mitochondrial DNA (mtDNA), inhibits mitochondrial bioenergetics, and alters mtDNA copy number in human lung epithelial cells and fibroblasts. Furthermore, Acr induces mitochondrial fission which is followed by autophagy/ mitophagy and Acr-induced DNA damages can trigger apoptosis. However, the autophagy/ mitophagy process does not change the level of Acr-induced mtDNA damages and apoptosis. We propose that Acr-induced mtDNA damages trigger loss of mtDNA via mitochondrial fission and mitophagy. **These processes and mitochondria dysfunction induced by Acr are causes that lead to lung diseases**.
PMCID:5642564 PMID: 29050289
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Oncotarget. 2017:8(11):18213-18226.DOI: 10.18632/oncotarget.15313

AFB1 hepatocarcinogenesis is via lipid peroxidation that inhibits DNA repair, sensitizes mutation susceptibility and induces aldehyde-DNA adducts at p53 mutational hotspot codon 249

Weng, Mao-Wen; Lee, Hyun-Wook; Choi, Bongkun; Wang, Hsiang-Tsui; Hu, Yu; Mehta, Manju; Desai, Dhimant; Amin, Shantu; Zheng, Yi; Tang, Moon-Shong
Aflatoxin B1 (AFB1) contamination in the food chain is a major cause of hepatocellular carcinoma (HCC). More than 60% of AFB1 related HCC carry p53 codon 249 mutations but the causal mechanism remains unclear. We found that 1) AFB1 induces two types of DNA adducts in human hepatocytes, AFB1-8,9-epoxide-deoxyguanosine (AFB1-E-dG) induced by AFB1-E and cyclic alpha-methyl-gamma-hydroxy-1,N2-propano-dG (meth-OH-PdG) induced by lipid

peroxidation generated acetaldehyde (Acet) and crotonaldehyde (Cro); 2) the level of meth-OH-PdG is >30 fold higher than the level of AFB1-E-dG; 3) AFB1, Acet, and Cro, but not AFB1-E, preferentially induce DNA damage at codon 249; 4) methylation at -CpG- sites enhances meth-OH-PdG formation at codon 249; and 5) repair of meth-OH-PdG at codon 249 is poor. AFB1, Acet, and Cro can also inhibit DNA repair and enhance hepatocyte mutational sensitivity. We propose that AFB1-induced lipid peroxidation generated aldehydes contribute greatly to hepatocarcinogenesis and that sequence specificity of meth-OH-PdG formation and repair shape the codon 249 mutational hotspot.
PMID: 28212554 ISSN: 1949-2553 CID: 2449422

Oncotarget. 2016:7(49):80450-80464.DOI: 10.18632/oncotarget.12608

Acrolein preferentially damages nucleolus eliciting ribosomal stress and apoptosis in human cancer cells

Wang, Hsiang-Tsui; Chen, Tzu-Ying; Weng, Ching-Wen; Yang, Chun-Hsiang; Tang, Moon-Shong
Acrolein (Acr) is a potent cytotoxic and DNA damaging agent which is ubiquitous in the environment and abundant in tobacco smoke. Acr is also an active cytotoxic metabolite of the anti-cancer drugs cyclophosphamide and ifosfamide. The mechanisms via which Acr exerts its anti-cancer activity and cytotoxicity are not clear. In this study, we found that Acr induces cytotoxicity and cell death in human cancer cells with different activities of p53. Acr preferentially binds nucleolar ribosomal DNA (rDNA) to form Acr-deoxyguanosine adducts, and induces oxidative damage to both rDNA and ribosomal RNA (rRNA). Acr triggers ribosomal stress responses, inhibits rRNA synthesis, reduces RNA polymerase I binding to the promoter of rRNA gene, disrupts nucleolar integrity, and impairs ribosome biogenesis and polysome formation. Acr causes an increase in MDM2 levels and phosphorylation of MDM2 in A549 and HeLa cells which are p53 active and p53 inactive, respectively. It enhances the binding of ribosomal protein RPL11 to MDM2 and reduces the binding of p53 and E2F-1 to MDM2 resulting in stabilization/activation of p53 in A549 cells and degradation of E2F-1 in A549 and HeLa cells. We propose that Acr induces ribosomal stress which leads to activation of MDM2 and RPL11-MDM2 binding, consequently, activates p53 and enhances E2F-1 degradation, and that taken together these two processes induce apoptosis and cell death.
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XIAP RING domain mediates miR-4295 expression and subsequently inhibiting p63alpha protein translation and promoting transformation of bladder epithelial cells

Jin, Honglei; Xu, Jiheng; Guo, Xirui; Huang, Haishan; Li, Jingxia; Peng, Minggang; Zhu, Junlan; Tian, Zhongxian; Wu, Xue-Ru; Tang, Moon-Shong; Huang, Chuanshu
The X-linked inhibitor of apoptosis protein (XIAP) contains three N-terminal BIR domains that mediate anti-apoptosis and one C-terminal RING finger domain whose function(s) are not fully defined. Here we show that the RING domain of XIAP strongly inhibits the expression of p63alpha, a known tumor suppressor. XIAP knockdown in urothelial cells or RING deletion in knockin mice markedly upregulates p63alpha expression. This RING-mediated p63alpha downregulation is critical for the malignant transformation of normal urothelial cells following EGF treatment. We further show that the RING domain promotes Sp1-mediated transcription of miR-4295 which targets the 3'UTR of p63alpha mRNA and consequently inhibits p63alpha translation. Our results reveal a previously unknown function of the RING of XIAP in promoting miR-4295 transcription, thereby reducing p63alpha translation and enhancing urothelial transformation. Our data offer novel insights into the multifunctional effects of the XIAP RING domain on urothelial tumorigenesis and the potential for targeting this frequently overexpressed protein as a therapeutic alternative.
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Scientific reports. 2016:6:25596-25596.DOI: 10.1038/srep25596

FGFR3b Extracellular Loop Mutation Lacks Tumorigenicity In Vivo but Collaborates with p53/pRB Deficiency to Induce High-grade Papillary Urothelial Carcinoma

Zhou, Haiping; He, Feng; Mendelsohn, Cathy L; Tang, Moon-Shong; Huang, Chuanshu; Wu, Xue-Ru

Missense mutations of fibroblast growth factor receptor 3 (FGFR3) occur in up to 80% of low-grade papillary urothelial carcinoma of the bladder (LGP-UCB) suggesting that these mutations are tumor drivers, although direct experimental evidence is lacking. Here we show that forced expression of FGFR3b-S249C, the most prevalent FGFR3 mutation in human LGP-UCB, in cultured urothelial cells resulted in slightly reduced surface translocation than wild-type FGFR3b, but nearly twice as much proliferation. When we expressed a mouse equivalent of this mutant (FGFR3b-S243C) in urothelia of adult transgenic mice in a tissue-specific and inducible manner, we observed significant activation of AKT and MAPK pathways. This was, however, not accompanied by urothelial proliferation or tumorigenesis over 12 months, due to compensatory tumor barriers in p16-pRB and p19-p53-p21 axes. Indeed, expressing FGFR3b-S249C in cultured human urothelial cells expressing SV40T, which functionally inactivates pRB/p53, markedly accelerated proliferation and cell-cycle progression. Furthermore, expressing FGFR3b-S243C in transgenic mouse urothelium expressing SV40T converted carcinoma-in-situ to high-grade papillary urothelial carcinoma. Together, our study provides new experimental evidence indicating that the FGFR3 mutations have very limited urothelial tumorigenicity and that these mutations must collaborate with other genetic events to drive urothelial tumorigenesis.
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Oncotarget. 2015:6(32):33226-33236.DOI: 10.18632/oncotarget.5429

Cigarette side-stream smoke lung and bladder carcinogenesis: inducing mutagenic acrolein-DNA adducts, inhibiting DNA repair and enhancing anchorage-independent-growth cell transformation

Lee, Hyun-Wook; Wang, Hsiang-Tsui; Weng, Mao-Wen; Chin, Chiu; Huang, William; Lepor, Herbert; Wu, Xue-Ru; Rom, William N; Chen, Lung-Chi; Tang, Moon-Shong

Second-hand smoke (SHS) is associated with 20-30% of cigarette-smoke related diseases, including cancer. Majority of SHS (>80%) originates from side-stream smoke (SSS). Compared to mainstream smoke, SSS contains more tumorigenic polycyclic aromatic hydrocarbons and acrolein (Acr). We assessed SSS-induced benzo(a)pyrene diol epoxide (BPDE)- and cyclic propano-deoxyguanosine (PdG) adducts in bronchoalveolar lavage (BAL), lung, heart, liver, and bladder-mucosa from mice exposed to SSS for 16 weeks. In SSS exposed mice, Acr-dG adducts were the major type of PdG adducts formed in BAL ($p < 0.001$), lung ($p < 0.05$), and bladder mucosa ($p < 0.001$), with no significant accumulation of Acr-dG adducts in heart or liver. SSS exposure did not enhance BPDE-DNA adduct formation in any of these tissues. SSS exposure reduced nucleotide excision repair ($p < 0.01$) and base excision repair ($p < 0.001$) in lung tissue. The levels of DNA repair proteins, XPC and hOGG1, in lung tissues of exposed mice were significantly ($p < 0.001$ and $p < 0.05$) lower than the levels in lung tissues of control mice. We found that Acr can transform human bronchial epithelial and urothelial cells in vitro. We propose that induction of mutagenic Acr-DNA adducts, inhibition of DNA repair, and induction of cell transformation are three mechanisms by which SHS induces lung and bladder cancers.
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PMID: 26431382
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Quantitative study of aldehyde content in electronic cigarettes

phys.org/news/2017-04-quantitative-aldehyde-content-electronic-cigarettes.html

Credit: CC0 Public Domain

(Phys.org)—Electronic cigarettes have had their share of both detractors and advocates since they hit the market in 2004. Many people believe that they are healthier than cigarettes, but others say that the effects of e-cigarette vapors are largely unknown. Medical organizations have generally taken a cautious approach and do not specifically recommend e-cigarettes for stopping smoking or as a healthier alternative to smoking.

One area of concern is the amount of aldehydes present in e-cigarette smoke. These aldehydes are present in tobacco cigarettes in larger quantities than in e-cigarettes, but the levels in e-cigarettes are still not known. Additionally, the amount that is considered dangerous for cardio vascular disease (CVD) is a topic of debate. Some studies have shown that even small amounts of certain aldehydes can lead to progression of CVD.

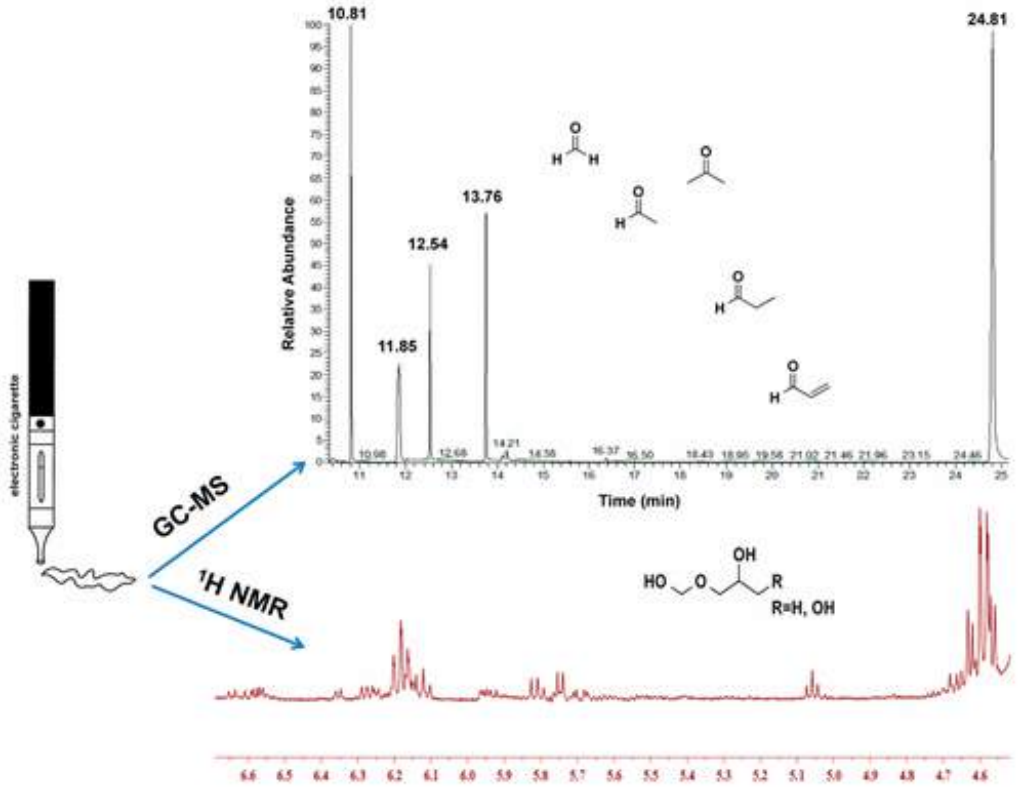
Researchers from the University of Louisville's Tobacco Regulation and Addiction Center conducted quantitative analyses of both older (first generation) and newer-model e-cigarette cartridges using a variety of flavors. They used a new method for trapping reactive carbonyls that are then subsequently stabilized using an oximation reaction. They found that newer devices produced more harmful aldehydes than first generation e-cigarettes. Their work appears in *ACS Omega*.

E-cigarettes cartridges contain battery-powered coils that serve to heat and vaporize e-Liquid. Based on this study, the amount of reactive aldehydes in e-cigarette vapor are largely due to the cartridge's battery power. The higher the battery power, the higher the

aldehyde levels. While e-cigarette aerosols contain aldehydes that are known to contribute to CVD, the exact levels have not been definitively determined largely because of the difficulties associated with trapping and studying reactive aldehydes.

New models, or "next-generation," e-cigarettes have a higher battery power than older ones. Furthermore, older models have a fixed battery output (4.6 W) while the next-generation ones have variable output (9.1 W, 11.7 W, 14.7 W, 16.6 W). The authors wanted to look at this next-generation of e-cigarettes to quantitatively determine aldehyde levels as well as determine if e-Liquid flavor makes a difference in aldehyde formation. In order to do this, they took into account the formation of hemiacetals from aldehydes, something that prior studies did not address.

The aldehydes that are of greatest concern are acetaldehyde, acrolein, and formaldehyde. Acrolein, in particular, has been shown to advance CVD, even when a person is exposed to low levels. Formaldehyde has also been associated with CVD in low concentrations.



Credit: ACS

E-Liquids are usually comprised of glycerin and propylene glycol along with a flavor additive. Glycerin, when heated, predominantly forms acrolein and formaldehyde, while propylene glycol predominantly forms acetone and acetaldehyde. Certain flavor additives have shown enhanced aldehyde formation, as well.

Ogunwale et al. used a microreactor-capture approach that they had previously developed to obtain an accurate look at aldehyde levels in e-cigarette vapor. This method employs a 4-(2-aminooxyethyl)-morpholin-4-ium chloride (AMAH) coating on a silicon base. Aldehydes selectively react with AMAH to form an oxime, which is more stable and easier to study than an aldehyde.

Aerosols were generated using a cigarette-smoking robot and were collected in Tedlar bags. The robot allowed for control over puff duration, puff volume, and puff frequency. The aerosols flowed through the microreactors from the bags using an evacuation process and then reacted with AMAH. The AMAH oxime compound was neutralized to form an AMA adduct that was then studied using gas chromatography.

Both the first generation and next generation e-cigarettes produced some amount of acetaldehyde, acrolein, and formaldehyde, but acealdehyde and formaldehyde were in higher concentrations than acrolein. All of the aldehydes were present in lower concentrations than what is found in cigarette smoke using Health Canada Intense Puffing Regime. Notably, the next-generation e-cigarettes, which have a tank-type atomizer, produced higher levels of aldehydes and acetone. The authors attribute this to the higher battery output.

To understand the puffing topology, Ogunwale et al., used 60-mL syringes to manually vary puff duration and volume to more accurately replicate real-life usage. Puffing duration and the particular flavor contributed to the formation of reactive aldehydes, although these factors played a smaller role than battery output in the amount of aldehydes present. If puffing duration was around 4.0 seconds/puff, more aldehydes were present compared to shorter or longer puffing. The average user puffs for 3.5 to 4.3 seconds.

Finally, Ogunwale et al. used ^{1}H NMR to detect and quantify the presence of hemiacetals formed from aldehydes. They found that hemiacetals did not form in any of the first-generation e-cigarettes flavors, and they did not form in three of the next-generation flavors tested. Only one flavor that was tested formed hemiacetals within a battery output that was within the range of normal use.

This study provides valuable information on the safety of e-cigarettes. In general, the higher the battery output, the higher the aldehyde levels in the vapor. Certain aldehydes, such as acrolein, acetaldehyde, and formaldehyde, have been shown to contribute to CVD even in low levels. All of the e-cigarettes tested in this study had some amount of these aldehydes present.

Explore further: Hazardous chemicals discovered in flavored e-cigarette vapor

More information: Mumiye A. Ogunwale et al. Aldehyde Detection in Electronic Cigarette Aerosols, *ACS Omega* (2017). DOI: 10.1021/acsomega.6b00489

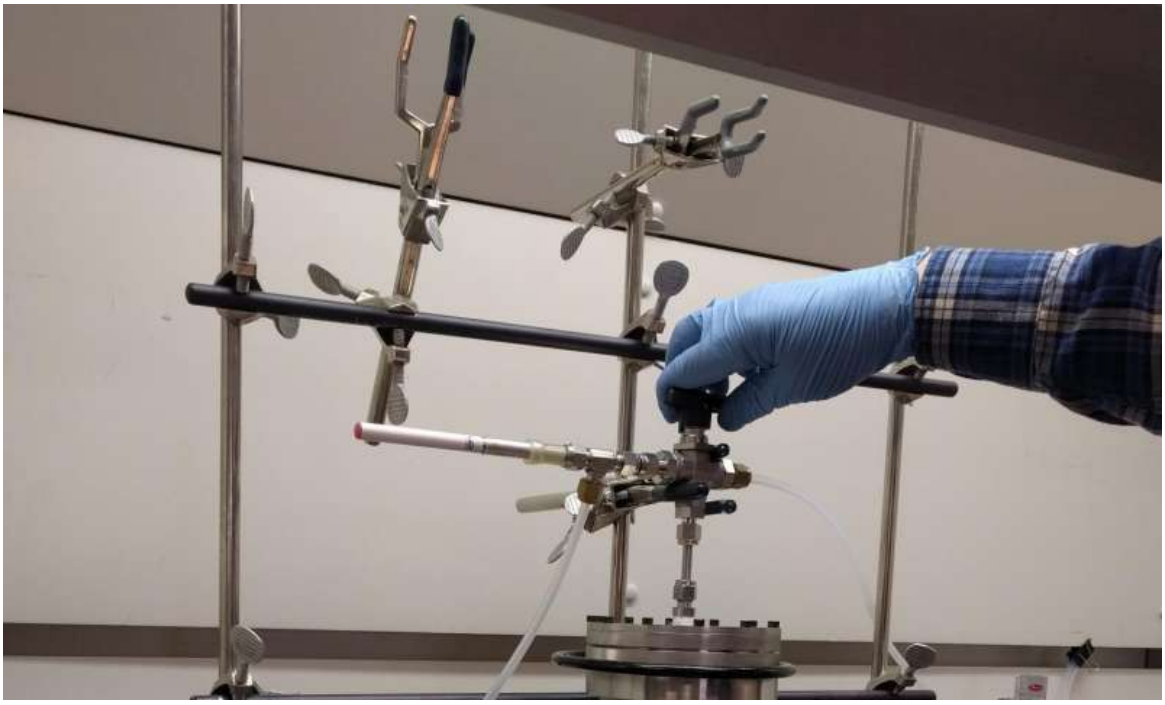
Abstract

Acetaldehyde, acrolein, and formaldehyde are the principal toxic aldehydes present in cigarette smoke and contribute to the risk of cardiovascular disease and noncancerous pulmonary disease. The rapid growth of the use of electronic cigarettes (e-cigarettes) has raised concerns over emissions of these harmful aldehydes. This work determines emissions of these aldehydes in both free and bound (aldehyde–hemiacetal) forms and other carbonyls from the use of e-cigarettes. A novel silicon microreactor with a coating phase of 4-(2-aminooxyethyl)-morpholin-4-ium chloride (AMAH) was used to trap carbonyl compounds in the aerosols of e-cigarettes via oximation reactions. AMAH–aldehyde adducts were measured using gas chromatography–mass spectrometry. 1H nuclear magnetic resonance spectroscopy was used to analyze hemiacetals in the aerosols. These

aldehydes were detected in the aerosols of all e-cigarettes. Newer-generation e-cigarette devices generated more aldehydes than the first-generation e-cigarettes because of higher battery power output. Formaldehyde–hemiacetal was detected in the aerosols generated from some e-liquids using the newer e-cigarette devices at a battery power output of 11.7 W and above. The emission of these aldehydes from all e-cigarettes, especially higher levels of aldehydes from the newer-generation e-cigarette devices, indicates the risk of using e-cigarettes.

Hazardous chemicals discovered in flavored e-cigarette vapor

phys.org/news/2016-11-hazardous-chemicals-flavored-e-cigarette-vapor.html



DRI scientists used a controlled sampling system to simulate the most common vaping conditions. E-cigarette vapor was produced from each device by a four-second, 40-ml controlled puff, with 30-second resting periods between puffs. Credit: DRI

Building on more than 30 years of air quality research in some of the most polluted urban environments on Earth, a team of atmospheric scientists at the Desert Research Institute (DRI) have turned their attention toward the growing e-cigarette industry and the unidentified effects of vaping on human health.

New research published this week in *Environmental Science & Technology*, a journal of the American Chemical Society, reports that the aerosols (commonly called vapors) produced by flavored e-cigarettes liquids contain dangerous levels of hazardous chemicals known to cause cancer in humans.

The study "Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping" confirms that these toxic aldehydes, such as formaldehyde, are formed not by evaporation, but rather during the chemical breakdown of the flavored e-liquid during the rapid heating process (pyrolysis) that occurs inside e-cigarettes or electronic nicotine delivery systems (ENDS).

"How these flavoring compounds in e-cigarette liquids affect the chemical composition and toxicity of the vapor that e-cigarettes produce is practically unknown," explained Andrey Khylstov, Ph.D., an associate research professor of atmospheric sciences at DRI. "Our results show that production of toxic aldehydes is exponentially dependent on the concentration of flavoring compounds."

E-cigarette liquids have been marketed in nearly 8,000 different flavors, according to a 2014 report from the World Health Organization. Recent reports have shown that many flavors, such as Gummy Bear, Tutti Fruitty, Bubble Gum, etc., were found to be especially appealing to adolescents and young adults.

The U.S. Food and Drug Administration (FDA) reports that 16-percent of high school and 5.3-percent of middle school students were current users of e-cigarettes in 2015, making e-cigarettes the most commonly used tobacco product among youth for the second consecutive year. In 2014, 12.6-percent of U.S. adults had ever tried an e-cigarette, and about 3.7-percent of adults used e-cigarettes daily or some days.

DRI scientists measured concentrations of 12 aldehydes in aerosols produced by three common e-cigarette devices shown here. To determine whether the flavoring additives affected aldehyde production during vaping, five flavored e-liquids …more

Khylstov and his colleagues measured concentrations of 12 aldehydes in aerosols produced by three common e-cigarette devices. To determine whether the flavoring additives affected aldehyde production during vaping, five flavored e-liquids were tested in each device. In addition, two unflavored e-liquids were also tested.

"To determine the specific role of the flavoring compounds we fixed all important parameters that could affect aldehyde production and varied only the type and concentration of flavors," explained Vera Samburova, Ph.D., an assistant research professor of chemistry at DRI.

Samburova added that the devices used in the study represented three of the most common types of e-cigarettes - bottom and top coil clearomizers, and a cartomizer.

The study avoided any variation in puff topography (e.g., puff volume, puff velocity, interval between puffs) by utilizing a controlled sampling system that simulated the most common vaping conditions. E-cigarette vapor was produced from each device by a four-second, 40-

ml controlled puff, with 30-second resting periods between puffs. The e-cigarette devices were manually operated to replicate real-life conditions and all samples were collected in triplicate to verify and confirm results. Specific care was taken to avoid "dry puff" conditions.

To provide further proof that the flavoring compounds, not the carrier e-liquid solvents (most commonly propylene glycol and/or vegetable glycerin) dominated production of aldehydes during vaping, the authors performed a series of experiments in which a test flavored e-liquid was diluted with different amounts of the unflavored e-liquid. Liquids with higher flavor content produced larger amounts of aldehydes due to pyrolysis of the flavoring compounds.

In all experiments, the amount of aldehydes produced by the flavored e-cigarette liquids exceeded the American Conference of Governmental Industrial Hygienists Threshold Limit Values (TLVs) for hazardous chemical exposure.

"One puff of any of the flavored e-liquids that we tested exposes the smoker to unacceptably dangerous levels of these aldehydes, most of which originates from thermal decomposition of the flavoring compounds," said Khylstov. "These results demonstrate the need for further, thorough investigations of the effects of flavoring additives on the formation of aldehydes and other toxic compounds in e-cigarette vapors."

Explore further: Study identifies two additional carcinogens not previously reported in e-cigarette vapor

More information: Andrey Khlystov et al, Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping, *Environmental Science & Technology* (2016). DOI: 10.1021/acs.est.6b05145

Study identifies two additional carcinogens not previously reported in e-cigarette vapor

phys.org/news/2016-07-additional-carcinogens-previously-e-cigarette-vapor.html

Berkeley Lab researchers (from left) Lara Gundel, Marion Russell, Hugo Destaillats demonstrate filling a glass syringe with vapor from an e-cigarette. Credit: Paul Mueller/Berkeley Lab

While previous studies have found that electronic cigarettes emit toxic compounds, a new study from Lawrence Berkeley National Laboratory (Berkeley Lab) has pinpointed the source of these emissions and shown how factors such as the temperature, type, and age of the device play a role in emission levels, information that could be valuable to both manufacturers and regulators seeking to minimize the health impacts of these increasingly popular devices.

The study, which was published in *Environmental Science & Technology*, found that the thermal decomposition of propylene glycol and glycerin, two solvents found in most "e-liquids" (the substance that is vaporized by the e-cigarette), leads to emissions of toxic chemicals such as acrolein and formaldehyde.

"Advocates of e-cigarettes say emissions are much lower than from conventional cigarettes, so you're better off using e-cigarettes," said Berkeley Lab researcher and the study's corresponding author Hugo Destaillats. "I would say, that may be true for certain users—for example, long time smokers that cannot quit—but the problem is, it doesn't mean that they're healthy. Regular cigarettes are super unhealthy. E-cigarettes are just unhealthy."

In the paper, "Emissions from electronic cigarettes: Key parameters affecting the release of harmful chemicals," Destaillats and a team of researchers simulated vaping using three types of e-liquids in two different vaporizers operated at various battery power settings. The two e-cigarettes were quite different, one fairly cheap with one heating coil, the other more expensive with two heating coils in parallel. The researchers used gas and liquid chromatography to determine what was in the vapor, looking at the first puffs as well as later puffs after the device heated up and reached a "steady state."

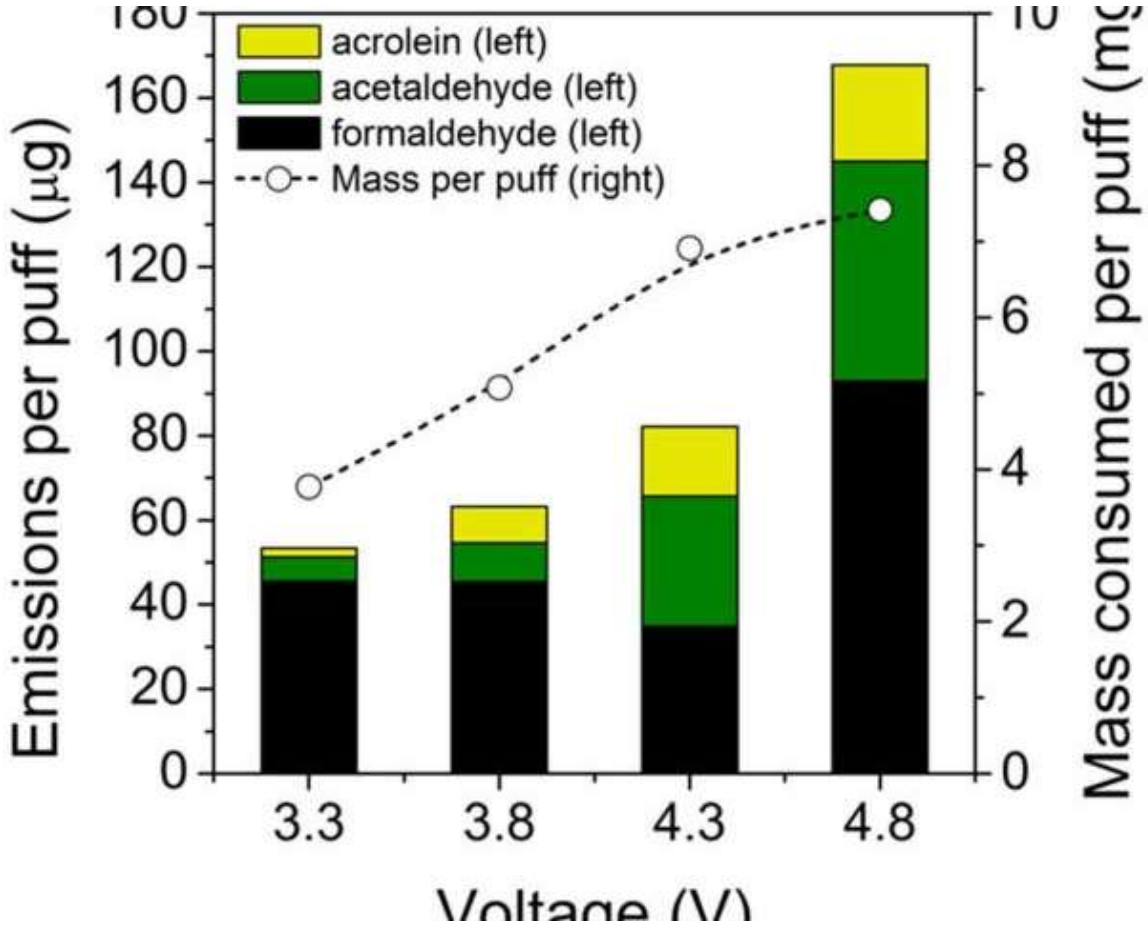
Not all puffs are equal

One finding was that the first and last puffs produce widely varying emissions. Using a custom-built vaping apparatus emulating realistic vaping habits, researchers drew on the e-cigarette by taking puffs lasting 5 seconds every 30 seconds. They found that vapor temperature rose quickly in the first 5 to 10 minutes until reaching a steady state temperature at around the twentieth puff.

Correspondingly, emissions levels between the first few puffs and the steady state increased by a factor of 10 or more in some cases, depending on the device, the battery voltage, and the emitted compound. For example, for acrolein, a severe eye and respiratory irritant, a single-coil e-cigarette operated at 3.8 volts emitted 0.46 micrograms per puff in the first five puffs, but at the steady state it emitted 8.7 micrograms per puff. "When you apply the same voltage to the double-coil e-cigarette you see a lot less emissions," said co-author and Berkeley Lab researcher Lara Gundel. "We think it has to do with lower temperatures at each of the coil surfaces."

For comparison, conventional cigarettes emit 400 to 650 micrograms of acrolein per cigarette, accounting for both mainstream and sidestream emissions. Assuming 20 puffs on an e-cigarette is equivalent to smoking a conventional cigarette, Gundel said, then total emissions of acrolein for an e-cigarette are about 90 to 100 micrograms.

Separately, to test effects due to device aging, researchers used a single device over nine consecutive 50-puff cycles without cleaning. Again, emissions of formaldehyde, acetaldehyde, and acrolein—all either carcinogens or respiratory irritants—increased with usage. "In some cases we saw aldehyde levels increase 60 percent between cycles 1 and 9," said co-author and Berkeley Lab researcher Mohamad Sleiman.



Emissions of potentially harmful compounds in e-cig vapor increase with device voltage. Credit: American Chemical Society

The researchers note in their paper: "This effect is consistent with the buildup of polymerization byproducts on or near the coil leading to accumulation of the sort of residues that are often referred to in the blogosphere as 'coil gunk' or 'caramelization.' Heating these residues would provide a secondary source of volatile aldehydes."

Lastly, because many e-cigarettes allow users to control the voltage, the researchers systematically investigated the effect of voltage on emissions. They found that as the voltage increased, both the amount of e-liquid consumed per puff and the vapor temperature were higher. In the case of acrolein and formaldehyde, the amount formed at the highest voltage of 4.8V was an order of magnitude higher than the amount at the lowest voltage of 3.3V.

Destaillats takes pains to note that the results do not mean that e-cigarettes are safe to use at lower temperatures. "We found there are emissions of toxic chemicals at any temperature at which you use the device," he said. "And the higher the temperature, the more emissions."

Two new carcinogens detected

Because there is an immense variety of e-cigarettes as well as e-liquids, the Berkeley Lab researchers decided to focus on an element that is common to all of them: the solvent in the e-liquid. Almost all e-liquids use a combination of propylene glycol and glycerin in varying proportions as a solvent.

"Both are used for making artificial smoke on stage," Destaillats said. "The ratio between the two determines things like the volume of vapor cloud that you produce. They are considered safe for food."

However, there have been few if any studies on the safety of heating and inhaling propylene glycol and glycerin. "People are not drinking the liquids—they're vaping them," said Sleiman. "So what counts is the vapor."

The researchers vaporized liquids consisting solely of the solvents to verify that they were the source of the emissions. In all, the researchers detected significant levels of 31 harmful chemical compounds, including two that had never been previously found in e-cigarette vapor—propylene oxide and glycidol, both of which are probable carcinogens.

"Understanding how these compounds are formed is very important," Destaillats said. "One reason is for regulatory purposes, and the second is, if you want to manufacture a less harmful e-cigarette, you have to understand what the main sources of these carcinogens are."

Explore further: Potentially dangerous molecules detected in e-cigarette aerosols

More information: "Emissions from electronic cigarettes: Key parameters affecting the release of harmful chemicals" pubs.acs.org/doi/abs/10.1021/acs.est.6b01741

Potentially dangerous molecules detected in e-cigarette aerosols

Credit: iStock/mauro grigollo

Electronic cigarettes produce highly-reactive free radicals—molecules associated with cell damage and cancer—and may pose a health risk to users, according to researchers at Penn State College of Medicine.

The use of e-cigarettes is on the rise. According to the Centers for Disease Control and Prevention, more than 20 percent of young adults have tried e-cigarettes, and current smokers and recent former smokers are most likely to have used them.

E-cigarettes deliver nicotine in water vapor instead of by burning tobacco. The battery-operated devices have been marketed as an alternative to traditional cigarettes.

Despite their growing popularity, very little is known about toxic substances produced by e-cigarettes and their health effects.

"There's a perception that e-cigarettes are healthier than regular cigarettes, or at least not as harmful as regular cigarettes," said John P. Richie Jr., professor of public health sciences and pharmacology. "While e-cigarette vapor does not contain many of the toxic substances that are known to be present in cigarette smoke, it's still important for us to figure out and to minimize the potential dangers that are associated with e-cigarettes."

Previous studies have found low levels of aldehydes, chemical compounds that can cause oxidative stress and cell damage, in e-cigarette "smoke." But until now, no one has looked for free radicals, the main source of oxidative stress from cigarette smoke. Highly reactive free radicals are a leading culprit in smoking-related cancer, cardiovascular disease and chronic obstructive pulmonary disease.

Instead of smoke, e-cigarettes produce aerosols, tiny liquid particles suspended in a puff of air. The researchers measured free radicals in e-cigarette aerosols.

They found that e-cigarettes produce high levels of highly reactive free radicals that fall in the range of 1,000- to 100-times less than levels in regular cigarettes.

"This is the first study that demonstrates the fact that we have these highly reactive agents in e-cigarette aerosols," Richie said. Results were published in the journal *Chemical Research in Toxicology*.

"The levels of radicals that we're seeing are more than what you might get from a heavily air-polluted area but less than what you might find in cigarette smoke," Richie said. The radicals are produced when the device's heating coil heats the nicotine solution to very high temperatures.

Further research is needed to determine the health effects of highly reactive free radicals

from e-cigarettes.

"This is the first step," Richie said. "The identification of these radicals in the aerosols means that we can't just say e-cigarettes are safe because they don't contain tobacco. They are potentially harmful. Now we have to find out what the harmful effects are."

Richie is currently conducting studies to carefully measure total numbers offree radicals in e-cigarette aerosols and to identify their chemical structures.

"That will help us interpret the data better to know how dangerous they are," he said.

Explore further: E-cigarette exposure impairs immune responses in mouse model, new research finds

More information: Reema Goel et al. Highly Reactive Free Radicals in Electronic Cigarette Aerosols, *Chemical Research in Toxicology* (2015). DOI: 10.1021/acs.chemrestox.5b00220

Chemicals in e-cigarette flavors linked to respiratory disease

medicalxpress.com/news/2015-12-chemicals-e-cigarette-flavors-linked-respiratory.html

Credit: TheNorlo/Wikipedia

Diacetyl, a flavoring chemical linked to cases of severe respiratory disease, was found in more than 75% of flavored electronic cigarettes and refill liquids tested by researchers at Harvard T.H. Chan School of Public Health. Two other potentially harmful related compounds were also found in many of the tested flavors, which included varieties with potential appeal to young people such as Cotton Candy, Fruit Squirts, and Cupcake.

The study will be published online December 8, 2015 in *Environmental Health Perspectives*.

The Occupational Safety and Health Administration and the flavoring industry have warned workers about diacetyl because of the association between inhaling this chemical and the debilitating respiratory disease bronchiolitis obliterans, colloquially termed "Popcorn Lung" because it first appeared in workers who inhaled artificial butter flavor in microwave popcorn processing facilities.

"Recognition of the hazards associated with inhaling flavoring chemicals started with 'Popcorn Lung' over a decade ago. However, diacetyl and other related flavoring chemicals are used in many other flavors beyond butter-flavored popcorn, including fruit flavors, alcohol flavors, and, we learned in our study, candy flavored e-cigarettes," said lead author Joseph Allen, assistant professor of exposure assessment science.

There are currently more than 7,000 varieties of flavored e-cigarettes and e-juice (liquid containing nicotine that is used in refillable devices) on the market. Although the popularity and use of e-cigarettes continues to increase, there is a lack of data on their potential

health effects. E-cigarettes are not currently regulated, but the U.S. Food and Drug Administration (FDA) has issued a proposed rule to include e-cigarettes under its authority to regulate certain tobacco and nicotine-containing products.

Allen and colleagues tested 51 types of flavored e-cigarettes and liquids sold by leading brands for the presence of diacetyl, acetoin, and 2,3-pentanedione, two related flavoring compounds that are listed as "high priority," i.e. they may pose a respiratory hazard in the workplace, by the Flavor and Extract Manufacturers Association. Each e-cigarette was inserted into a sealed chamber attached to a lab-built device that drew air through the e-cigarette for eight seconds at a time with a resting period of 15 or 30 second between each draw. The air stream was then analyzed.

At least one of the three chemicals was detected in 47 of the 51 flavors tested. Diacetyl was detected above the laboratory limit of detection in 39 of the flavors tested. Acetoin and 2,3-pentanedione were detected in 46 and 23 and of the flavors, respectively.

"Since most of the health concerns about e-cigarettes have focused on nicotine, there is still much we do not know about e-cigarettes. In addition to containing varying levels of the addictive substance nicotine, they also contain other cancer-causing chemicals, such as formaldehyde, and as our study shows, flavoring chemicals that can cause lung damage," said study co-author David Christiani, Elkan Blout Professor of Environmental Genetics.

Explore further: Case report finds 'popcorn lung' in patient using e-cigarettes

More information: "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 1 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes," Joseph G. Allen, Skye S. Flanigan, Mallory LeBlanc, Jose Vallarino, Piers MacNaughton, James H. Stewart, David C. Christiani, *Environmental Health Perspectives*, December 8, 2015, DOI: 10.1289/ehp.1510185

This study was supported by NIH/NIEHS Center Grant P30ES000002.

What's to know about popcorn lung?

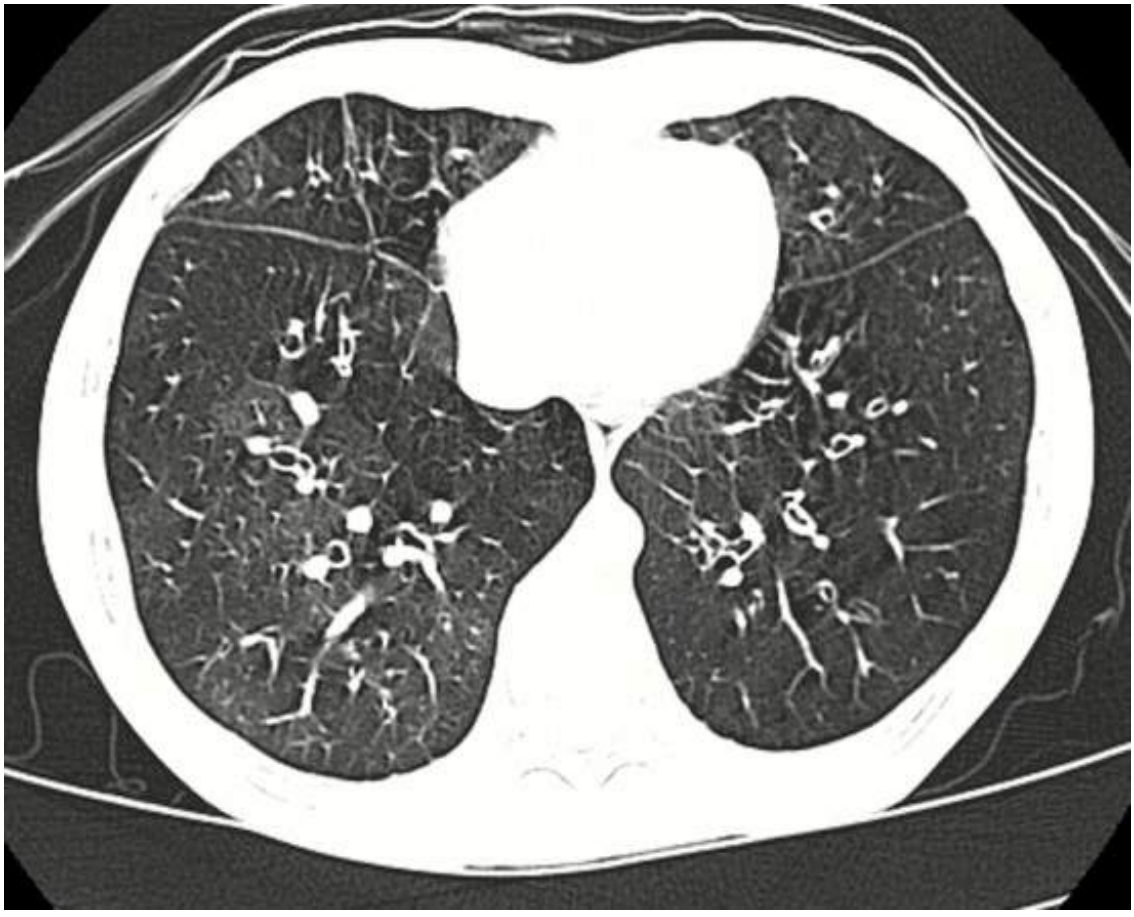
medicalnewstoday.com/articles/318260.php

By Judith Marcin, MD

1.

Popcorn lung is a rare condition that causes airway scarring due to inflammation and eventually lung damage.
While treatments exist to limit and manage symptoms, currently there is no cure for popcorn lung, and it is considered life-threatening.

What is popcorn lung?



Popcorn lung is characterized by the lung tissue scarring and becoming narrow. This can lead to breathing problems.
Image credit: Xie, B-Q, et al., PLOS, 2014 March
Popcorn lung is a rare medical condition that damages the bronchioles, the lung's smallest airways.

Over time, inflammation associated with popcorn lung causes lung tissues and airways to scar and narrow, causing breathing difficulties.

Popcorn lung gets its name from a chemical called diacetyl, which was once commonly used to give food products, such as popcorn, a rich, buttery flavor. In fact, the condition was first identified among popcorn factory workers who inhaled the chemical in the workplace.

Popcorn lung is also known as obliterative bronchiolitis, bronchiolitis obliterans, or constrictive bronchiolitis. Popcorn lung can be mistaken for a different condition called bronchiolitis obliterans organizing pneumonia (BOOP).

Symptoms

The symptoms of popcorn lung may be subtle and therefore easy to overlook, and the condition may be mistaken for other lung diseases. People with other respiratory conditions, especially chronic conditions such as asthma, may not be able to tell new symptoms apart from long-term complaints.

Besides diacetyl, there are a variety of other chemicals that can cause popcorn lung. Certain lung infections can cause it as well.

Symptoms typically occur within 2 to 8 weeks after infection or exposure to a chemical and slowly worsen over weeks to months. Some people may develop popcorn lung after transplant surgery, but it may take months to years to develop.

The most common signs and symptoms of popcorn lung include:

- wheezing that is not related to another health condition, such as bronchitis or asthma
- dry cough
- shortness of breath or difficulty breathing deeply, especially with physical activity
- unexplained exhaustion
- rapid breathing
- persistent skin, eye, mouth, or nose irritation if caused by a chemical

People should seek immediate medical attention whenever breathing becomes difficult, or if they experience chest pain or shortness of breath that leads to dizziness. People should also see their doctor if symptoms occur or chronic symptoms worsen.

Causes

Chemical damage to the lung tissues can cause popcorn lung, as can a few other factors. Although some hereditary conditions can cause popcorn lung, it is not considered an inheritable disorder.

Breathing in harmful chemicals, particles, or toxins can lead to popcorn lung. Food-flavoring fumes produced during the manufacture of candies, potato chips, popcorn, and dairy products, are major culprits.

Other examples include:

- fumes from industrial or cleaning chemicals, such as ammonia or chlorine
- nitrous oxide, also known as laughing gas
- metallic fumes from construction activities, such as welding

- industrial air particles, such as complex dust

Other factors that have been shown to cause or increase the likelihood of developing popcorn lung include:

- certain viral or bacterial respiratory infections
- having had a transplant
- immune conditions, such as rheumatoid arthritis and hypersensitivity pneumonitis
- certain drugs, such as penicillamine, 5-fluorouracil, and gold

Transplant surgeries may cause a condition called graft-versus-host disease, which occurs when the body rejects organ transplantation, particularly after lung, bone marrow, or stem cell transplants. This reaction can also lead to popcorn lung.

E-cigarette use

The chemicals found in e-cigarette liquid, known as "e-juice," may be a potential cause of popcorn lung.

According to the American Lung Association, using electronic cigarettes or vaping, particularly the flavored varieties, can cause popcorn lung.

Once the dangers associated with diacetyl were discovered in the early 2000s, the majority of popcorn producers stopped using the chemical. However, e-cigarette vapor has been proven to contain diacetyl.

A 2015 study of flavored e-cigarettes found that 39 out of 51 tested brands contained diacetyl. The same study concluded that most of these brands also contained the toxic chemicals acetoin and 2,3 pentanedione.

Manufacturers add diacetyl to the "e-juice" that is vaporized by e-cigarettes, most commonly to the strongly-flavored varieties. Diacetyl occurs in a wide range of different flavored e-cigarette products, ranging from vanilla to caramel and coconut.

E-cigarettes only came under the control of the U.S. Food and Drug Administration (FDA) in 2016. Changes to regulations may be required in the coming years as more research is carried out.

Diagnosis

A diagnosis of popcorn lung usually follows after a person has presented with the symptoms but has no other respiratory conditions.

Once a doctor suspects the condition, they will often perform a full exam and review the person's medical history. In particular, the doctor will look for possible causes, such as exposure to toxic fumes or infection.

Doctors may recommend further tests to confirm the diagnosis.

Commonly used tests include:

- Bronchoscopy: using a small, flexible, lighted instrument to look inside the airways. Airway washes can be done during the procedure to collect cell samples.
- Biopsy: removal of a portion of affected lung tissue for examination under a microscope.
- Pulmonary function tests (PFT): breathing tests used to assess and monitor the progress of symptoms.
- Computer tomography (CT) scans of the chest: detailed images of the lungs and airways can appear as a "mosaic" pattern.
- Chest X-rays: may be used alongside other tests.

Treatment

Steroids may be prescribed to treat popcorn lung.
The lung tissue scarring caused by popcorn lung is irreversible. Also, there is no cure for the condition once it has developed and begun constricting the airways.

There are treatment options to manage or reduce symptoms and limit further lung damage, however.

It is crucial to recognize symptoms and diagnose popcorn lung early. As symptoms progress, the lung damage becomes more severe, and treatment becomes far more challenging.

The type of treatment recommended depends on the cause and severity of the case. If cases are due to chemicals or toxins, the individual should immediately leave the environment where exposure occurred and not return.

Treatment options for popcorn lung can include:

- macrolide antibiotics for the treatment of bacterial respiratory infections may work in some individuals
- steroids, specifically corticosteroids to lessen inflammation
- immunosuppressive drugs that reduce the activity of the immune system and limit inflammation
- supplemental oxygen
- a medication called Singulair (montelukast), which blocks specific immune cells that produce inflammation
- a lung transplant for very severe cases

The long-term outlook for many cases of popcorn lung depends on the cause and how fast the disease worsens. Cases due to rheumatoid arthritis can have an especially poor outcome. It is important to work with a doctor to develop a treatment plan that is specific to the cause and other underlying health problems.

Popcorn lung is also a leading cause of death associated with heart-lung and lung transplants. An estimated 50 to 60 percent of those who survive 5 years after lung transplantation experience the most severe cases of popcorn lung.

Prevention

The best way to prevent popcorn lung is to avoid lung damage. It is crucial to avoid the factors known to increase or cause the condition.

Ways to prevent the chances of developing popcorn lung include:

- Not using e-cigarettes or other tobacco or vaping products, such as hookahs, especially those that use flavored products.
- Avoiding areas or environments where it is possible to inhale chemicals or toxins, such as construction, demolition, and manufacturing sites.
- Watching carefully for symptoms that may develop after organ transplants, especially lung, lung-heart, bone marrow, or stem cell transplants.

E-cigarettes are as bad as cigarettes, flavouring can impair lung function

hindustantimes.com/fitness/e-cigarettes-are-as-bad-as-cigarettes-flavouring-can-impair-lung-function/story-Kl4G1ps7vUUGlyjONW46CM.html

May 29, 2018

Do you think that e-cigarettes are a safer alternative to smoking? Beware, this latest study adds to evidence that they are not safe for you.

fitness Updated: May 29, 2018 11:56 IST

Soma Das

Hindustan Times

E-cigarette flavouring has toxic chemicals similar to those found in tobacco smoke. (Shutterstock)

For smokers looking to quit smoking, e-cigarettes often seem to be a viable alternative. But there are many disadvantages to e-cigarettes, and many studies raise doubts about its safety. A new study done by the University of North Carolina in the US shows that a common e-cigarette flavouring has toxic chemicals similar to those found in tobacco smoke. The chemicals can even disrupt the lungs' antibacterial defense system, the study has found.

Previous studies have shown that while people who use e-cigarettes smoke less and are more likely to quit smoking, they are also more likely to suffer from lung infection and liver problems. A study done by the Penn State suggested that the chemicals that make up different flavours in e-cigarettes also produce different levels of free radicals, toxins often associated with cancer and other diseases.

Aldehydes in cigarettes cause lung inflammation, and increase susceptibility to bacterial and viral infections. (Shutterstock)

What the study says

The data suggests that cinnamaldehyde used in e-cigarettes to give a cinnamon flavour/odour has an effect similar to the toxic aldehydes in cigarette smoke. While aldehydes cause lung inflammation, and increase susceptibility to bacterial and viral infections, cinnamaldehyde disrupts normal cell physiology in ways that can develop and increase levels of respiratory disease. "...(The findings) demonstrate that a common, food-safe flavouring agent, in the context of e-cigarette use, is capable of dysregulating a critical anti-bacterial defense system in the lungs," said Phillip Clapp, at the University of North Carolina in the US.

Researchers performed their experiment by exposing human bronchial epithelial cell (HBEC) cultures to diluted cinnamon e-liquids and e-liquid aerosols from a third generation e-cigarette device. "E-cigarette emissions contain chemicals that have not been evaluated for inhalation toxicities," said Clapp, adding, "The inhalation of flavouring agents poses a significant unknown in regards to the potential health risks of e-cigarette use, as many of these chemicals are structurally similar to toxic aldehydes in cigarette smoke," he said.

Moreover, aldehyde flavouring agents are often used in high concentrations in e-cigarettes, which may lead to high exposure doses, he said.

3 other ways to quit smoking

*** Money can help you quit the habit**

A study done by researchers from the University of Pennsylvania in the US shows that cash incentives are three times more effective to help smokers kick the butt than smoking cessation aids.

*** Watch this graphic video**

A North Carolina-based nurse Amanda Eller posted a couple of videos on Facebook that show the difference between healthy lungs and a black-coloured cancer-ridden lung. It is especially relevant in India, given latest reports suggesting 6.25 lakh children smoke cigarettes daily in India, according to the Tobacco Atlas report.

*** Use Facebook to motivate you**

A clinical trial done by the University of California-San Francisco (UCSF) shows that smokers were 2.5 times more likely to quit post a cessation intervention programme delivered entirely on Facebook than by other online quit-smoking programmes.

(With inputs from PTI)

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JAMA Pediatrics | Original Investigation

Association of Noncigarette Tobacco Product Use With Future Cigarette Smoking Among Youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015

Shannon Lea Watkins, PhD; Stanton A. Glantz, PhD; Benjamin W. Chaffee, DDS, PhD

IMPORTANCE Approximately 90% of adult smokers first tried a cigarette by 18 years of age, and even infrequent smoking in adolescence is associated with established adult smoking. Noncigarette tobacco use is increasing and could stimulate subsequent conventional cigarette smoking in youths.

OBJECTIVE To estimate the longitudinal association between noncigarette tobacco use and subsequent cigarette smoking initiation among US youth.

DESIGN, SETTING, AND PARTICIPANTS In this prospective cohort study of the Population Assessment of Tobacco and Health (PATH) waves 1 (September 12, 2013, to December 14, 2014) and 2 (October 23, 2014, to October 30, 2015), a nationally representative sample of youths who never smoked a conventional cigarette at baseline and completed wave 2 follow-up (N = 10 384) was studied. PATH retention at follow-up was 87.9%.

EXPOSURES Ever use and past 30-day use of electronic cigarettes (e-cigarettes), hookah, noncigarette combustible tobacco, or smokeless tobacco at baseline.

MAIN OUTCOMES AND MEASURES Ever use and past 30-day use of cigarettes at follow-up.

RESULTS The present analysis was based on the 10 384 PATH youth respondents who reported never having smoked a cigarette in wave 1 and whose cigarette ever or past 30-day use was reported in wave 2 (mean [SD] age, 14.3 [1.7] years; age range, 12-17 years; 5087 [49.1%] female; 4829 [52.5%] white). At 1-year follow-up, 469 (4.6%) of all baseline never-smoking youths had tried a cigarette and 219 (2.1%) had smoked a cigarette within the past 30 days. Cigarette ever use at follow-up was higher among youths who had ever used e-cigarettes (78 [19.1%]), hookah (60 [18.3%]), noncigarette combustible tobacco (45 [19.2%]), or smokeless tobacco (29 [18.8%]) at baseline. After adjusting for sociodemographic, environmental, and behavioral smoking risk factors and for baseline ever use of other tobacco products, the odds of past 30-day cigarette use at follow-up were approximately twice as high among baseline ever users of e-cigarettes (odds ratio [OR], 1.87; 95% CI, 1.15-3.05), hookah (OR, 1.92; 95% CI, 1.17-3.17), noncigarette combustible tobacco (OR, 1.78; 95% CI, 1.00-3.19), and smokeless tobacco (OR, 2.07; 95% CI, 1.10-3.87). Youths who had tried more than 1 type of tobacco product at baseline had 3.81 (95% CI, 2.22-6.54) greater adjusted odds of past 30-day cigarette smoking at follow-up than did baseline never tobacco users.

CONCLUSIONS AND RELEVANCE Any use of e-cigarettes, hookah, noncigarette combustible tobacco, or smokeless tobacco was independently associated with cigarette smoking 1 year later. Use of more than 1 product increased the odds of progressing to cigarette use.

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Supplemental content

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Approximately 90% of adult smokers used their first cigarette by 18 years of age,[1] and smoking as few as 1 cigarette per month in adolescence is associated with future daily smoking and smoking in adulthood.[2,3] In 2016, a total of 3.9 million middle and high school students were currently using at least 1 tobacco product, and 1.8 million reported using 2 or more products.[4] With increasing popularity among youths of noncigarette tobacco products, including electronic cigarettes (e-cigarettes) and hookah (tobacco waterpipe),[4] it is important to know whether use of these alternative products diverts youths from smoking conventional cigarettes or encourages smoking initiation. In addition to their direct health effects, how these products affect youth cigarette smoking is a major consideration in determining their net influence on public health.[5]

To our knowledge, no prospective study has simultaneously estimated the associations of e-cigarette, cigar, hookah, and smokeless tobacco product use with subsequent cigarette smoking initiation. A meta-analysis[6] of 9 longitudinal studies found that e-cigarette use by never-smoking adolescents was associated with approximately 4 times greater odds of future cigarette smoking. Two of the studies[7,8] controlled for baseline use of other noncigarette tobacco products, and 1 study[8] reported the association (baseline use of a tobacco product other than e-cigarettes was not associated with future cigarette smoking after adjusting for e-cigarette use). Other longitudinal studies found that smokeless tobacco use[9-11] and hookah use[11,12] were associated with cigarette initiation in youths. This is the first longitudinal study, to our knowledge, that simultaneously assessed e-cigarettes, hookah, noncigarette combustible tobacco, and smokeless tobacco as determinants of future cigarette smoking, including whether polyuse of noncigarette products has a greater association with future smoking compared with use of 1 product alone.

Key Points

Question Does noncigarette tobacco use among never-smoking youth determine subsequent cigarette smoking initiation?

Findings In this cohort study of the Population Assessment of Tobacco and Health, ever and past 30-day use of electronic cigarettes, hookah (tobacco waterpipe), noncigarette combustible tobacco, or smokeless tobacco was associated with cigarette initiation within 1 year.

Meaning Youths who use any tobacco product may be at greater risk of initiating cigarette smoking.

Methods

The Population Assessment of Tobacco and Health (PATH) study protocol received approval from the Westat Institutional Review Board and a National Institutes of Health certificate of confidentiality. Parental consent was requested on behalf of participating youths. Youths who completed the questionnaire were given $25. The University of California San Francisco Institutional Review Board exempted the present analysis from review. All data were deidentified.

Survey Population

The PATH study includes a nationally representative longitudinal cohort of 13 651 US youth ages 12 to 17 years at baseline with follow-up 1 year later.[13] We used PATH data to test the hypothesis that among youth who had never tried a cigarette at baseline, ever and past 30-day use of e-cigarettes, hookah, noncigarette combustible tobacco, or smokeless tobacco is associated with initiation of cigarette smoking (ever and past 30 days) within 1 year.

PATH questionnaires were administered through in-person computer-assisted interviews at home. Questionnaires included detailed self-assessments of behaviors related to 8 types of combustible and noncombustible tobacco and nicotine products: bidis, cigarettes, cigars (traditional, filtered, and cigarillos), e-cigarettes, hookah, kreteks, pipes, and smokeless tobacco (chewing tobacco, dissolvable tobacco, moist snuff, and snus).

The PATH study featured a 4-stage, stratified probability sample design. Adults (age ≥18 years, up to 2 per household) were oversampled for tobacco users, African American individuals, and young adults (age 18-24 years). The PATH youth sample consists of individuals whose parents were sampled for the PATH adult survey. Up to 2 youths were selected per household; sample and replicate weights were generated so that the sampled population reflected the noninstitutionalized youth population at baseline.

The wave 1 youth survey was administered from September 12, 2013, to December 14, 2014, and wave 2 from October 23, 2014, to October 30, 2015. Of 13 651 wave 1 youth participants, 11 996 completed wave 2 (unweighted retention, 87.9%), including 1915 individuals who reached 18 years of age before follow-up and were administered the wave 2 adult survey. The weighted wave 1 response rate for the youth survey was 78.4% among households screened for participation.[13]

Study Measures

We measured the outcome new cigarette initiation between waves 1 and 2 in 2 ways: (1) whether the respondent ever smoked a cigarette, even 1 or 2 puffs (ever use, yes/no), and (2) whether the respondent smoked a cigarette at least 1 day in the past 30 days (past 30-day use, yes/no). Because of low baseline prevalence of ever use for pipes, bidis, kreteks, snus, and dissolvable tobacco (all <1%), we created 4 categories of products: e-cigarettes, hookah, noncigarette combustible tobacco (bidis, cigarillos, filtered cigars, kreteks, pipes, and traditional cigars), and smokeless tobacco.

We defined wave 1 use of noncigarette tobacco products in 3 ways. First, we defined ever use as having used a product, even once or twice, regardless of use of any other tobacco product. Second, we divided ever use into former use and past 30-day use. Former use indicated having ever used a product but not having used in the prior 30 days. Third, we defined ever only use as having tried only a single product and no other tobacco product. Under this definition, respondents who had ever used 2 or more products comprised a separate category of poly-ever users.

The statistical analyses included baseline variables that were presumed to be causal influences of youth cigarette smoking that would be associated with but not caused by wave 1 use of noncigarette tobacco products.[14] We did not include mediators, such as perceived cigarette harm, cigarette social acceptability, and nicotine dependence. To account for variation in smoking across sociodemographic groups, we adjusted for sex, age, race/ethnicity (black or African American, Latino, or other), parental educational level (bachelor's degree or higher), and urban residence. The models included other established determinants of cigarette use: the extent to which the respondent was sensation seeking[15] (a score from 3 to 15 that aggregated three 5-point Likert-type measures of affinity for frightening things, new and exciting experiences, and exciting and unpredictable friends), had ever used alcohol, lived with a tobacco user, frequency of noticing health warning labels on cigarette packages (5-point scale from never to very often), and receptivity to tobacco advertising (measured by recalling the brand of their favorite tobacco advertisement).[16] We included whether the wave 1 questionnaire was administered during the summer to capture potential seasonal variation in tobacco use.

Statistical Analysis

We fitted weighted logistic regression models to obtain unadjusted and adjusted relative odds of wave 2 cigarette smoking initiation across groups of wave 1 noncigarette tobacco use. Each unadjusted model included all noncigarette tobacco products as risk indicators of future cigarette use. Adjusted models added baseline variables described above. All models used wave 2 sample weights that account for nonresponse (could not contact or refusal) so that the weighted sample reflected the US civilian household population at the time of wave 1.[17] We used multiple imputation by chained equations (30 imputations) to account for missing data in independent variables (0.9% of data). We calculated weighted, unadjusted prevalences of wave 1 tobacco use after imputation. Analyses were completed using Stata statistical software (version 14.2, StataCorp) and the svy and mi command suites.

We conducted 6 sensitivity analyses. First, we reestimated all model specifications using listwise deletion rather than multiple imputation. Then we repeated that analysis using PATH replicate weights in addition to sample weights. We reestimated the listwise deletion models adding wave 1 cigarette susceptibility[18] and marijuana ever use as model covariates. We estimated unadjusted and adjusted regressions for each noncigarette tobacco product determinant without controlling for other tobacco use. Finally, we estimated polytomous models with a categorical dependent variable of cigarette never, former, or past 30-day use.

Table 1. Characteristics of the Study Participants

Characteristic	No./Total No. (%)[a]
Wave 2	
Cigarette use initiation	
Cigarette ever use	469/10 384 (4.6)
Cigarette use in the past 30 d	219/10 380 (2.1)
Wave 1	
Ever use	
E-cigarettes	425/10 348 (4.2)
Hookah	339/10 365 (3.3)
Other combustibles	226/10 044 (2.3)
Smokeless	155/10 256 (1.6)
Past 30-d use	
E-cigarettes	87/10 329 (0.9)
Hookah	63/10 362 (0.6)
Other combustibles	59/10 031 (0.6)
Smokeless	NR[b]
Ever only use	
E-cigarettes only	255/9909 (2.6)
Hookah only	189/9909 (1.9)
Other combustibles only	114/9909 (1.1)
Smokeless only	93/9909 (1.0)
Polyuse (≥2 product types)	200/9909 (2.1)
Covariates[c]	
Female	5271/10 358 (49.1)
Age group, y	
12	1983/10 383 (18.9)
13	1979/10 383 (18.3)
14	1861/10 383 (17.6)
15	1704/10 383 (16.5)
16	1555/10 383 (15.2)
17	1301/10 383 (13.5)
Race/ethnicity	
White	4829/10 384 (52.5)
African American	1422/10 384 (13.9)
Latino	3009/10 384 (22.3)
Other	1124/10 384 (11.3)
Parent's educational level (bachelor's degree or higher)	4187/10 318 (44.8)
Urban residence	8359/10 384 (80.7)
Has ever used alcohol	3217/10 336 (32.2)
Lives with tobacco user	3212/10 292 (30.2)
Tobacco advertising receptivity	728/10 177 (7.2)
Questionnaire completed in the summer months	2701/10 384 (25.9)

Abbreviation: NR, not reported.

[a] Counts were calculated before multiple imputation, and percentages were weighted using wave 2 weights before multiple imputation.

[b] Results suppressed because of limited sample size.

[c] Additional covariates: sensation seeking, a score from 3 to 15 that aggregated three 5-point Likert-type measures of affinity for frightening things, new and exciting experiences, and exciting and unpredictable friends (n = 10 187; mean [SD], 7.6 [2.8]); noticed cigarette health warning, a score on a 5-point scale, with 1 indicating never and 5 indicating very often (n = 10 108; mean [SD], 2.0 [1.3]).

Results

Study Population

The present analysis was based on the 10 384 PATH youth respondents who reported never having smoked a cigarette in wave 1 and whose cigarette ever or past 30-day use was reported in wave 2 (mean [SD] age, 14.3 [1.7] years; age range, 12-17 years; 5087 [49.1%] female; 4829 [52.5%] white). At baseline, 851 (9.1%) of never-smoking youths had tried at least 1 noncigarette tobacco product and 242 (2.2%) had used at least 1 noncigarette tobacco product in the past 30 days (**Table 1**). The most commonly tried product was e-cigarettes. Ever use of 2 or more noncigarette tobacco products was reported by 200

Table 2. Associations of Noncigarette Tobacco Ever Use With Subsequent Cigarette Use

Wave 1 Use	No. of Observations Before Multiple Imputation	Wave 2 Cigarette Ever Use (n = 10 384)[a]			Wave 2 Cigarette Past 30-d Use (n = 10 380)[b]		
		Weighted, Unadjusted Cigarette Ever Use, %	OR (95% CI)		Weighted, Unadjusted Cigarette Past 30-d Use, %	OR (95% CI)	
			Model 1[c]	Model 2[d]		Model 3[c]	Model 4[d]
E-cigarettes							
Never	9923	3.9	1 [Reference]	1 [Reference]	1.8	1 [Reference]	1 [Reference]
Ever	425	19.1	3.50 (2.48-4.94)	2.53 (1.80-3.56)	8.2	2.39 (1.42-4.00)	1.87 (1.15-3.05)
Hookah							
Never	10 026	4.1	1 [Reference]	1 [Reference]	1.9	1 [Reference]	1 [Reference]
Ever	339	18.3	2.67 (1.81-3.93)	1.79 (1.23-2.62)	9.4	2.85 (1.69-4.79)	1.92 (1.17-3.17)
Noncigarette combustibles							
Never	9818	4.2	1 [Reference]	1 [Reference]	1.9	1 [Reference]	1 [Reference]
Ever	226	19.2	2.23 (1.42-3.49)	1.64 (1.06-2.54)	10.8	2.47 (1.36-4.47)	1.78 (1.00-3.19)
Smokeless							
Never	10 101	4.4	1 [Reference]	1 [Reference]	1.9	1 [Reference]	1 [Reference]
Ever	155	18.8	2.64 (1.60-4.35)	1.66 (1.00-2.76)	12.5	3.78 (2.07-6.89)	2.07 (1.10-3.87)

Abbreviation: OR, odds ratio.

[a] For cigarette use ever, the *F* statistic was 56.1 in model 1 and 24.6 in model 2, and the largest fraction of missing information was 0.011 in model 1 and 0.0186 in model 2.

[b] For past 30-day cigarette use, the *F* statistic was 36.8 in model 1 and 19.7 in model 2, and the largest fraction of missing information was 0.028 in model 1 and 0.032 in model 2.

[c] Model includes all ever tobacco use categories.

[d] Model includes all ever tobacco use categories and the following wave 1 covariates: female, age, race/ethnicity, parental educational level, urban residence, sensation seeking, alcohol ever use, living with tobacco user, notice of cigarette warning labels, tobacco advertising receptivity, and summer season. Coefficient values for adjustment variables are given in eTable 8 in the Supplement.

(2.1%) of youths, of whom 170 (73.9%) had tried e-cigarettes and 150 (64.8%) had tried hookah.

Cigarette Use Initiation

Of wave 1 never-smoking youths, 469 (4.6%) tried a cigarette for the first time between waves 1 and 2 and 219 (2.1%) had smoked a cigarette within the past 30 days at wave 2 (Table 1). Among youths who had never smoked a cigarette at baseline, adjusted odds of any cigarette use initiation were approximately double for ever users of e-cigarettes (odds ratio [OR], 2.53; 95% CI, 1.80-3.56), hookah (OR, 1.79; 95% CI, 1.23-2.62), noncigarette combustible tobacco (OR, 1.64; 95% CI, 1.06-2.54), and smokeless tobacco (OR, 1.66; 95% CI, 1.00-2.76) compared with never users (**Table 2**). Odds of past 30-day cigarette use at follow-up were also approximately double for ever users of e-cigarettes (OR, 1.87; 95% CI, 1.15-3.05), hookah (OR, 1.92; 95% CI, 1.17-3.17), noncigarette combustible tobacco (OR, 1.78; 95% CI, 1.00-3.19), and smokeless tobacco (OR, 2.07; 95% CI, 1.10-3.87) compared with never users.

Both former and past 30-day use of each baseline tobacco product was associated with cigarette initiation and past 30-day cigarette smoking in wave 2. In adjusted models, past 30-day use of e-cigarettes (OR, 2.65; 95% CI, 1.38-5.10; $P = .004$), hookah (OR, 2.58; 95% CI, 1.20-5.55; $P = .02$), and noncigarette combustibles (OR, 3.05; 95% CI, 1.37-6.77; $P = .006$) were significantly associated with subsequently trying cigarettes. Former use of e-cigarettes (OR, 2.58; 95% CI, 1.77-3.76; $P<.001$), hookah (OR, 1.54; 95% CI, 1.02-2.34; $P = .04$), and smokeless tobacco (OR, 2.26; 95% CI, 1.34-3.81; $P = .002$) were also independently associated with smoking initiation (**Table 3**). These ORs were similar for former and past 30-day use and similar to the ORs for ever use (Table 2). Baseline past 30-day use of noncigarette combustible tobacco was associated with 3 times greater odds of past 30-day cigarette use at follow-up compared with baseline combustible tobacco never use (Table 3). Former e-cigarette users had 1.84 times the odds of reporting wave 2 past 30-day cigarette use than e-cigarette never users.

Baseline ever exclusive use (ever only use) of noncigarette tobacco products was also positively associated with future cigarette smoking (**Table 4**). Youths who had used only e-cigarettes, used only hookah, or used only noncigarette combustibles had 2 to 3 times greater odds than tobacco never users of reporting cigarette ever use or past 30-day use 1 year later (Table 4). Baseline use of only smokeless tobacco was also positively associated with future smoking but was not statistically significant in the adjusted model (OR, 1.53; 95% CI, 0.56-4.19; $P = .41$). Ever use of 2 or more types of products (polyuse) was associated with nearly 4 times greater adjusted odds of ever using a cigarette (OR, 3.95; 95% CI, 2.65-5.90; $P < .001$) and past 30-day cigarette use (OR, 3.81; 95% CI, 2.22-6.54; $P < .001$).

There was little collinearity among baseline tobacco use variables (all variance inflation factors <1.4). Sensitivity analyses yielded similar findings to the main analyses (eTables 1-7 in the Supplement). Associations decreased in magnitude with adjustment for marijuana use (eTable 4 in the Supplement). The ORs not adjusted for other noncigarette tobacco products were consistently larger than the ORs with simultaneous control for other products (eTable 5 and eTable 6 in the Supplement).

Discussion

We report 3 central findings. First, youths who initiated tobacco use with noncigarette products were more likely to have smoked cigarettes 1 year later than were youths who had never used tobacco. Second, the ORs were of similar magnitude across

Table 3. Associations of Noncigarette Tobacco Current and Former Use With Subsequent Cigarette Use[a]

Wave 1 Use	No. of Observations Before Multiple Imputation	Wave 2 Cigarette Ever Use (n = 10 384)[b]			Wave 2 Cigarette Past 30-d Use (n = 10 380)[c]		
		Weighted, Unadjusted Cigarette Ever Use, %	OR (95% CI)		Weighted, Unadjusted Cigarette Past 30-d Use, %	OR (95% CI)	
			Model 1[d]	Model 2[e]		Model 3[d]	Model 4[e]
E-cigarettes							
Never	9923	3.9	1 [Reference]	1 [Reference]	1.8	1 [Reference]	1 [Reference]
Former	319	18.6	3.66 (2.52-5.32)	2.58 (1.77-3.76)	7.5	2.42 (1.40-4.19)	1.84 (1.07-3.15)
Past 30 d	87	23.8	3.61 (1.82-7.16)	2.65 (1.38-5.10)	11.6	2.48 (0.91-6.78)	2.08 (0.81-5.40)
Hookah							
Never	10 026	4.1	1 [Reference]	1 [Reference]	1.9	1 [Reference]	1 [Reference]
Former	273	16.4	2.32 (1.52-3.53)	1.54 (1.02-2.34)	8	2.39 (1.41-4.05)	1.57 (0.92-2.68)
Past 30 d	63	26.4	3.78 (1.69-8.44)	2.58 (1.20-5.55)	15	3.86 (1.24-12.0)	2.69 (0.91-7.98)
Noncigarette combustibles							
Never	9818	4.2	1 [Reference]	1 [Reference]	1.9	1 [Reference]	1 [Reference]
Former	154	15.4	1.65 (0.95-2.84)	1.22 (0.73-2.04)	7.8	1.68 (0.84-3.36)	1.23 (0.62-2.40)
Past 30 d	59	30.6	3.98 (1.91-8.32)	3.05 (1.37-6.77)	19.7	4.99 (1.92-13.0)	3.55 (1.27-9.93)
Smokeless							
Never	10 101	NR[f]	1 [Reference]	1 [Reference]	NR[f]	1 [Reference]	1 [Reference]
Former	114	NR[f]	3.19 (1.95-5.22)	2.26 (1.34-3.81)	NR[f]	4.48 (2.53-7.92)	2.83 (1.49-5.38)
Past 30 d	56	NR[f]	1.42 (0.25-8.00)	0.62 (0.14-2.77)	NR[f]	2.60 (0.33-20.3)	0.93 (0.18-5.38)

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio.

[a] Former use indicates having ever used the product but not within the past 30 days.

[b] For cigarette use ever, the *F* statistic was 30.4 in model 1 and 20.9 in model 2, and the largest fraction of missing information was 0.009 in model 1 and 0.021 in model 2.

[c] For past 30-day cigarette use, the *F* statistic was 17.8 in model 1 and 16.4 in model 2, and the largest fraction of missing information was 0.018 in model 1 and 0.033 in model 2.

[d] Model includes all former and past 30-day tobacco use categories.

[e] Model includes all former and past 30-day tobacco use categories and the following wave 1 covariates: female, age, race/ethnicity, parental educational level, urban residence, sensation seeking, alcohol ever use, living with tobacco user, notice of cigarette warning labels, tobacco advertising receptivity, and summer season. Coefficient values for adjustment variables are shown in eTable 9 in the Supplement.

[f] Results suppressed because of limited sample size.

products and between ever use (Table 2) and former and current use (Table 3), suggesting that any use of noncigarette tobacco, whether former or current, is similarly associated with future smoking. Ever users of multiple tobacco products were more likely to initiate smoking than were ever users of a single product, and product-specific associations with future smoking were essentially independent, suggesting that the risk of progressing to conventional cigarette smoking is increased with use of multiple forms of noncigarette tobacco.

Cigarette ever use is a meaningful outcome given that nicotine dependence can manifest in adolescents soon after their first puff, but other smoking milestones, such as daily smoking, can take years to develop.[19] Past 30-day use is the standard surveillance measure for current smoking among youths and is associated with smoking in adulthood.[2,3]

Recent scholarship has focused on the potential of e-cigarettes to engage youths in tobacco use.[6,20-22] Our findings confirm that use of the full range of tobacco products, including cigars, hookah, and smokeless tobacco, is associated with future cigarette smoking. E-cigarette use, combustible tobacco use, and noncombustible tobacco use have positively determined cigarette smoking intentions.[23] Our findings confirm that use of these products is also independently associated with greater odds of future cigarette smoking.

The OR point estimates in models that simultaneously accounted for use of all noncigarette tobacco products are generally smaller than previously reported associations. For example, we estimated that ever use of e-cigarettes was associated with 2.53 times greater odds of subsequent cigarette use (Table 2), which is lower than the summary OR of 3.62 (95% CI, 2.24-5.41) reported in a meta-analysis[6] of 7 longitudinal studies, although the 95% CIs overlap. We estimated an OR of 1.79 for the association between hookah ever use and subsequent cigarette ever use, whereas Soneji and colleagues[11] estimated an OR of 2.56 (95% CI, 1.46-4.47). These differences likely occurred because in our sample, 40% of youths who used e-cigarettes and 44% of youths who used hookah were poly-tobacco users. Not accounting for poly-tobacco use will overestimate the magnitude of the effects of e-cigarettes or hookah alone. A sensitivity analysis without other tobacco use variables yielded similar adjusted odds of subsequent cigarette smoking as reported in other studies (ORs of 3.24 [95% CI, 2.35-4.48] for e-cigarettes and 2.59 [95% CI, 1.82-3.68] for hookah).

Adolescent use of noncigarette tobacco increased between 2011 and 2015, particularly use of e-cigarettes and hookah.[24] In the past decade, the rate of decrease in youth smoking has slowed.[24] Poly-tobacco users comprise nearly half of all youth tobacco users[4]; in our study, having tried more than 1 noncigarette tobacco product had a greater association with future smoking than did ever use of a single tobacco product. In light of these observed associations between noncigarette tobacco use and future smoking, novel tobacco products have the potential to undermine public health gains in combatting the smoking epidemic.

Table 4. Associations of Noncigarette Tobacco Single-Product Ever Use and Polyuse With Subsequent Cigarette Use

Wave 1 Use	No. of Observations Before Multiple Imputation	Wave 2 Cigarette Ever Use (n = 10 384)[a]			Wave 2 Cigarette Past 30-d Use (n = 10 380)[b]		
		Weighted, Unadjusted Cigarette Ever Use, %	OR (95% CI)		Weighted, Unadjusted Cigarette Past 30-d Use, %	OR (95% CI)	
			Model 1[c]	Model 2[d]		Model 3[c]	Model 4[d]
Never use	9058	3.5	1 [Reference]	1 [Reference]	1.6	1 [Reference]	1 [Reference]
E-cigarettes only	255	15.3	4.98 (3.39-7.31)	2.99 (1.98-4.53)	5.4	3.59 (1.96-6.60)	2.12 (1.11-4.03)
Hookah only	189	13.6	4.35 (2.79-6.76)	2.35 (1.46-3.77)	6.3	4.17 (2.24-7.78)	2.15 (1.11-4.16)
Combustibles only	114	11.4	3.57 (1.96-6.48)	2.14 (1.14-4.04)	7.9	5.34 (2.65-10.8)	3.08 (1.43-6.66)
Smokeless only	93	12	3.77 (1.97-7.24)	1.88 (0.91-3.86)	6.4	4.28 (1.72-10.6)	1.53 (0.56-4.19)
Polyuse	200	23.7	8.57 (6.00-12.20)	3.95 (2.65-5.90)	12.4	8.86 (5.54-14.20)	3.81 (2.22-6.54)

Abbreviation: OR, odds ratio.

[a] For cigarette use ever, the *F* statistic was 46.0 in model 1 and 24.0 in model 2, and the largest fraction of missing information was <0.001 in model 1 and 0.019 in model 2.

[b] For past 30-day cigarette use, the *F* statistic was 24.4 in model 1 and 18.38 in model 2, and the largest fraction of missing information was <0.001 in model 1 and 0.030 in model 2.

[c] Model includes all ever-only and poly–tobacco use categories.

[d] Model includes all ever-only and poly–tobacco use categories and the following wave 1 covariates: female, age, race/ethnicity, parental educational level, urban residence, sensation seeking, alcohol ever use, living with tobacco user, notice of cigarette warning labels, tobacco advertising receptivity, and summer season. Coefficient values for adjustment variables are shown in eTable 10 in the Supplement.

Multiple factors could explain our findings. Nontobacco cigarette products might induce nicotine dependence, symptoms of which have been reported by youths who use tobacco, including cigars and smokeless tobacco, as few as 1 to 5 days per month.[25] Youths who use noncigarette tobacco products find conventional cigarettes to be more convenient and effective in satisfying nicotine cravings.[12,26,27] Use of noncigarette tobacco could change how youths perceive cigarettes. Of all tobacco products, adolescents generally perceive cigarettes to convey the most health risks.[28,29] In a Monitoring the Future follow-up sample, among youth never-smokers who reported that cigarettes pose great risk, baseline e-cigarette users were approximately 4 times more likely than e-cigarette nonusers to later change their cigarette harm perception away from great risk.[30] A structural modeling analysis found other social mediators between youth e-cigarette use and subsequent smoking: perceived benefits of smoking, social affiliation with smokers, and favorable opinions of cigarette smoking peers.[22] Alternatively, our findings might reflect a general propensity toward tobacco use or risk taking: youths who try noncigarette tobacco may be likely to smoke cigarettes regardless of other product use. However, when we accounted for confounders, including risk-taking affinity (sensation seeking), meaningful and statistically significant associations between other tobacco use and cigarette smoking persisted. Other studies[11,31] have also found consistent associations after adjusting for confounders.

A proposed catalyst model comprehensively summarizes possible causal pathways from initial use of e-cigarettes to tobacco smoking among youths.[32] This model includes e-cigarette characteristics initially favored by youths (eg, flavors, social acceptability, and lower perceived harm) before transition to smoking through nicotine dependence, sensorimotor stimulation, increasing accessibility, and other pathways.[32] Similarly comprehensive models are lacking for other noncigarette tobacco products, but factors such as flavors and nicotine experiences may apply analogously.

Future work could directly compare these proposed mechanisms by observing patterns of use, addiction, risk perception, and subsequent smoking longitudinally. Regardless of the explanation for the observed associations, this study found that any noncigarette tobacco use is significantly associated with risk of future cigarette use. Given the heterogeneity of polyuse patterns among adolescents, future work should explore distinct patterns of polyuse and their implications for future cigarette use.

Limitations

Lack of statistical significance in adjusted models of baseline past 30-day tobacco use to determine wave 2 past 30-day cigarette use may reflect power limitations. Despite the large sample size of PATH overall, the number of past 30-day users of some products limited statistical power. By analyzing ever use, past 30-day use, and ever only use, this analysis demonstrated that measurement choice in defining risk variables is not a major determinant of study findings.

The PATH study has strong external validity, featuring a large, nationally representative sample with excellent retention. The longitudinal design and multiple imputation for missing covariate data further strengthen the internal validity of this analysis. Despite these advantages, residual confounding is possible, as is true in any observational study, despite statistical adjustment for known youth smoking risk factors and for baseline use of the other tobacco products. In-home, computer-assisted interviews used in PATH may have resulted in different prevalence estimates compared with in-school surveys, with an unknown effect on associations between noncigarette tobacco use and cigarette use initiation.

Conclusions

Although e-cigarettes are the most common form of noncigarette tobacco used by youths (exceeding cigarette use), any use of all forms of noncigarette tobacco was independently associated with greater risk of future cigarette smoking; risk was greatest with use of multiple products, a use pattern that is increasing among youths. Strategies to prevent cigarette use initiation in youths, such as pack size requirements and flavor restrictions, should be extended to other tobacco products. Even for

youths who had not used tobacco recently, having ever tried a noncigarette product at any point was associated with smoking initiation within a year. This study's findings provide evidence that despite their differences, disparate alternative-cigarette products contribute to a similar process that leads to cigarette use initiation. In policy terms, the findings provide a rationale to treat alternative cigarette products as a group and potentially extend policies that work for one product to the others (such as a ban on flavoring). Even if youths do not progress to smoking cigarettes, any tobacco use is harmful. The estimated health risks of noncigarette tobacco products should include the additional health consequences of future cigarette use.

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