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Daughters of mothers who smoke: A population-based cohort study of maternal prenatal tobacco use and subsequent prenatal smoking in offspring

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Abstract

Background—Prenatal exposure to tobacco is associated with adverse health outcomes for the mother and child, and has been associated with an increased risk of tobacco smoking and nicotine dependence in offspring. The objective of this study was to examine the risk of prenatal smoking, among daughters, associated with maternal prenatal smoking.

Methods—We used a population-based cohort study design, with linked vital records data of mothers and daughters delivering 1984–1996 and 1996–2013, respectively, in Washington State. The exposure of interest was mothers' prenatal smoking (any versus no smoking at any time during pregnancy), while the outcome was daughters' prenatal smoking (similarly assessed). We used multivariable log-binomial regression to obtain estimates of the relative risk (RR) and 95% confidence interval (CI).

Results—Daughters exposed to maternal prenatal smoking were more likely to smoke during their pregnancy, compared to unexposed daughters (RR = 1.78; 95% CI: 1.72, 1.84, adjusted for the year the daughter delivered, her marital status and educational attainment, and the mothers' race/ethnicity).

Conclusions—In this relatively young population, we found that daughters exposed to maternal prenatal smoking have an increased risk of smoking later on during their own pregnancy, emphasizing the importance of exposures during the prenatal period. The mechanisms leading to prenatal smoking are multifactorial and likely include behavioral, genetic, epigenetic and environmental factors. An understanding of this risk factor for prenatal smoking may guide healthcare providers to better target smoking cessation interventions to at-risk populations.

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Competing Interests

None

INTRODUCTION

Prenatal exposure to tobacco is associated with adverse health outcomes for the mother and child, including obstetric complications, low birthweight, restricted fetal growth, sudden infant death syndrome, acute lower respiratory infections, reduced lung function,¹ behavioral problems in early childhood and young adulthood,^{2,3} and an increased risk of tobacco smoking and nicotine dependence in offspring.² In spite of these risks, in 2013 an estimated 9% of women in the United States (US) smoked during pregnancy. Rates have decreased from 20% in 1989, but there still remain disparities by race/ethnicity and socioeconomic status. American Indian/Alaska Native (18%) and non-Hispanic white mothers (12%), and those with a ninth to twelfth grade (17%) and only high school education (14%) have higher rates of prenatal smoking.⁴

Nicotine acetylcholine receptors in the fetal brain develop early in gestation. With nicotine easily crossing the placenta, exposure to nicotine is high among infants of smoking mothers,⁵ resulting in alterations in fetal brain development and, possibly, in behavior later in life.⁶ Daughters of mothers who smoked prenatally and after delivery have a greater probability of tobacco experimentation and early smoking initiation, and early initiation is associated with higher daily tobacco consumption and a lower likelihood of quitting.⁶ It is proposed that the mesolimbic dopamine system is involved in nicotine reinforcement, predisposing the infant to nicotine addiction when consumed years later.⁷ There is evidence supporting an association between mothers' tobacco smoking and offspring risk of tobacco use (cigarette smoking or smokeless tobacco) during adolescence and young adulthood;^{2,8–11} however, the risk of prenatal smoking among women who were themselves exposed to tobacco constituents *in utero* is not known. The purpose of this cohort study was to determine the risk of prenatal smoking among women whose mothers smoked during pregnancy relative to those whose mothers did not smoke during pregnancy.

METHODS

Study setting and population

We conducted a population-based cohort study using linked birth records of mothers and daughters delivering in Washington State from 1984–1996 and 1996–2013, respectively. We identified mother-daughter pairs with complete prenatal smoking data for the mothers' delivery of the daughter and the daughters' first singleton delivery on record, and restricted the sample to one observation per mother – her first-born singleton live-born daughter on record, if multiple births were recorded, and the daughters' first singleton delivery on record (live birth or fetal death >20 weeks gestation, regardless of parity or gravidity). For the vast majority of daughters (>94%) this was their first-ever delivery, and a live birth (>99%). This study was approved by the Washington State Institutional Review Board.

Data collection

Data were obtained from the Washington State birth and fetal death certificates, which contain information about maternal and paternal characteristics, the pregnancy and delivery, and infant/delivery outcomes. A variable for maternal smoking during pregnancy was

included in the Washington birth certificate starting in 1984. Longitudinal linkage of birth/fetal records, including for intergenerational studies,¹² has been conducted for research projects in the State for many years based on identifiers within the vital record using a combination of sequential deterministic and probabilistic steps. Identifiers such as first, last, and middle names of mother and infant; mother's maiden name and father's name; and dates of birth from the maternal birth records of 1984–1996, were used to link birth and fetal death records of female offspring born 1996–2013. Initially, 74,314 mother-daughter pair units were identified as potential subjects. Of these, 4,630 had missing prenatal smoking information for mother or daughter and an additional 5,572 pairs were excluded because they represented subsequent female siblings born to the same mother, resulting in a total of 64,112 unique mother-daughter pairs for analysis.

Our exposure of interest was mothers' prenatal smoking, operationalized as any versus no smoking at any time during pregnancy. The outcome (daughters' prenatal smoking status) was similarly assessed.

Statistical analysis

Because our outcome was not rare, we used multivariable log-binomial regression to estimate the relative risk (RR) and 95% confidence intervals (CI)¹³ of the association between daughters' prenatal smoking and mothers' prenatal smoking, adjusted for year in which the daughter delivered (as a continuous variable), to control for possible cohort effects. Other factors from the vital records for the mothers' and daughters' pregnancies that were considered as potential confounders included both mothers' and daughters' self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Native American, non-Hispanic Asian, and non-Hispanic Native Hawaiian and other Pacific Islander), age (as a continuous variable, and categorically as < 20, 20–24, 25–34, 35+ years), marital status (married, unmarried), trimester of prenatal care initiation, number of prior births and number of prior pregnancies (0, 1, 2+), daughters' birth year (as a continuous variable, and categorically as 1984, 1985–1989, 1990–1994, 1995–1996), and daughters' educational attainment (< high school, high school graduate, some college, and at least a bachelor's degree). Education was only available for deliveries occurring 1992 or later, therefore mothers' educational attainment could not be assessed. There was little data missing for most variables: <1% for all other variables except daughters' education (1.1%) and parity (1.7%), and daughters' (8.1%) and mothers' (2.8%) trimester of first prenatal care.

We assessed the bivariate associations of the potential confounders with the outcome and exposure, and identified those associated with both. After adjustment for daughter's year of delivery (as a continuous variable), the other factors were assessed for their effects on the risk estimate. Factors that altered the RR by 10% or greater were considered to confound the relationship between the exposure and outcome and were adjusted for;¹⁴ only daughters' marital status and educational attainment, and mothers' race/ethnicity met this criterion. We also recalculated the RR after excluding the 271 pairs in which the daughter's pregnancy resulted in a fetal death, to examine the effect of any potential bias in results by including daughters who may have altered their smoking behavior during pregnancy due to high risk

pregnancies that resulted in fetal deaths. In order to examine whether the magnitude of this association varied by selected characteristics which could begin to inform future development of smoking prevention strategies, we also explored possible differences in the association by mothers' race/ethnicity and daughters' age (< 20, ≥ 20 years). We explored these possible differences initially by stratification to examine stratum-specific adjusted RRs and subsequently by inclusion of relevant interaction terms in the models and using Wald's test to obtain P-values to assess possible effect modification. Analyses were performed using Stata 13.1 (College Station, TX).

RESULTS

In this cohort study (N=64,112), 32% of mothers smoked during their pregnancy; 29% of daughters with mothers who smoked, also smoked during their pregnancy, compared to 12% of daughters whose mothers did not smoke (Tables 1A, 1B). Mothers and daughters who smoked were more likely to be non-Hispanic white, younger, unmarried, multigravida, and less likely to initiate prenatal care in the first trimester. Daughters who smoked also had lower levels of educational attainment.

Daughters exposed to maternal prenatal smoking were more likely to smoke during their own pregnancy, than were unexposed daughters (adjusted RR = 1.78; 95% CI: 1.72, 1.84) (Table 2; see Appendix for adjusted RRs for all covariates). This result was not altered by exclusion of the 271 mother-daughter pairs in which the daughter's pregnancy resulted in a fetal death [data not shown]. The RRs for this association remained increased in daughters aged <20 and ≥ 20 years, the estimates for these subgroups were not statistically significantly different (interaction P = 0.819). All of the race-specific RRs were increased, with the greatest magnitude observed for Hispanic (RR = 7.02; 95% CI: 5.25, 9.40) and Asian (RR = 2.44; 95% CI: 1.80, 3.31) daughters, the only groups with estimates statistically significantly different from whites (interaction P < 0.001 and P = 0.017, respectively).

COMMENTS

Our results demonstrate an intergenerational association of mothers' and daughters' smoking habits during pregnancy, indicating that daughters with fetal tobacco exposure are more likely to smoke during their own pregnancy compared to those whose mothers did not smoke during their pregnancy. Although not specifically focused on daughters' prenatal smoking as an outcome among offspring, other studies examining maternal prenatal smoking and offspring risk of smoking during adolescence and young adulthood report similar findings. An offspring-of-twins retrospective cohort study in the US reported an odds ratio (OR) = 1.74 [95% CI: 1.18, 2.58] for regular smoking among adolescent and adult offspring (ages 12–32 years) born to mothers who smoked during pregnancy;¹⁵ and a prospective cohort study in Australia reported an OR = 1.53 [95% CI: 1.19, 1.96] for nicotine dependence or withdrawal among 21 year olds born to mothers who smoked during pregnancy.¹⁶ As the majority of prenatal smokers continue smoking after delivery,¹⁷ it is possible that these observed associations may be at least partly due to indirect behavioral effects (vs. direct physiological fetal effects) among children growing up with smoking vs. non-smoking

mothers. However, a population-representative study using data from the US Children and Young Adults of the National Longitudinal Survey of Youth 1979 cohort examined possible indirect behavioral effects by separately assessing the risks of smoking (early initiation at 14–16 years of age; early experimentation; and late initiation at 16+ years) in children of prenatal smokers who did and did not quit smoking after delivery, relative to children of nonsmoking mothers and reported similarly increased (1.6- to 2.8-fold) ORs regardless of whether maternal smoking stopped after delivery, suggesting that one pathway for intergenerational transmission of smoking via maternal prenatal smoking likely involves a direct physiological mechanism.¹⁸

One likely biologic pathway to explain our findings relates to nicotine, an organic alkaloid and the active component of tobacco.¹⁹ Nicotine addiction may be mediated by both environmental factors²⁰ and multiple genes that together influence exposure, nicotine metabolism, habit formation, and reinforcement of addiction.²¹ Nicotine acts on cell membrane-bound acetylcholine receptors encoded in multiple genes and distributed throughout the body, including neurons.¹⁹ These receptors are present in high concentrations in brain regions that moderate nicotine reward, tolerance, sensitization, and addiction via regulation of brain monoamine levels, including norepinephrine and dopamine.²² Neuronal acetylcholine receptors affect fetal brain development through effects on synaptic transmission and plasticity.²³ Genome-wide association studies have identified gene variations on chromosomes 1, 8, 15, and 20 that produce acetylcholine receptor subunits and are associated with nicotine addiction.¹⁹ One variation, rs2304297, potentially interacts with prenatal exposure to maternal smoking to influence fetal brain structure, adolescent smoking initiation, and lifelong smoking.²⁴

Our observation that the greatest RR of smoking in relation to maternal prenatal smoking exposure was among Hispanic and Asian mothers may be due to their generally lower levels of prenatal smoking.²⁵ However, it is also possible that racial differences in nicotine metabolism^{26,27} or other biological or environmental factors may be partly responsible for this difference.

Our study has limitations; we excluded mother-daughter pairs wherein either woman had no smoking information on the birth record. If these women are more likely to have been smokers, then the risk may be underestimated. Although variables existed in these data to indicate the median income levels of residence census tract, we were unable to evaluate the possible effects of income level or poverty due to missing data for 50% of mothers and 30% of daughters. We were also unable to assess the possible influence of mothers' education, nor were we able to examine specific smoking characteristics such as the number of cigarettes smoked daily, or patterns of smoking by trimester, as the data were not available for the mothers, and were only available for daughters with deliveries since 2003. Self-reported smoking on birth records is less accurate than biochemical assays of nicotine exposure;²⁸ inconsistent results have been reported in validity studies comparing self-reported smoking on birth certificates to cotinine levels obtained from dried blood spots collected at newborn screening, although data from Washington State²⁹ suggest this is less problematic in studies (such as ours) considering birth certificate-reported smoker status dichotomously, rather than in assessments of smoking dose or cessation. Individuals may

under-report smoking behavior due to social desirability, leading to the possibility of misclassification of exposure and outcome. We suspect that the older generation's smoking is more likely to be accurately reported than the younger's due to the increasing stigma associated with smoking over time, and that daughters will equally misreport smoking regardless of their maternal prenatal exposure status. The direction of bias as a consequence of underreporting of prenatal smoking by the daughter is unknown. Due to the years of our study, the daughters we studied were relatively young, and thus had lower educational attainment and were more likely to be unmarried than if we had been able to include a longer time period. Therefore, to the degree that maternal age or education influences prenatal smoking, and possibly for other reasons, our results may not be generalizable to daughters who deliver at older ages.

The data linkage procedures we used were similar to those we have used earlier, which resulted in successful linkage of 89% of maternal and offspring birth records.¹² However, errors may have occurred. We examined potential effect modification by mother's race/ethnicity, but observed some differences in race/ethnicity between the mother and daughter, likely due to discordant parental race/ethnicity, but also possibly at least partly due to errors in data linkage. Additionally, we were unable to consider the influence of daughters' exposure to environmental tobacco smoke during early childhood or any environmental and genetic factors that could contribute risk or confound the association.³⁰ Thus, our findings likely reflect the influences of exposure to a smoking parent during childhood,³¹ as well as unmeasured environmental/behavioral, genetic, and background familial factors.^{32,33}

Children with fetal tobacco exposure from maternal smoking may be predisposed to later tobacco addiction, with subsequent increased risk for multiple adverse health effects; among girls, this cycle appears likely to be repeated in their own subsequent pregnancies. Pregnancy and early childhood/infancy offer potential windows for interventions by health care professionals to decrease smoking in mothers and children, and there is some evidence that selected interventions (e.g., maternal postpartum smoking relapse prevention) may be effective.³⁴ Interventions targeted at young children, prior to the initiation of risky behaviors in adolescence, would be particularly novel. Animal studies suggest that behavioral and environmental interventions can moderate the effect of epigenetic changes induced by harmful exposures.³⁵ Future studies with more detailed information on amount and timing of *in utero* and early childhood tobacco exposure, and genetic variants data could further elucidate the relationship between mothers and daughters smoking during pregnancy.

Conclusion

Daughters exposed to maternal prenatal smoking were more likely to smoke during their own pregnancy. The results of this study, which identify this novel risk factor for prenatal smoking in a population of young women, may guide healthcare providers to better target smoking cessation interventions to at-risk populations. In order to reduce adverse health effects of smoking and its effects on offspring, it will be important to identify strategies for intervening in this cycle of intergenerational smoking. The relevant mechanisms for this association, which appear to be consistent across age, and generally across race/ethnic categories, likely include nicotine-induced alterations of the fetal brain, as well as genetic,

epigenetic, and environmental factors, although further studies are needed of women of all ages to more fully evaluate possible mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1A

Characteristics of Mothers in Washington State Delivering Daughters Born 1984–1996, by Prenatal Smoking Status

Mothers	Mothers did not smoke N = 43,639	Mothers smoked N = 20,473
	n (%)	n (%)
Race/ethnicity ^a		
White ^b	33,533 (77.5)	17,893 (88.1)
Black ^b	1,530 (3.5)	772 (3.8)
Hispanic	5,319 (12.3)	423 (2.1)
Native American ^b	1,512 (3.5)	971 (4.8)
Asian ^b	1,283 (3.0)	222 (1.1)
NHOPI ^{b,c}	87 (0.2)	33 (0.2)
Age (years) ^d		
<20	7,100 (16.3)	4,177 (20.4)
20–24	14,469 (33.2)	7,602 (37.2)
25–34	19,563 (44.9)	7,938 (38.8)
35+	2,460 (5.6)	731 (3.6)
Marital status ^e		
Married	32,402 (74.4)	11,198 (54.8)
Unmarried	11,159 (25.6)	9,235 (45.2)
Trimester of first prenatal care ^f		
First	32,432 (76.3)	13,847 (69.6)
Second	8,253 (19.4)	4,898 (24.6)
Third	1,809 (4.3)	1,163 (5.8)
Number of prior live births ^g		
0	18,054 (41.4)	7,986 (39.0)
1	13,295 (30.5)	6,797 (33.2)
2+	12,224 (28.1)	5,682 (27.8)
Daughters' birth year		
1984	7,312 (16.8)	2,914 (14.2)
1985–1989	24,516 (56.2)	12,491 (61.0)
1990–1994	10,938 (25.1)	4,760 (23.3)
1995–1996	873 (2.0)	308 (1.5)
Census tract median income ^h		
<\$15,000	940 (4.5)	544 (5.4)
\$15,000	20,204 (95.6)	9,589 (94.6)

^aMissing for 375 unexposed (mother did not smoke) and 159 exposed (mother smoked)

^bNon-Hispanic ethnicity;

^cNHOPI: Native Hawaiian and other Pacific Islander

^dMissing for 47 unexposed and 25 exposed

^eMissing for 78 unexposed and 40 exposed

^fMissing for 1,145 unexposed and 565 exposed

^gMissing for 66 unexposed and 8 exposed

^hMissing for 22,495 unexposed and 10,340 exposed.

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Table 1B

Characteristics of Daughters Born in Washington State, Delivering 1996–2013, by Their Mothers' Prenatal Smoking Status

	Mothers did not smoke N = 43,639	Mothers smoked N = 20,473
Daughters	n (%)	n (%)
Prenatal smoking		
Did not smoke	38,434 (88.1)	14,451 (70.6)
Smoked	5,205 (11.9)	6,022 (29.4)
Race/ethnicity ^a		
White ^b	31,202 (71.8)	16,649 (81.7)
Black ^b	2,015 (4.6)	1,092 (5.4)
Hispanic	7,513 (17.3)	1,463 (7.2)
Native American ^b	1,458 (3.4)	945 (4.6)
Asian ^b	1,148 (2.6)	201 (1.0)
NHOPI ^{b,c}	125 (0.3)	31 (0.2)
Age		
<20	15,622 (35.8)	8,922 (43.6)
20–24	20,397 (46.7)	9,237 (45.1)
25–29	7,620 (17.5)	2,314 (11.3)
Education ^d		
< High school	10,797 (25.0)	7,387 (36.5)
High school	14,267 (33.0)	7,553 (37.3)
Some college	14,196 (32.8)	4,767 (23.5)
Bachelor's degree+	3,989 (9.2)	548 (2.7)
Marital Status ^e		
Married	15,142 (34.8)	4,363 (21.4)
Unmarried	28,400 (65.2)	16,052 (78.6)
Trimester of first prenatal care ^f		
First	31,254 (77.4)	14,141 (75.2)
Second	7,480 (18.5)	3,849 (20.5)
Third	1,670 (4.1)	822 (4.4)
Number of prior live births ^g		
0	40,758 (94.7)	18,853 (93.7)
1	1,831 (4.3)	983 (4.9)
2+	458 (1.1)	281 (1.4)
Infants' birth year		
1996–1999	80 (0.2)	47 (0.2)
2000–2004	3,733 (8.6)	2,649 (12.9)
2005–2009	17,013 (39.0)	9,136 (44.6)

	Mothers did not smoke N = 43,639	Mothers smoked N = 20,473
Daughters	n (%)	n (%)
2010–2013	22,813 (52.3)	8,641 (42.2)
Census tract median income ^h		
<\$20,000	488 (1.6)	311 (2.0)
\$20,000	29,924 (98.4)	15,335 (98.0)

^aMissing for 178 unexposed (mother did not smoke) and 92 exposed (mother smoked)

^bnon-Hispanic ethnicity

^cNHOPI: Native Hawaiian and other Pacific Islander

^dMissing for 390 unexposed and 218 exposed

^eMissing for 97 unexposed and 58 exposed

^fMissing for 3,235 unexposed and 1,661 exposed

^gMissing for 592 unexposed and 356 exposed

^hMissing for 13,227 unexposed and 4,827 exposed

Table 2

Prenatal Smoking Risk in Relation to Maternal Prenatal Smoking Status, by Selected Characteristics

	Daughter smoked during pregnancy		Adjusted
	N	n (%)	RR (95% CI)
Overall ^a			
Mother didn't smoke	43,639	5,205 (11.9)	1.0
Mother smoked	20,473	6,022 (29.4)	1.8 (1.7, 1.8)
Mothers' Race ^b			
White ^c			
Mother didn't smoke	33,533	4,598 (13.7)	1.0
Mother smoked	17,893	5,465 (30.5)	1.7 (1.7, 1.8)
Black ^c			
Mother didn't smoke	1,530	118 (7.7)	1.0
Mother smoked	772	110 (14.2)	1.9 (1.5, 2.4)
Hispanic			
Mother didn't smoke	5,319	110 (2.1)	1.0
Mother smoked	423	66 (15.6)	7.0 (5.3, 9.4)
Native American ^c			
Mother didn't smoke	1,512	224 (14.8)	1.0
Mother smoked	971	281 (28.9)	1.9 (1.6, 2.2)
Asian ^c			
Mother didn't smoke	1,283	106 (8.3)	1.0
Mother smoked	222	49 (22.1)	2.4 (1.8, 3.3)
NHOPI ^{cd}			
Mother didn't smoke	87	7 (8.0)	1.0
Mother smoked	33	6 (18.2)	1.5 (0.5, 4.3)
Daughters' Age ^a			
< 20 years			
Mother didn't smoke	15,622	2,103 (13.5)	1.0
Mother smoked	8,922	2,763 (31.0)	1.8 (1.7, 1.9)
20 years			
Mother didn't smoke	28,017	3,102 (11.1)	1.0
Mother smoked	11,551	3,259 (28.2)	1.7 (1.6, 1.8)

^a Adjusted for daughters' marital status, educational attainment, delivery year, and mothers' race^b Adjusted for daughters' marital status, educational attainment, and delivery year^c non-Hispanic ethnicity^d NHOPI: Native Hawaiian and other Pacific Islander