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Early-life exposure to cigarette smoke and adult-onset SLE

Julia F. Simard^{1,2}, Karen H. Costenbader^{3,4}, Matthew H. Liang^{3,5}, Elizabeth W. Karlson^{3,4}, and Murray A. Mittleman^{1,2}

¹ Department of Epidemiology, Harvard School of Public Health, Boston, MA

² Cardiovascular Epidemiology Research Unit, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

³ Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, MA

⁴ Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁵ Massachusetts Veterans Epidemiology and Research Center, Boston, MA

Abstract

Objective—One's own cigarette smoking is a risk factor for systemic lupus erythematosus (SLE), and recent work has demonstrated that early-life smoke exposure was related to the risk of related rheumatic conditions in female children. Therefore, we sought to investigate whether early-life cigarette smoke exposure might be associated with incidence of SLE in adult women.

Methods—We studied 93,054 NHS and 95,554 NHSII participants free of SLE at baseline who provided information on perinatal exposures. By medical record review 236 incident SLE cases were confirmed (142 NHS and 94 NHSII) among these women using American College of Rheumatology criteria. We used stratified Cox models to estimate the association of smoke exposure with SLE adjusting for race, birth weight, preterm birth, and parents' occupation. Combined estimates were computed using random effects meta-analytic techniques..

Results—Maternal cigarette smoking did not increase the risk of SLE (RR=0.9, 95% CI: 0.6 to 1.4) nor did paternal smoking during the participant's childhood (RR=1.0, 95% CI: 0.8 to 1.3) in combined analyses.

Conclusion—Early-life exposure to cigarette smoke due to mothers' or fathers' smoking does not increase the risk of adult-onset SLE in women.

Introduction

Cigarette smoke exposure through active smoking, as well as passive and chronic second-hand smoke have documented health consequences. Exposure to cigarette smoke *in utero* has had far less study but is identified as a risk factor for cognitive dysfunction (1), asthma (2,3), and obesity (4,5). Fetal exposure to smoke has a number of biological and clinical effects, which may play a role in systemic rheumatic diseases. Fetal exposure to tobacco smoke affects hypothalamic-pituitary-adrenal axis functioning(6,7) disturbs regulatory T-cell development (8,9); elevates the risk of low birth weight or preterm status (10); and increases the permeability of the placenta to viral antigens (11–13). Maternal smoking during pregnancy is associated with increased risk of autoimmune rheumatic diseases

including adult-onset rheumatoid arthritis (RA), juvenile RA, and other inflammatory polyarthropathies in offspring(14) (15); however, maternal smoking was not associated with RA in the Nurses Health Study(16).

In utero exposure to cigarette smoke might be associated with an incidence of SLE through a number of potential pathways. Women who smoke have lighter placentas, and the chemical constituents of cigarette smoke affect the permeability of the placenta and increase fetal exposure to viruses such as cytomegalovirus, which have been linked to SLE pathogenesis (13,17–19). *In utero* smoke exposure might also disturb regulatory T-cell development. Additionally, maternal cigarette smoking is associated with preterm birth, and recent work in the NHS and NHSII found a twofold increased risk of adult-onset SLE with preterm birth(10). We used data from over 200,000 women followed prospectively in Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) to study whether early-life exposure to cigarette smoke was prospectively associated with SLE incidence. Women in these cohorts were born between 1921 and 1964, before the first Surgeon General's report on smoking and health in 1964 and before the Federal Cigarette Labeling and Advertising Act of 1965 and thus providing a unique opportunity to study the effect of exposure to maternal smoking and incident SLE(20).

Methods

Study Population

The study population included NHS and NHSII participants. NHS was started in 1976 when 121,701 U.S. registered nurses between 30 and 55 years old were enrolled. In 1989, NHSII began with 116,608 registered nurses from the U.S. aged 25 to 42 at baseline. Both female cohorts were contacted every two years by questionnaire asking about diet, medications, anthropometrics, physical activity, and incident physician-diagnosed illnesses. For these analyses, cohort participants were followed through May 21, 2004 (NHS) and May 31, 2003 (NHSII). In this study, we excluded participants who did not provide data on their early-life smoke exposure as well as those reporting a prevalent connective tissue disease at enrollment, leaving 93,054 NHS and 95,554 NHSII participants in the study population.

Early Cigarette Smoke Exposure

In 1982, NHS participants were asked whether their parents smoked while they were living with them. In 1999, NHSII participants were asked two questions on this topic; first whether their mother smoked during her pregnancy with them, and second if their parents smoked in the house during their childhood. In both NHS and NHSII, participants reported that either: no parent, their mother, their father, or both parents smoked cigarettes during the nurse's childhood. In 2001, the Nurses' Mothers Cohort (NMC) was assembled and included approximately 40,000 mothers of NHS and NHSII participants to obtain further data on experiences during pregnancy with the nurse daughter, as well as early-life exposures. Participation was solicited from mothers of NHS and NHSII participants alive and free of cancer in 2001. Approximately 90% were mothers of NHSII participants. We studied whether the nurse's report of childhood smoke exposure is a reasonable proxy for fetal exposure in a validation study using mother-daughter pairs from the NHSII and the NMC. The nurse daughter's report of exposure to cigarette smoke during childhood was found to be 86% sensitive and 88% specific when compared to the gold standard of mother's report of smoking during pregnancy (21). As early childhood exposure to cigarette smoke data were available in both cohorts, this variable was used as a surrogate for *in utero* exposure to cigarette smoke.

Incident Systemic Lupus Erythematosus

Incident SLE was identified and confirmed using a two-stage case validation process previously described elsewhere in detail (22). Briefly, any connective tissue disease (e.g. SLE, RA, scleroderma, Sjögrens) reported on the biennial follow-up surveys was followed by a request to complete a previously validated, Connective Tissue Disease Screening Questionnaire and for permission to review their medical records to confirm their self-reported diagnoses(23,24). Two board-certified rheumatologists, trained in chart abstraction, then reviewed the medical records of participants who screened positively to either confirm or refute the diagnosis of SLE. We defined our primary outcome of incident SLE as reviewers' consensus for SLE as well as three or more American College of Rheumatology (ACR) classification criteria(25,26). A more stringent case definition was also used defining SLE as reviewers' consensus and a minimum of four ACR criteria.

Other Covariates

Data from NHS and NHSII questionnaires were available on additional covariates such as parents' occupations (as a proxy for socioeconomic status), race/ethnicity, and maternal diabetes. Participants were asked their birth weight in categories (not sure; < 5.5 lbs; 5.6 - 7 lbs; 7.1 - 8.5 lbs; 8.6- 10 lbs; > 10 lbs), whether they were born at least two weeks preterm, whether they were part of a multiple birth, and whether they were breastfed. In a sample of NHSII participants self-reported birth weight was previously validated against state birth records and showed a correlation of 0.74(27). Using data from mother-daughter pairs in the NMC and NHSII, nearly 90% agreement was found for mother's and daughter's report of preterm status(28). Breastfeeding during infancy was previously validated in a random sample by comparing to their mothers' independent report (82% sensitivity, 86% specificity) (27). Data were also collected on a number of intermediate variables and possible effect modifiers including the participant's cigarette smoking history in adulthood.

Statistical Analysis

Cohort characteristics were summarized and stratified by exposure to maternal cigarette smoking in childhood. Cox proportional hazards models were stratified on age and time on study was used as the time scale to estimate the hazard ratio, a measure of relative risk (RR). The proportional hazards assumption was evaluated using the Wald test of the statistical interaction between time and early-life smoke exposure. We performed a sensitivity analysis further adjusting for the nurses' own cigarette smoking at baseline to explore the pathway by which parents' smoking cigarettes might impact the risk of SLE. Random effects meta analytic techniques were used to obtain a single combined estimate for each association of interest across the two cohorts.

Results

Incident SLE was confirmed in 142 NHS participants and 94 in NHSII participants using a minimum of three ACR criteria and reviewer's consensus opinion of SLE; 91% (n=215) met at least four ACR criteria for SLE. Participants who reported having mothers who smoked during their childhood were more likely to have fathers who smoked, as well as to become smokers themselves. There was little difference between participants exposed to maternal smoking with regard to perinatal factors, race/ethnicity, or other factors with the exception that childhood smoke exposure was more common among nurses with low birth weight in both cohorts (Table 1).

In neither cohort were mother's nor father's smoking during the nurse's childhood associated with an increased risk of SLE, in crude or multivariable adjusted models (Table 2). Results were essentially unchanged when we adjusted for other early-life factors such as

preterm birth and birth weight. Adjustment for other sources of early-life smoke exposure (i.e. the other parent) did not appreciably change the results. When exposure was redefined as any early-life smoke exposure (i.e. either mother or father) results were similar (RR=1.1, 95% CI: 0.8 to 1.4). Furthermore, self-reported fetal exposure to cigarette smoke, which was only available in the NHSII cohort, was not associated with developing SLE (RR=1.0, 95% CI: 0.6 to 1.6). The results were nearly identical when we used the stricter SLE case definition requiring at least four ACR criteria for confirmation of SLE, however the confidence intervals were slightly wider due to fewer cases.

Discussion

Fetal exposure to cigarette smoke, though declining during the past half century, is still prevalent worldwide (29) and our study adds to the body of literature on its consequences. We used childhood exposure to maternal smoking as a proxy for *in utero* exposure, a validated surrogate (21). Neither maternal nor paternal smoking during childhood or pregnancy was associated with an increased rate of adult-onset SLE in the offspring. Adjusting for potential confounders did not appreciably change the results. Results were similar for the secondary outcome definition that required at least four ACR criteria.

The primary hypothesis of this study was that *in utero* exposure to mother's cigarette smoking would increase the risk of SLE. Offspring could be exposed *in utero* to either mother's active smoking, mother's passive exposure attributed to father's smoking, or both, and also later exposed during childhood by either parent's smoking. Maternal cigarette smoking is a determinant of preterm birth, and recent work in the NHS and NHSII found a twofold increased rate of adult-onset SLE with preterm birth(10). We further adjusted our multivariable models for the nurse's self-reported smoking history at enrollment because parents' smoking in the home is a predictor of their offspring smoking as adults (30) and an individual's own smoking may be a risk factor for SLE (15). This sensitivity analysis explored whether the mechanism by which fetal and early-life exposure to cigarette smoke might be associated with SLE is through the increased likelihood of the nurse participant becoming a smoker herself, which has been shown to be a risk factor (15). This additional adjustment did not appreciably change our results. Moreover, when we restricted the study population to only include nonsmokers, the association was also essentially unchanged (data not shown).

Limitations and Strengths

As with any epidemiologic study based on observational data, the possibility of confounding by factors both measured and unmeasured cannot be excluded. In addition, the study population is from two large prospectively followed cohorts of predominantly Caucasian women, and therefore the findings of this study should not be generalized to non-Caucasian populations who are the most likely to develop SLE.

The use of self-reported exposure data, particularly on a sensitive and controversial topic such as smoking during pregnancy and childhood, leads to concerns about exposure misclassification. However, a recent validation study demonstrated good agreement between mother's report of daughter's fetal exposure and the daughter's report of childhood exposure suggesting that childhood exposure is a good surrogate for fetal exposure in these data. It is unlikely that a participant or her mother would systemically misreport cigarette smoke exposure so early in life because of the nurse participant's SLE status unlike conditions such as asthma or lung cancer. Additionally, we could not study whether childhood smoke exposure could affect SLE risk earlier in life, such as during teenage years or early adulthood. The long duration between one's exposure during fetal development and childhood with adult-onset SLE among women aged 25–50 at baseline, may not represent

the etiologically relevant time period. The available data may not represent the etiologically relevant exposure as we could not classify early-life smoke exposure according to amount or duration.

Despite participants having the opportunity to self-report a connective tissue disease at each two year period, it is possible that some cases of SLE might have been missed: they may have either neglected to report their condition, did not screen positively on the screening questionnaire, did not provide their medical records, or failed to meet enough of the ACR classification criteria upon medical record review. However if these false negatives exist, their number is probably small: the incidence rate of SLE estimated in the NHS and NHSII is consistent with incidence rate estimates for Caucasian women in the U.S.(31) and the multi-stage case identification and validation process, would also screen out a large number of false positives. The majority of confirmed SLE had at least four ACR criteria at diagnosis. Analyses restricted to these cases yielded identical results to those with the additional 21 cases who had three criteria and clinical lupus according to their own rheumatologist and two board-certified rheumatologists serving as reviewers.

Using the rich, prospectively collected cohort data from the NHS and NHSII provided us with a large number of covariates and a large sample size. From the nearly 200,000 female nurses in our study population, almost 250 incident cases of SLE were confirmed, one of the largest numbers of incident cases in any cohort study. In addition, numerous validation studies have shown that self-report of covariates and exposure in the present study is reliable (21,27). Furthermore our findings were robust across both the primary and secondary definitions of incident SLE; however, these two classifications did not allow us to define specific phenotypes of SLE.

This study found that early exposure to cigarette smoke does not increase the risk of SLE in adulthood among women. As mentioned, future work is necessary to investigate additional time periods between exposure and disease, as well as determine whether these results are applicable to other populations including non-Caucasians and males.

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Table 1

Characteristics of participants in NHS and NHSII by maternal smoking during participant's childhood. Presented as means or %, unless noted otherwise.

	NHS		NHSII	
	Yes	No	Yes	No
Participants at enrollment [*] , n (%)	21296 (18.5%)	71510 (62.1%)	33338 (34.9%)	58318 (61.0%)
Age, yrs	40	44	35	34
African-American	1.0	1.2	1.4	1.5
Hispanic	0.68	0.53	1.0	1.6
BMI at age 18	20.0	19.8	21.5	21.1
Low birth weight [†] , <5.5 lbs	8.7	6.8	9.2	5.2
High birth weight [†] , >10lbs	1.3	1.7	0.6	1.3
Preterm birth [†]	4.7	3.7	8.5	6.3
Multiple Birth [†]	1.4	1.4	1.6	1.4
Current smoker [*]	40.3	28.8	16.1	10.5
Past smoker [*]	27.4	23.2	24.2	20.0

^{*} Enrollment in 1976 (NHS) and 1989 (NHSII)

[†] Asked 1992 in NHS and 1991 in NHSII

Table 2

Estimated hazard ratios of association between early cigarette smoke exposure and SLE.

	NHS	NHSII	Pooled**
Mother Smoked *	0.7 (0.5, 1.1)	1.1 (0.7, 1.7)	0.9 (0.6, 1.3)
Multivariable adjusted ‡	0.7 (0.5, 1.2)	1.1 (0.7, 1.7)	0.9 (0.6, 1.4)
Father Smoked *	0.9 (0.7, 1.3)	1.0 (0.7, 1.5)	1.0 (0.8, 1.3)
Multivariable adjusted ‡	1.0 (0.7, 1.4)	1.0 (0.6, 1.5)	1.0 (0.8, 1.3)

* adjusted for age and time on study

‡ additionally adjusted for race, parents' occupations (NHS only), preterm birth, birthweight (5 categories), and exposure from other parent's smoking during childhood.

** pooled with random effects meta-analysis