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Age at Pubertal Onset in Girls and Tobacco Smoke Exposure during Pre- and Post-natal Susceptibility Windows

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Abstract

Background—Tobacco smoke contains known hormonally active chemicals and reproductive toxicants. Several studies have examined prenatal maternal smoking and offspring age at menarche, but few examined earlier pubertal markers, nor accounted for exposure during childhood. Our objective was to examine pre- and post-natal smoke exposure in relation to timing of early pubertal events.

Methods—An ethnically diverse cohort of 1239 girls was enrolled at age 6–8 years for a longitudinal study of puberty at three U.S. sites. Girls participated in annual or semi-annual exams to measure anthropometry and Tanner breast and pubic hair stages. Prenatal and current tobacco smoke exposures, as well as covariates, were obtained from parent questionnaire. Cotinine was measured in urine collected at enrollment. Using accelerated failure time models, we calculated adjusted time ratios for age at pubertal onset (maturation stages 2 or higher) and smoke exposure.

Results—Girls with higher prenatal (≥5 cigarettes/day) or secondhand smoke exposure had earlier pubic hair development than unexposed (adjusted time ratio = 0.92 (95% CI 0.87–0.97) and

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Conflicts of Interest: none declared

Statement on availability of data and code for replication: Deidentified data to replicate the findings can be obtained after applying to and receiving approval from the BCERP Publication-Data Resource Sharing Committee, which requires agreement as to scientific aims and across the three study sites, generally collaboration (or at least contact) with one or more BCERP investigators, and appropriate IRB approvals. First author can be contacted to begin the process for such approvals and to provide computing code after appropriate approvals are obtained.

0.94 (95% CI 0.90–0.97), respectively). Including both exposures in the same model yielded similar associations. Higher urinary cotinine quartiles were associated with younger age at breast and pubic hair onset in unadjusted models, but not after adjustment.

Conclusions—Greater prenatal and childhood secondhand smoke exposure were associated with earlier onset of pubic hair, but not breast, development. These exposures represent modifiable risk factors for early pubertal development that should be considered for addition to the extensive list of adverse effects from tobacco smoke.

Keywords

puberty; Tanner stages; prenatal smoking; secondhand smoke; cotinine; breast development; pubic hair development

Introduction

The recent trend towards earlier pubertal development in girls living in developed countries is well-established[1–4] and is of concern because of effects on later health outcomes, particularly breast and other reproductive system cancers.[5–7] In addition, earlier age at puberty may lead to increased risky behaviors and adverse health effects including depression, anxiety, early sexual activity, substance abuse, and smoking.[8–11] Increased awareness about concomitant rises in widespread exposure to hormonally active chemicals led to concerns that these exposures may be contributing to changes in pubertal timing.[6,12–14] Further, breast cancer might result from exposures during a susceptible period of rapid breast growth and development.[15–19] Thus, the Breast Cancer and the Environment Research Program (BCERP) was designed to investigate whether exposures to a variety of exogenous chemicals may affect the timing of puberty in girls.[1,15]

Tobacco smoke contains thousands of chemicals, some of which are known carcinogens, reproductive and developmental toxicants, or associated with hormonal changes in women, such as anti-estrogen and progesterone effects.[20,21] Several studies have examined prenatal maternal smoking in relation to age at menarche, with many, but not all, showing earlier onset.[22] In most of these studies, prenatal smoke exposure or age at menarche, or both, were determined retrospectively. Furthermore, menarche is a late–stage indicator of puberty. Only one study reported breast and pubic hair development in relation to prenatal exposure and also found evidence of earlier onset.[23] Women who smoke during pregnancy are also likely to smoke postnatally, so offspring continue to be exposed. Few studies have examined secondhand smoke exposure in relation to age at menarche, with inconsistent results,[24–27] and none to our knowledge have examined earlier markers of pubertal transition.

Our objective was to examine pre- and postnatal smoke exposure in relation to pubertal timing among the BCERP cohort of over 1200 girls followed longitudinally. This is the first study to examine breast and pubic hair development determined by standardized exam in relation to multiple smoke exposure variables representing different potential windows of susceptibility.

Methods

Study Population

The BCERP includes a study of girls, recruited at ages 6–8 years in 2004–2007, and followed up to 10 years to measure onset and progression of pubertal maturation. As reported previously,[1,2] the study was conducted using consistent methods at three sites to obtain a diverse sample: Kaiser Permanente in the San Francisco Bay Area ("California"), Cincinnati Children's Hospital/University of Cincinnati, Ohio ("Ohio"), and Icahn School of Medicine at Mount Sinai, New York City ("New York").

Eligibility criteria included no underlying endocrine-associated medical conditions (e.g., overt thyroid disease). The sample sources were defined as age-eligible girls in Kaiser Permanente area membership files at enrollment and birth , at selected schools in the greater Cincinnati area, and at clinics in East Harlem, NY (Black and Hispanic race/ethnicity only).[1,2] Written informed consent was obtained from parent/guardian and child assent was obtained; oversight of the study was conducted by Institutional Review Boards at each site and the Centers for Disease Control and Prevention (CDC).

Sources of Data

In-person clinic visits, conducted annually in California and New York, and semi-annually in Ohio, included child anthropometry and pubertal assessment. Information on demographics, reproductive and child health history, and other factors potentially related to puberty was collected annually by standardized questionnaire from a primary caregiver (usually the mother). For this report, most variables analyzed were from the baseline assessment at study enrollment. Girl's race/ethnicity was classified from detailed questions into mutually exclusive categories in the following hierarchical order: Black, Hispanic, Asian or Pacific Islander, and White or Other. Other potential covariates included household income, home ownership, maternal education and age at delivery, and daughter's birthweight.

Pubertal maturation was determined by inspection (and palpation for breast stage) at each visit, and classified into breast (B1–B5) and pubic hair (PH1–PH5) Tanner stages.[1] Examiners were trained, and tested, by clinical co-investigators at each site to follow a written protocol, with photographs demonstrating maturation stages. Inter-rater reliability across sites was assessed by a master trainer with "substantial agreement" found.[1] Height and weight were measured using calibrated scales and stadiometers. Body mass index (BMI) was calculated as weight/height-squared (kg/m^2) and classified into percentiles using age and sex-specific CDC growth charts,[28] with ≥85th percentile indicating overweight (and ≥95^{th} obesity). Clinical exam data were included in this analysis for up to 10 years (median 7) of follow-up.

Exposure Assessment

We estimated exposure to tobacco smoke by three variables, representing different times in the child's life: parent-reported maternal prenatal smoking, secondhand smoke exposure during the year prior to interview, and a biomarker (urine cotinine). "Prenatal exposure" is defined as maternal smoking during pregnancy reported on the baseline questionnaire as the

usual number of cigarettes and frequency smoked for each trimester. Trimester-specific levels were calculated as the total number of cigarettes smoked and categorized as: none, <400, ≥ 400. These amounts were summed and a daily average calculated over a nine-month duration of pregnancy, and then categorized as: none, <5/day, and ≥5/day (termed “high”).

Secondhand smoke exposure was estimated by questions on regular exposure during the past year; the number of smokers among household members or weekly visitors and the amount smoked inside the home (open-ended) were combined and categorized as: none (no smokers in the home, 73%), 1–35 cigarettes per week (6%), >35 cigarettes per week (7%), and a category for at least one smoker in the home but amount smoked was either missing or zero (e.g., smoked outside, 14%). If at least weekly exposure to smoke had regularly occurred away from home during the past year (18%), the number of hours per week was asked. An aggregate secondhand smoke measure was created by combining home and away, categorized as: none (no regular smokers at home nor regular exposure away), "high" (>35 cigarettes per week in home, or >5 hrs/week exposed away from home and at least one household smoker), and low/moderate (everyone else).

We measured total cotinine in urine collected at baseline by high performance liquid chromatography/atmospheric pressure ionization tandem mass spectrometry (LC/MS/MS), using modifications of previously described methods, [29,30] in the National Center for Environmental Health at CDC. Briefly, urine aliquots were fortified with trideuterated cotinine as the internal standard, hydrolyzed overnight with β-glucuronidase, extracted with methylene chloride, concentrated, and injected into the LC/MS/MS. Each analytical run included one water blank and two quality control samples analyzed along with a set of calibration standards. Cotinine was quantified by comparing the peak area ratio of analyte to internal standard to the calibration standards using weighted least squares linear regression. All reported data were from runs confirmed as being in statistical control based on standard criteria. [31] Cotinine results were reported as nanograms per milliliter (ng/mL) with a limit of detection (LOD) of 0.036 ng/mL. In addition to laboratory-specific quality control procedures, each site included an additional 10% blinded samples drawn from the same non-study urine sample pool; coefficients of variation from these samples were <5% across sites. Cotinine measurements were available for 1175 girls, of which 98% had detectable levels; values <LOD were imputed as LOD/√2. Cotinine levels were corrected for creatinine concentration and categorized into quartiles. For a subset of 215 girls in NY and CA, we had cotinine measurements from two additional visits. We examined within-person reliability over time, calculating pairwise correlation coefficients and the intra-class correlation across the repeated measures (spanning 3–4 years).[32]

Statistical analysis

Questionnaire and exam data were collected for 1239 girls; including only girls with cotinine measured and the smoke exposure questionnaire data yielded 1129 in primary survival-type analyses. Bivariate analyses of exposures by demographic variables shown to be potentially associated with puberty in our prior analyses or the literature was performed initially to identify potential confounders. Geometric mean cotinine and quartiles of log-

transformed levels were compared across categories of demographics and self-reported smoking variables.

The association of each exposure with age at onset of breast or pubic hair development, defined as stage 2 or higher (B2+ or PH2+), was evaluated in separate accelerated failure time models using a Weibull distribution, with left and right censoring to account for pubertal transitions taking place before or after observation, and interval censoring to account for pubertal transitions between exam visits (Proc Lifereg, SAS v.9.3, Cary, NC). The time ratios compare the median age at onset among girls with the characteristic of interest, or the exposure, to girls in the reference category. With typical median ages of B2+ and PH2+ between nine and 10 years old, small time ratios can reflect large differences in age (e.g., 10.5y/10y = 1.05, representing a six-month lag or 5% later onset). For girls who reached Tanner stage 2+ during observed follow-up visits, the interval was defined as the period from the last exam visit consistently at stage 1 to the first visit where the girl was consistently at stage 2+ (i.e. no return to stage 1 in a subsequent visit). To calculate adjusted time ratios we included study site, annual household income, maternal education, maternal age at delivery, girl's race/ethnicity, baseline BMI, and birth weight. We ran models that included secondhand and prenatal smoke exposures singly and together to tease apart associations. Too few girls had exposure only prenatally and not postnatally to examine separately, but we did examine the opposite (secondhand smoke, but no prenatal, exposure). In the later years of follow-up, girls self-reported smoking, but the few reporting any smoking were post-pubertal at the time and so we retained them in these analyses.

Because birthweight and BMI have been associated with prenatal smoking, they may be on the causal pathway to puberty, so we examined possible mediation or effect modification. Analytic models were run with and without BMI to assess mediation qualitatively (≥85th percentile vs. <85th), and in separate BMI strata or by including interaction terms with the smoke exposure variables to assess effect modification. A similar strategy was used to examine birth weight (defined as low: <5.5 lb (equivalent to <2500g), high: >9.0 lb, and mid: 5.5–9.0 lb). Some prior studies found differential effects of smoke exposure by race, so we stratified results by race/ethnicity, as well as by site, to determine their robustness. Sensitivity analyses were conducted excluding girls who later reported smoking (a whole cigarette, n=12), who had baseline urinary cotinine concentrations >50 ng/ml (n=16), who were pubertal at baseline (n=136–165), or who dropped out after the baseline visit (n=86).

Results

This sample of girls was racially diverse with 66% non-White, nearly one-third overweight at enrollment, and 10% born with low birthweight (Table 1). Over one-third of girls had questionnaire-reported regular secondhand smoke exposure (38%), with 8% classified as "high" exposure. The frequency of any exposure was highest for girls from NY (50%), with annual household incomes <$50,000 (53%), or whose mothers were younger at delivery (52%) (Table 1). Secondhand smoke exposure also varied by race; Blacks had the highest reported exposure (54%) and Asians the lowest (18%). As expected, regular postnatal exposure was more common (84%) among the girls whose mothers reported any prenatal smoking. Almost all the girls who had baseline cotinine levels in the lowest quartile had no

reported regular secondhand smoke exposure (93%), but so did 19% of girls in the highest quartile (Table 1).

At enrollment, about 15% of the girls had reached B2+ and 12% PH2+, and before dropping out or by the last follow-up exam, 89% had reached B2+ and 86% PH2+ (Table 2). As recently reported,[2] modeled median age at B2+ in the overall cohort was lowest in Black participants (8.8 years), highest in White and Asian participants (each 9.7y), and mid-range in Hispanics (9.3y). Onset of PH2+ also varied by race, with earlier age for Blacks, but older for Asians, compared to Whites. Pubertal onset was earlier among girls in Ohio (for B2+), with higher BMI, with lower household income, or whose mothers had a younger age at delivery or menarche.[33] In this unadjusted cross-sectional view, more than twice as many girls with high secondhand smoke exposure had reached puberty (B2+ or PH2+) at entry than non-exposed girls, and similarly for the highest versus lowest quartiles of urinary cotinine, but less clear by prenatal smoke exposure (Table 2).

Prenatal Smoke or Childhood Secondhand Exposure and Puberty

In longitudinal models, high prenatal smoke exposure (>5 cigarettes/day) was associated with earlier B2+ (Table 3), but not after adjustment (time ratio=1.02, 95%CI 0.96–1.06), and with earlier PH2+ onset, even after adjustment (time ratio=0.92, 95%CI 0.87–0.97). Some dose-response pattern was suggested with lower exposure for PH2+. The median age of PH2+ is ~10.2 years in the referent group; adjusted models suggest PH2+ onset 8% earlier (~10 months younger) among highest exposed versus unexposed. When we examined the trimester smoking averages separately, no specific trimester was implicated as a more susceptible risk period.

Similarly, highest secondhand smoke exposure was associated with earlier B2+ in the crude model only (time ratio=0.96, Table 3), not after adjustment (time ratio=1.0, 95% CI 0.96–1.04). For PH2+, we found high secondhand smoke exposure associated in both crude and adjusted models (adjusted time ratio=0.94, 95%CI 0.90–0.97), with no association at low/moderate exposure after adjustment. Modeling both exposures together, associations with PH2+ were modified only slightly; adjusted time ratio for high secondhand smoke was 0.95 (95% CI 0.91–0.98) and for high prenatal exposure was 0.94 (95%CI 0.89–1.01) (Table 3), and there were no associations with B2+. Examining the subset of girls with no prenatal exposure, the postnatal associations were similar to overall (high secondhand smoke and PH2+ adjusted time ratio=0.94 (95% CI 0.90–0.98)).

The earlier PH2+ with either smoke exposure was generally consistent in additional analyses across race and site. An even stronger association was seen among Hispanic girls with high prenatal exposure (adjusted time ratio=0.78, 95% CI 0.66–0.93) (eTable 1). There was more variation in the B2+ associations. Some sub-groups had later B2+ with high prenatal exposure; e.g., CA girls (adjusted time ratio=1.16, 95%CI 1.0–1.34) and Black girls (adjusted time ratio=1.12, 95%CI 1.02–1.22), whereas White girls had earlier B2+ with either exposure (adjusted time ratio for high prenatal =0.92, 95%CI 0.84–1.0, and for high secondhand smoke exposure=0.91, 95%CI 0.85–0.96) (eTable 1). Stratifying by BMI (eTable 2), in the overweight group we found even earlier PH2+ with high exposures, however, there was some tendency for later B2+ with higher prenatal exposure (aTR=1.07,

95%CI 0.98–1.17). Interactions of BMI and secondhand smoke exposure were seen for B2+ (p=0.005) and PH2+ (p=0.015) and with prenatal exposure for B2+ (p=0.07). Stratifying by birth weight (eTable 3) confirmed the associations of earlier PH2+ with high levels of either smoke exposure in the mid-weight girls. However, girls with low birthweight had opposite patterns; e.g. later breast or pubic hair onset with higher exposures (adjusted time ratios 1.10–1.11).

Including or removing BMI or birth weight from models did not materially change the effect estimates, suggesting these were not mediators of the early pubic hair development with higher prenatal smoke exposure association. None of the sensitivity analyses excluding various girls yielded materially different results.

Cotinine Levels and Puberty

For the CDC National Report on Human Exposure to Environmental Chemicals,[34] cotinine is measured in serum. Urinary levels are typically 7–10 times higher, so using this rough conversion, our median level (0.52 ng/ml) was close to that of the U.S. sample of 3–11 year olds in 2005–06 (0.35–0.50 estimated). Geometric mean cotinine concentrations varied by demographic variables in the same patterns as reported secondhand smoke exposure; higher in girls from NY who were of lower SES, Black, or to some extent, of higher BMI (eTable 4). Geometric mean cotinine concentrations also showed strong increasing trends with number of household smokers (leveling off at ≥3), total number of cigarettes smoked in the home weekly, smoke exposure away from home, and maternal prenatal smoking. The intra-class correlation across repeated measures was 0.59 (95%CI 0.52–0.66), representing moderate to substantial agreement. [32]

In unadjusted models, age at B2+ was younger with increasing cotinine quartile, with some dose-response pattern, as was age at PH2+ (Q4 vs Q1 time ratios=0.94 for B2+ and 0.95 for PH2+, Table 4). Adjustment attenuated the associations to nearly null. Sensitivity analyses, including deleting girls (~10%) with very low or high creatinine levels (<20 or >200 mg/dL), yielded very similar results. Stratifying by race, Hispanic (and Asian, but based on small numbers) girls had earlier pubertal onset among those with cotinine concentrations in Q4 compared to Q1 (adjusted time ratios = 0.92, 95%CI 0.86–0.98 for B2+, and 0.95, 95%CI 0.89–1.0 for PH2+). Adding cotinine to the model did not affect the association of prenatal smoke exposure and earlier PH2+.

Discussion

Our findings indicate associations between earlier pubic hair development and both prenatal and secondhand smoke exposure assessed by questionnaire, with robust findings across different sub-groups defined by race, site, or BMI, and various exclusions. These are consistent with prior literature on menarche; a recent meta-analysis[22] reported a pooled effect estimate of 1 month earlier age at menarche among girls with prenatal smoke exposure, which was slightly stronger in birth cohorts since 1965. Prenatal smoking rates have greatly decreased since then, consistent with our relatively low self-reported rate, but nevertheless we found even greater differences (≥6 months) in age at pubic hair onset with higher exposure. Our data were obtained close in time to when exposure occurred (i.e., 6–8

years after birth) in contrast to some studies that ascertained exposure when offspring were adults. The meta-analysis included studies from several countries with similar findings, but had stronger effect estimates among Caucasians. We found some variation by race, with White (and to some extent Hispanic) girls showing earlier breast development, but Black girls later, with higher prenatal exposure. Reasons for this are unclear; there has been suggestion of differences in nicotine metabolism by race,[35] but this seems an unlikely explanation given pubic hair development did not differ in the same way. Black girls have earlier breast development than White girls,[1,3] so other un-controlled factors or genetic markers related to breast development might be at play.

Only one prior study of adequate size examined prenatal smoking in relation to breast and pubic hair staging, although based on self-assessment.[23] The authors reported earlier age at B2+, B3+, PH3+, and menarche among offspring whose mothers smoked prenatally compared to those whose did not. A very small study (n=69) reported no association of breast development (or menarche) with prenatal smoking.[36]

A handful of studies examined childhood secondhand smoke exposure and age at menarche.[24–27,37] In our prior analysis of a 1960's birth cohort, compared to daughters of non-smokers, girls with the highest secondhand smoke exposures had an earlier mean age at menarche (almost 2 months) and girls with highest exposures to both prenatal and postnatal even earlier (~4 months).[27] Both findings were somewhat stronger among non-Whites, which we did not observe in our current study. A study of a Danish birth cohort[25] reported no association of only postnatal exposure with age at menarche, despite seeing earlier age with prenatal exposure. Two other very large studies[26,37] that defined secondhand smoke exposure as living with smokers during childhood also reported earlier age at menarche, whereas a third, smaller study[24] (n=262), reported higher risk of "late" (>12 yrs) menarche with secondhand (or prenatal) smoke exposure. Thus associations between secondhand smoke and menarche are inconsistent in the literature, perhaps because of differences in exposure definitions and limited separation of prenatal exposure. No prior studies examined secondhand smoke and earlier markers of pubertal development.

Nor have prior studies included cotinine, a specific biomarker of tobacco smoke exposure. While cotinine represents an exposure variable not subject to recall mis-classification, it only reflects recent exposure, i.e. within hours to days. If exposures are consistent over time, as our intra-class correlation suggested, cotinine may reflect longer term exposure, so it is not clear why findings differed from the self-reported exposures. One reason may be that the later were designed to identify more chronic, regular exposures, whereas very low-level secondhand smoke exposure may be difficult to avoid. Cotinine levels could represent other sources of nicotine not ascertained on the questionnaire, but we would not expect this to diminish an association. Alternatively, cotinine may not best represent the toxic chemical(s) in secondhand smoke that are related to pubertal onset, perhaps via a hormonal mechanism.[38] Last, the cotinine analyses were more affected by adjustment for co-factors than the other smoke exposures. Perhaps one or more co-factors was related to creatinine, which we corrected for as recommended by the laboratory. Excluding girls with high and low creatinine values did not change results. Among Hispanic girls there was an association of higher cotinine concentrations with earlier onset of puberty.

Our study is one of the few to examine early markers of pubertal transition in relation to prenatal smoke exposure and the first to examine childhood secondhand smoke exposure. Other strengths include assessment of puberty by clinical examination using standardized measures, in a large, diverse sample of pre-pubertal (mostly) girls followed prospectively. We collected data on a number of covariates and had good follow-up rates. There are also limitations, including that results may not be widely generalizable as the sample draws from families in urban settings who were willing to participate in a longitudinal study. Pubertal maturation assessments at two sites were conducted annually and thus estimates of timing of onset within intervals reflect some imprecision. Furthermore, self-reported prenatal smoking may be subject to misclassification or reporting bias, but perhaps less so in a study of puberty, an endpoint that has not been widely seen as a concern in relation to smoking. Though we controlled for some measures of SES, SES may also be related to other exposures affecting puberty that we did not account for, potentially resulting in residual confounding. Some exposures we have examined that varied by SES were associated with older age at pubertal onset (i.e. brominated flame retardants), so are unlikely to explain the smoke association.[33] Another exposure, proximity to traffic, that we found associated with earlier pubertal onset,[39] could be a potential confounder, or could reflect supportive evidence, as traffic-related air pollution would include some of the same chemical components as tobacco smoke, e.g., combustion products, metals, etc.

Puberty is a complex process leading to sexual maturation, governed by the hormonal milieu, yet not completely understood.[4,6] There are two related processes: 1) maturation of the hypothalamic–pituitary–gonadal (HPG) system, or gonadarche, which affects breast tissue growth, and 2) maturation of the hypothalamic-pituitary-adrenal system, or adrenarche, more related to growth of pubic or axillary hair. Tobacco smoke contains hundreds of chemicals, including known reproductive toxicants and endocrine disruptors that could influence reproductive maturation.[20] Smoking was long thought to have anti-estrogenic effects in adult women, but also appears to affect progesterone and perhaps more importantly for puberty, pituitary hormones.[21,40] Smoking may also effect adrenal androgen secretion, with increases seen in cortisol, dehydroepiandrosterone sulfate (DHEAS), DHEA (which increases prior to or early in puberty and is a precursor of other androgens), adrenaline, and catecholamine.[40] Although little work has been done examining hormonal effects of smoke exposure in children, there is ample basis to suspect disruption of hormone-sensitive processes. The smoke effects on adrenal hormones may be related to our finding of early pubic hair development, while anti-estrogenic effects to the absence of earlier breast development (or later in some sub-groups). Prenatal smoking is known to be associated with low birthweight or intra-uterine growth retardation and more recently sufficient evidence has accumulated to implicate obesity in offspring, potentially related to hormonal pathways as well.[20,41] While obesity is strongly associated with age at puberty, neither it nor birthweight appeared to mediate the associations we observed. However, there were some indications of later development in exposed girls with high BMI or low birthweight, which merit further investigation. Lastly, age at pubertal onset has a genetic component, and genetic polymorphisms are involved in metabolism of smoke components, so such factors may also play a role.[42–44]

In conclusion, this is the first study to examine the effects of several measures of tobacco smoke exposure on the early physical signs of pubertal onset using a longitudinal design. Our finding of earlier onset of pubic hair development with secondhand exposure is, to our knowledge, new. Results for both exposures are consistent with studies showing earlier onset of menarche. If associations are causal, pre- and post-natal smoke exposure represent risk factors for early puberty and its sequelae that are modifiable, yet exposure in the home is an area that is difficult to control by regulation. Early puberty potentially represents yet another adverse outcome associated with smoking during pregnancy or around children that could be added to health education messages for reducing exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of Girls in BCERP[a] by Childhood Secondhand Smoke (SHS) Exposure[b]

	No Exposure (N=700, 62%)	Low/Moderate (N=344, 30%)	High (N=85, 8%)	Total (N=1129)
	N (row %)	N (row %)	N (row %)	N (column %)
Study Site				
New York	189 (50)	136 (36)	53 (14)	378 (33)
Ohio	196 (58)	112 (33)	28 (8)	336 (30)
California	315 (76)	96 (23)	4 (1)	415 (37)
Annual household income				
<$50,000	251 (47)	225 (42)	60 (11)	536 (47)
≥$50 – <100,000	218 (69)	77 (24)	22 (7)	317 (28)
≥$100,000	231 (84)	42 (15)	3 (1)	276 (24)
Maternal education				
High School or less	165 (51)	124 (39)	32 (10)	321 (29)
Some College	166 (48)	138 (40)	39 (11)	343 (31)
College grad or higher	365 (80)	80 (18)	12 (3)	457 (41)
Maternal age at delivery				
<25 years	146 (48)	123 (40)	37 (12)	306 (28)
25–35 years	340 (65)	146 (28)	34 (7)	520 (48)
>35 years	204 (77)	53 (20)	9 (3)	266 (24)
Maternal prenatal smoking				
None	685 (66)	300 (29)	50 (5)	1035 (92)
<5 cigs/day	11 (17)	34 (53)	19 (30)	64 (6)
≥5 cigs/day	4 (13)	10 (33)	16 (53)	30 (3)
Child race				
Black	166 (46)	147 (41)	44 (12)	357 (32)
Hispanic	200 (61)	107 (33)	21 (6)	328 (29)
Asian	45 (82)	9 (16)	1 (2)	55 (5)
White	289 (74)	81 (21)	19 (5)	389 (34)
Child BMI (at baseline)				
<85th %ile CDC	488 (64)	221 (29)	49 (6)	758 (67)
≥85th %ile CDC	212 (57)	123 (33)	36 (10)	371 (33)
Birth weight				
Low (<5.5 lbs)	65 (62)	33 (31)	7 (7)	105 (10)
Mid (5.5–9.0 lbs)	560 (62)	268 (30)	71 (8)	899 (83)
High (>9.0 lbs)	53 (73)	17 (23)	3 (4)	73 (7)
Cotinine at baseline (creatinine-adjusted)				
Q1: ≤0.25 ug/g	266 (93)	21 (7)	0 (0)	287 (25)
Q2: 0.26–0.61 ug/g	211 (75)	68 (24)	2 (1)	281 (25)
Q3: 0.62–2.24 ug/g	169 (61)	104 (37)	6 (2)	279 (25)
Q4: ≥2.25 ug/g	54 (19)	151 (54)	77 (27)	282 (25)

[a]Girls with all smoke exposure variables (self-report and cotinine concentrations) non-missing, N=1129; some girls were missing data on characteristics.

[b]SHS categories determined from combination of number of household smokers and amount smoked at home, as well as hours exposed away from home. No exposure reflects no regular household smokers in the home or exposure outside, High is defined as >35 cigarettes smoked per week in home or > 5 hrs/week SHS outside the home and at least one regular smoker at home, and Low/Moderate includes everyone else with at least some exposure at home or away.

BCERP indicates Breast Cancer and the Environment Research Program; BMI, body mass index; CDC, Centers for Disease Control and Prevention growth charts used to define overweight as BMI ≥ 85th percentile; Q1–4 indicates quartiles.

Table 2

Proportion of Pubertal Status (Breast and Pubic Hair Development) at Study Entry and End, by Smoke Exposures

Exposure[a]	At entry to study		At end of study period[b]	
	B2+ (15%)	PH2+ (12%)	B2+ (89%)	PH2+ (86%)
Secondhand smoke				
None	89 (13%)	64 (9%)	631 (90%)	612 (87%)
Low/Moderate	54 (16%)	48 (14%)	301 (88%)	290 (84%)
High	23 (27%)	19 (22%)	72 (85%)	71 (84%)
Maternal prenatal smoking				
None	150 (14%)	115 (11%)	929 (90%)	899 (87%)
<5cigs/day	12 (19%)	13 (20%)	51 (80%)	50 (78%)
≥5cigs/day	4 (13%)	3 (10%)	25 (83%)	25 (83%)
Child Cotinine[c] (baseline)				
Q1: ≤0.25 ug/g	24 (8%)	23 (8%)	263 (92%)	255 (89%)
Q2: 0.26–0.61 ug/g	40 (14%)	34 (12%)	252 (90%)	250 (89%)
Q3: 0.62–2.24 ug/g	46 (16%)	28 (10%)	249 (89%)	235 (84%)
Q4: ≥2.25 ug/g	56 (20%)	46 (16%)	241 (85%)	234 (83%)

[a] For total N's by category (denominators), see Table 1

[b] Includes girls lost to follow-up before reaching puberty, as well as those not pubertal by last exam.

[c] Urinary cotinine, corrected for creatinine

B2+ indicates onset of breast development, defined as Tanner stage 2 or higher; PH2+, onset of pubic hair development, defined as Tanner stage 2 or higher

Table 3

Associations of Maternal Prenatal Smoking and Childhood Secondhand Smoke Exposure with Pubertal Onset[a], Crude and Adjusted Time Ratios (TRs) with 95% Confidence Intervals (CIs)

Smoke exposure	Crude model		Adjusted model[b]		Adjusted model including both smoke exposures[c]	
	Breast Onset TR (95% CI)	Pubic Hair Onset TR (95% CI)	Breast Onset Adjusted TR (95% CI)	Pubic Hair Onset Adjusted TR (95% CI)	Breast Onset Adjusted TR (95% CI)	Pubic Hair Onset Adjusted TR (95% CI)
Maternal Prenatal Smoke						
≥5 cigs/day	0.95 (0.90–1.00)	0.91 (0.86–0.97)	1.02 (0.96–1.06)	0.92 (0.87–0.97)	1.02 (0.96–1.06)	0.94 (0.89–1.01)
<5 cigs/day	0.98 (0.94–1.02)	0.97 (0.93–1.01)	1.01 (0.97–1.05)	0.98 (0.94–1.03)	1.01 (0.97–1.05)	1.00 (0.96–1.04)
None	ref	ref	ref	ref	ref	ref
Secondhand smoke [d]						
High	0.96 (0.92–0.99)	0.91 (0.88–0.95)	1.00 (0.96–1.04)	0.94 (0.90–0.97)	0.99 (0.96–1.03)	0.95 (0.91–0.98)
Low/Moderate	0.98 (0.96–1.00)	0.98 (0.96–1.00)	1.01 (0.99–1.03)	1.00 (0.97–1.02)	1.01 (0.98–1.03)	1.00 (0.98–1.02)
None	ref	ref	ref	ref	ref	ref

[a] Pubertal onset defined (separately) as breast or pubic hair development at Tanner stage 2 or higher (B2+ or PH2+).

[b] Adjusted model includes: child race, study site, household income, primary caregiver's education, maternal age at delivery, child BMI (baseline), and birth weight, in separate models for each exposure.

[c] Adjusted model includes both smoking variables, along with the above covariates.

[d] Secondhand smoke categories determined from combination of number of cigarettes smoked in the home and hours exposed away from home. No exposure reflects no regular household smokers in the home or exposure outside (>1hr/week), High is defined as >35 cigarettes smoked per week in home or > 5 hours/week secondhand smoke exposure outside the home and at least one regular smoker at home, and Low/Moderate includes everyone else with at least some exposure at home or away.

Table 4

Association of Baseline Urinary Cotinine Levels with Pubertal Onset[a]; Crude and Adjusted Time Ratios (TRs) with 95% Confidence Intervals (CI)

Smoke exposure	Crude model		Adjusted[b] model	
	Breast Onset TR (95% CI)	Pubic Hair Onset TR (95% CI)	Breast Onset Adjusted TR (95% CI)	Pubic Hair Onset Adjusted TR (95% CI)
Cotinine quartile (creatinine-adjusted)				
Q4: ≥2.25ug/g	0.94 (0.92–0.97)	0.95 (0.92–0.98)	0.99 (0.96–1.01)	1.00 (0.97–1.03)
Q3: 0.62–2.24ug/g	0.95 (0.93–0.97)	0.98 (0.95–1.00)	0.98 (0.96–1.01)	1.02 (0.99–1.05)
Q2: 0.26–0.61ug/g	0.97 (0.95–1.00)	0.99 (0.97–1.02)	0.99 (0.97–1.02)	1.02 (0.99–1.04)
Q1: ≤0.25ug/g	ref	ref	ref	ref

[a]Pubertal onset defined (separately) as breast or pubic hair development at Tanner stage 2 or higher (B2+ or PH2+).

[b]Adjusted model includes: child race, study site, household income, primary caregiver's education, maternal age at delivery, child BMI (baseline) and birth weight.