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Estimating Cotinine Associations and a Saliva Cotinine Level to Identify Active Cigarette Smoking in Alaska Native Pregnant Women

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Abstract

Studies indicate nicotine metabolism varies by race and can change during pregnancy. Given high rates of tobacco use and limited studies among Alaska Native (AN) women, we estimated associations of saliva cotinine levels with cigarette use and second-hand smoke (SHS) exposure and estimated a saliva cotinine cutoff to distinguish smoking from non-smoking pregnant AN women. Using questionnaire data and saliva cotinine, we utilized multivariable linear regression (n = 370) to estimate cotinine associations with tobacco use, SHS exposure, demographic, and pregnancy-related factors. Additionally, we estimated an optimal saliva cotinine cutoff for indication of active cigarette use in AN pregnant women using receiver operating characteristic (ROC) curve analysis (n = 377). Saliva cotinine significantly decreased with maternal age and significantly increased with cigarettes smoked per day, SHS exposure, and number of previous full term pregnancies. Using self-reported cigarette use in the past 7 days as indication of active smoking, the area under the ROC curve was 0.975 (95 % CI: 0.960–0.990). The point closest to 100 % specificity and sensitivity occurred with a cotinine concentration of 1.07 ng/mL, which

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corresponded to sensitivity of 94 % and specificity of 94 %. We recommend using a saliva cotinine cutoff of 1 ng/mL to distinguish active smoking in pregnant AN women. This cutoff is lower than used in other studies with pregnant women, most likely due to high prevalence of light or intermittent smoking in the AN population. Continued study of cotinine levels in diverse populations is needed.

Keywords

Maternal cigarette smoking; Pregnant women; Saliva cotinine; Alaska native women

Introduction

Prenatal tobacco exposure is associated with higher likelihood of preterm delivery, intrauterine growth retardation, and placenta previa [1, 2]. Neonates with prenatal tobacco exposure are more likely to have low birth weight, wheezing, and otitis media, and are at higher risk of sudden infant death syndrome [1, 3–6]. Prenatal tobacco exposure is associated with adverse health outcomes later in life such as high body mass index, asthma, and early aging of lungs [7–10].

Alaska Native and American Indian (AN/AI) people have the highest prevalence of cigarette smoking and smokeless tobacco (ST) use of ethnic groups in the United States (US) [11]. In Alaska, 46 % of AN men and 39 % of AN women report smoking cigarettes, while 14 and 7 %, respectively, report ST use [12]. More than one of four (28 %) AN women smoke during the last 3 months of pregnancy, compared to 10 % of non-Native women [13, 14]. Importantly, many AN smokers are intermittent or light daily smokers [15–17]. Among pregnant AN women, 68 % report smoking an average of five or fewer cigarettes per day (CPD) and another 23 % report between five and ten [14].

Studies have shown self-report of tobacco use and SHS exposure can be inaccurate possibly due to factors such as perceived lack of acceptability, difficulty in recall, embarrassment, or denial, signifying a need for additional methods of confirming tobacco use and SHS exposure [18–22]. Cotinine is a biomarker of nicotine exposure and can be measured in blood, urine, and saliva; in all three matrices, it has a half-life of approximately 17 h in non-pregnant individuals [23–28].

Previous studies have recommended saliva cotinine cutoff levels ranging from 10 to 30 ng/mL to indicate active smoking [25, 26, 29]. However, these recommended values may not be applicable to AN pregnant women. For example, metabolism of nicotine changes during pregnancy with faster nicotine clearance and shorter cotinine half-life [30, 31]. There have been studies establishing saliva cutoffs for pregnant women, however these studies did not include AN women [32, 33], and evidence indicates that nicotine intake and metabolism differ by race [34–36].

We are aware of only two studies that measured cotinine in pregnant AN women. One aimed to test utility of immunoassay test strips [37]. The second aimed to assess neurobehavioral effects of tobacco use in neonates and occurred in western Alaska where tobacco use often

includes Iq'mik, a unique form of ST with high pH and fast nicotine delivery [38]. Neither study established a cutoff to identify active cigarette smoking. In the context of high prevalence of cigarette use and limited studies among AN women, we estimated associations of cotinine with cigarette use and SHS exposure and estimated a saliva cotinine cutoff to distinguish smoking from non-smoking AN pregnant women.

Methods

Setting

This study was conducted at the Women's Health Clinic in Southcentral Foundation's Anchorage Primary Care Center (SCF-ANPCC) from 2006 to 2010. SCF-ANPCC provides pre-paid primary healthcare to approximately 60,000 AN/AI people living in Anchorage, Alaska and surrounding rural areas. Women eligible for care at SCF-ANPCC could enroll in the study during pregnancy, and those women who enrolled in the first or second trimester were contacted for follow-up visits in each remaining trimester of pregnancy. Advertisements were run on radio stations and in newspapers, and a recruitment table was placed in the SCF-ANPCC Women's Health Clinic. All interested individuals presented at this clinic and enrolled with a research associate or administrative assistant from the study team who was trained in survey administration and confidentiality procedures. All participants signed an informed consent or assent (signed by a parent or guardian for those participants aged sixteen to eighteen), and the Alaska Area Institutional Review Board and two tribal health boards approved this study. At enrollment and each follow-up visit, women provided a saliva sample by chewing on a sterile cotton wool Salivette® (Sarstedt, Newton, NC) and answered a questionnaire in English about past and active tobacco use and SHS exposure. Instructions were read to participants with an offer to read the questions aloud, though most participants chose to read questions silently themselves. All participants wrote their own responses. Women received a $20 gift card for their time.

Measurement of Cotinine Levels and Tobacco Exposure Definitions

Salivettes were stored frozen at −20 °C for up to 2 years and shipped to the Tobacco Exposure Biomarkers Laboratory at Centers for Disease Control and Prevention for cotinine analysis. Saliva cotinine was measured by high-performance liquid chromatography atmospheric-pressure chemical ionization tandem mass spectrometry (LC APCI MS/MS) using a modification of a method described elsewhere in detail [39–41]. Salivettes were thawed and centrifuged to recover saliva on the day of analysis. Briefly, saliva samples (0.5 mL) were equilibrated with a tri-deuterated cotinine internal standard for 15 min, extracted with methylene chloride, dried, reconstituted in water, and analyzed on an AB Sciex API 4000 tandem mass spectrometer with heated nebulizer installed. Cotinine concentrations were quantified by comparison with standards using least squares linear regression. Standard calibrators ranged from 0 to 20.0 ng/mL. Samples with cotinine values above 20 ng/mL were diluted with water and reanalyzed. The limit of detection (LOD) was 0.015 ng/mL. For statistical analysis, samples with cotinine levels below LOD were set to LOD/√2 (approximately 0.011 ng/mL). All analytical runs included a blank and two quality control samples. Reported results were from analytical runs determined to be in statistical control by the laboratory's standard quality assurance procedures described elsewhere in detail [42].

Women were categorized as active smokers if reporting smoking at all, even a puff, in the past 7 days. Women were categorized as exposed to SHS if reporting being exposed at home, work, or other places. Women who reported using ST in the 2 days prior to any visit were excluded from analysis, as nicotine intake from ST differs from that of cigarettes.

Statistical Methods

Given a high rate of enrollment in later trimesters and some missed visits, we present data from only one visit, the first one, in these analyses. However, we investigated intermittent cigarette use and SHS exposure across all visits available, and repeated analysis using the last visit for sake of comparison. Descriptive statistics were calculated, and associations with tobacco exposure status were estimated and tested with the Chi square or Kruskal–Wallis test for categorical and continuous factors, respectively. The test of ever-smoking applied only to non-active smokers, and the test of CPD applied only to active smokers. The Kruskal–Wallis test was utilized as some data were non-normal.

A multivariable linear regression model was fit using natural logarithm of cotinine concentrations as the dependent variable and the following as independent variables: natural logarithm of CPD smoked 7 days prior to the visit, an indicator of SHS exposure, age, trimester of pregnancy, number of previous full term pregnancies, a partner or husband living in the home, and number of other adults living in the home. The logarithm transformation was used due to strong skew in cotinine and CPD values. Interactions were also tested through inclusion in the model (data not shown in table).

To estimate optimal cotinine cutoffs for indication of active smoking, a receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was estimated. The ROC curve was a plot of sensitivity (true positive rate) versus 1—specificity (false positive rate) where self-reported smoking in the past 7 days was the “true” indicator of active smoking. Therefore, for this study, sensitivity was the probability a self-reported active smoker had saliva cotinine concentration higher than the specified cutoff and hence was identified as a smoker by the cotinine value. Similarly, specificity was the probability a self-reported non-smoker had a saliva cotinine concentration less than the specified cutoff. The optimal cutoff was considered to be the point closest to 100 % sensitivity and specificity. All analyses were performed with SAS version 9.2 (Cary, NC). *P*-values less than 0.05 indicated statistical significance.

Results

Information about the study was shared in over 2800 encounters with pregnant women and 2300 encounters with other individuals, and 387 women consented to participate. Among the 387 consented women, 377 were not ST users and provided a saliva sample of at least 0.5 mL for cotinine analysis at one or more visits, and thus were included in this analysis. Data from the first trimester visit with valid cotinine measurement was utilized in this analysis as shown in Fig. 1. Average age of participants at the infant’s due date was 25.5 years (standard deviation 5.4 years). Of the 377 women, 272 (73 %) reported smoking at least one-hundred cigarettes in their lifetime, and 43 (11 %) reported ST use at least twenty times in their lifetime.

At the visit of data analysis, active smoking was reported by 116 (31 %) participants. Among these participants, median CPD was three (interquartile range, IQR = 5.75), CPD was ten or fewer for 91 %, and median time since the last cigarette was 3 h (IQR = 19.2 h) with about one in four visits (n = 27) occurring more than a day since smoking a cigarette. Over half of participants (n = 225) reported exposure to SHS, of which approximately 60 % (n = 136) reported no active smoking.

Descriptive statistics stratified by active smoking status and SHS exposure are presented in Table 1. SHS exposure and active smoking status were associated with younger age, no husband or partner living in the home, and increased number of other adults living in the home. Active smoking status was associated with increased previous full term pregnancies. Median of saliva cotinine concentration was significantly higher for active smokers.

Linear associations with cotinine are presented in Table 2. Increased CPD and SHS exposure were significantly associated with increased cotinine concentration levels. Additionally, women with more previous pregnancies had increased cotinine levels, while cotinine decreased with maternal age. Women in later trimesters of pregnancy had decreased cotinine levels, though statistical significance was borderline ($p = 0.104$). The included factors explained 66.2 % of the variation in cotinine. Significant interaction was found between SHS exposure and both CPD and maternal age ($p < 0.001$ and $p = 0.008$, respectively; data not included in table). Specifically, the increase in cotinine concentration levels with increased CPD was less strong among women with SHS expsorue, and the decrease in cotinine concentration levels with increased maternal age was less strong with SHS exposure.

The ROC curve using cotinine to predict active smoking status is shown in Fig. 2. AUC was 0.975 (95 % CI: 0.960–0.990). In comparison, a model with perfect prediction of both active and non-active smokers would have AUC of 1.0. The optimal cutoff occurred at cotinine level 1.07 ng/mL, which corresponded to sensitivity of 94 % and specificity of 94 %, indicating the cutoff of 1.07 ng/mL correctly identifies both active and non-active smoking status (self-reported), respectively, 94 % of the time. For the remainder of this analysis, we will compare to a rounded cutoff of 1 ng/mL which also has a sensitivity and specificity of 94 %. This cutoff, 1 ng/mL, was also found in repeated analyses using data from the last visit instead of the first visit.

For comparison, if the cotinine cutoff of 11 ng/mL were used to identify active smokers as suggested by another study with a different population [32], sensitivity and specificity would be 78 and 97 %, respectively. Generally, increasing the cutoff leads to more cases of incorrect identification of active smokers as non-active (lower sensitivity) and identifying more self-reported non-active smokers as non-active (higher specificity); for example, the cutoff of 24 ng/mL yielded sensitivity of 66 % and specificity of 98 %. A histogram of cotinine concentration levels for active smokers and non-smokers on a logarithmic scale is shown in Fig. 3 with reference lines at cutoffs 1 and 11 ng/mL included.

Seven women reported active smoking and yet had cotinine level lower than 1 ng/mL, for a false negative rate of 6 %. All of these women (n = 7) reported at least 2 days since smoking their last cigarette and low cigarette consumption with CPD of three or less.

Sixteen women reported no active smoking and yet had a cotinine level higher than 1 ng/mL, for a false positive rate of 6 %. Of these, two women reported no nicotine exposure (cotinine range 6.0–6.5) and four reported only SHS exposure (cotinine range 1.82–4.34 ng/mL with one value of 30.3 ng/mL) across all available trimesters. The remaining ten women indicated some smoking during pregnancy, either in the 30 days prior to the visit of misclassification or on a later trimester questionnaire. Cotinine values for four of these misclassifications were between 1 and 11 ng/mL, while two were between 11 and 24 ng/mL, and the remaining four were at levels unusual for non-smokers ranging from 30 to 237 ng/mL.

Of 116 active smokers, eighteen active smokers (16 %) would not have been classified as smokers if a cutoff of 11 ng/mL was used instead of 1 ng/mL. The majority of these women reported light smoking, with thirteen reporting at most one CPD and only two reporting more than three CPD. Two-thirds of these women reported more than 20 h since smoking a cigarette.

Conclusions

Smoking cessation during pregnancy, even for light and intermittent smokers, can improve health outcomes for infants. According to the US Surgeon General, stillbirth rates and infant mortality rates would drop by 11 and 5 %, respectively, if tobacco use during pregnancy were to stop [1]. While there has been a 6 % decline in the AN rate of smoking during pregnancy from 1996 to 2007, this rate remains three times higher than Alaska White women [43]. Similar to other estimates, more than one in four of AN participants in this study reported smoking during pregnancy with reported CPD of ten or less for 91 % of smoking women [13, 14, 44].

As expected, we saw increased saliva cotinine concentration levels associated with increased cigarette consumption and exposure to SHS. In addition, increased prior pregnancies and younger age were associated with smoking during pregnancy, as found in previous studies of AN women [12, 45] and with other populations [46–48].

We estimated a saliva cotinine cutoff value of approximately 1 ng/mL to distinguish active smokers from non-smokers in this population. This cutoff is lower than the cutoff of 13 ng/mL reported for Danish pregnant women of unknown race [33] and lower than cutoffs of 25 ng/mL for Black pregnant women and 11 ng/mL for White pregnant women in the US [32]. Roughly one in six self-reported AN pregnant active smokers, most with low cigarette consumption, would not have been identified as smokers if we utilized the lowest of these cutoffs (11 ng/mL). Specifically focusing on cotinine values between 1 and 11 ng/mL, eighteen (67 %) were measurements of active smokers. An additional four (15 %) appear to be of intermittent or light smokers who did not report active smoking at the visit of data analysis, but had reported some smoking during pregnancy either in the 30 days prior to the visit of data analysis or at a follow-up visit. Only two cotinine concentration levels between

1 and 11 ng/mL (7 %) were associated with women who had reported no SHS exposure or cigarette use during pregnancy.

The results of our study have important implications for public health practice in the AN population. The identification of tobacco use and SHS exposure is important, as evidence suggests that health risks are present for fetus and mother, even at low-levels of use and exposure [49, 50]. However nondisclosure of smoking by pregnant women is common, most likely due to the stigma attached to smoking in spite of widespread warnings of the dangers of tobacco use to the developing fetus [32, 51]. In order to identify pregnancies at risk for tobacco exposure, public health practitioners need to have an objective measure of tobacco exposure. Saliva cotinine measurements are an easy, non-invasive way to obtain tobacco exposure data which can then be used to direct public health intervention efforts, though use in practice may be limited by maternal interest in testing. The saliva cotinine cutoff level that we estimated in this study indicates that in order to identify AN pregnant women smokers, a much lower cotinine cutoff level should be used than the cutoffs previously estimated from other pregnant populations.

The methodology of our study differs in some ways from the two cited studies that estimated a saliva cotinine cutoff to distinguish between pregnant smokers and non-smokers. Boyd et al. analyzed saliva cotinine via radio-immunoassay while Hegaard et al. utilized gas chromatography. Both of these methods had higher LODs than ours, however, the cutoffs they calculated were even higher, so lower LODs would not have made a difference. Further, since the study period of Boyd et al. more policies related to indoor smoking bans have been enacted in the US. This change could mean that non-smoking pregnant women in our study experienced less SHS exposure, and hence fewer non-smokers had elevated cotinine levels. This would translate to a lower false positive rate and increased specificity with a lower cutoff than would be seen in the 1990s. Finally, Hegaard et al. removed all observations with no reported cigarette use and values typically associated with smokers (n = 3; cotinine = 43, 46, and 405 ng/mL). For comparison, we repeated our ROC analysis removing women with cotinine measurement greater than 30 ng/mL (n = 5; cotinine = 30.3, 32.9, 77.3, 103, and 237 ng/mL) and no report of smoking in the past 7 days. AUC did not significantly change (0.986, 95 % CI: 0.976–0.996), and the optimal cutoff was 0.897 ng/mL, still suggesting an optimal cutoff of approximately 1 ng/mL for AN women. Hegaard et al. also excluded women who smoked in the month prior to pregnancy but were not smoking at the first prenatal visit. Given higher rates of intermittent smoking among AN women, we felt it important to include these women in our study.

A recent study of diverse American people found lower serum cotinine cutoffs similar to the saliva cotinine cutoff found in this study. Specifically, a serum cotinine cutoff of 3 ng/mL was estimated to distinguish smokers from non-smokers of any race/ethnic background. Further, race/ethnicity-specific cutoffs varied from 1 ng/mL to 6 ng/mL, with the cutoff of 1 ng/mL estimated to distinguish Mexican–American smokers, a population with high rates of light smoking [36].

There are some limitations to this study which may impact generalizability and validity of results. First, the reliability and validity of the study questionnaire, which was developed

from Robert Wood Johnson Smoke-Free Families evaluation measures [52] along with questions developed by the study team, is unknown. Further, AN women who participated in this study were volunteers who enrolled at an urban tribal healthcare organization. Thus, there may be self-selection bias which may have over-sampled light or intermittent smokers or enrolled smoking participants during periods of reduced smoking. We cannot be certain how smoking patterns and nicotine metabolism compared between participants and AN women who did not enroll. However, the rate of smoking during pregnancy and reported CPD seen in this study were similar to estimates for AN pregnant women from a study with random participation [13, 14, 44], and other studies have shown high rates of light and intermittent smoking among AN people [15–17].

Another potential limitation of our study is long storage time of Salivettes. Cotinine levels could possibly change during storage from initial values; they could have increased due to evaporation of water or decreased from degradation of cotinine. However, previous results point to long-term stability of cotinine in saliva and in Salivettes. Bernert et al. (2000) tested stability of cotinine in contact with Salivettes. They found saliva cotinine levels and volumes unchanged in spiked saliva samples after 2 weeks at room temperature in Salivettes. They also reported no difference in cotinine levels between Salivettes processed immediately and Salivettes processed after being frozen for several days. Pirkle et al. (2006) reported serum cotinine levels unchanged in quality control samples that had been stored for 14 years at −60 °C. Long-term stability of cotinine in saliva is not as well established, but unpublished results from our laboratory confirm that cotinine concentrations are stable at least 28 days in saliva kept at room temperature and at 37 °C.

In conclusion, we recommend using a saliva cotinine cutoff of 1 ng/mL to distinguish active smoking in pregnant AN women. This cutoff is lower than the cutoff used in studies with pregnant women of different races and ethnicities, most likely due to the high incidence of light or intermittent smoking in the AN population. Continued study of cotinine levels in diverse populations is needed.

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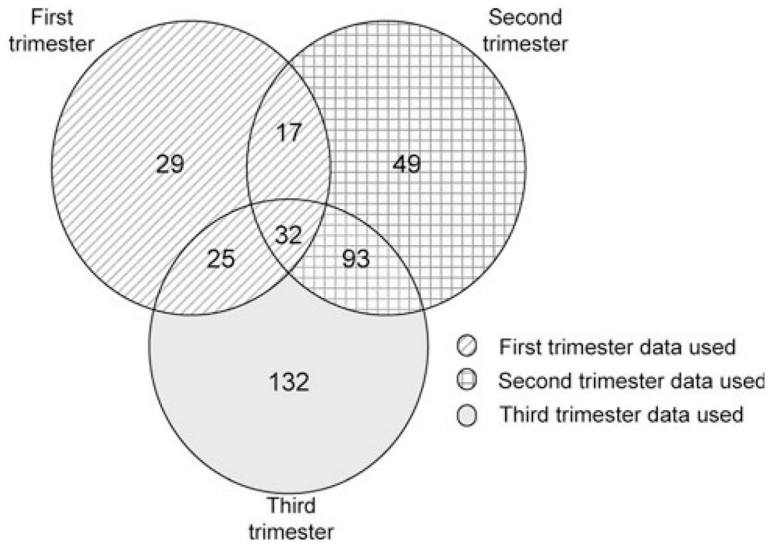

Fig. 1.

Participant visits with cotinine data available. The first visit with cotinine data available was included in analysis

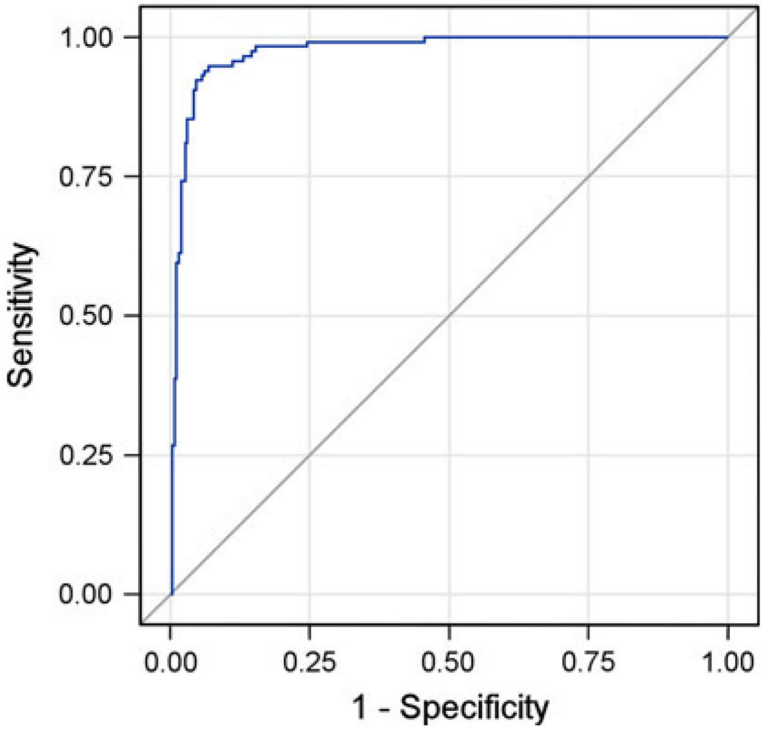

Fig. 2.

Receiver operating characteristic (ROC) curve to classify active smoking/not active smoking using saliva cotinine concentration levels (n = 377). The area under the *curve* is 0.975

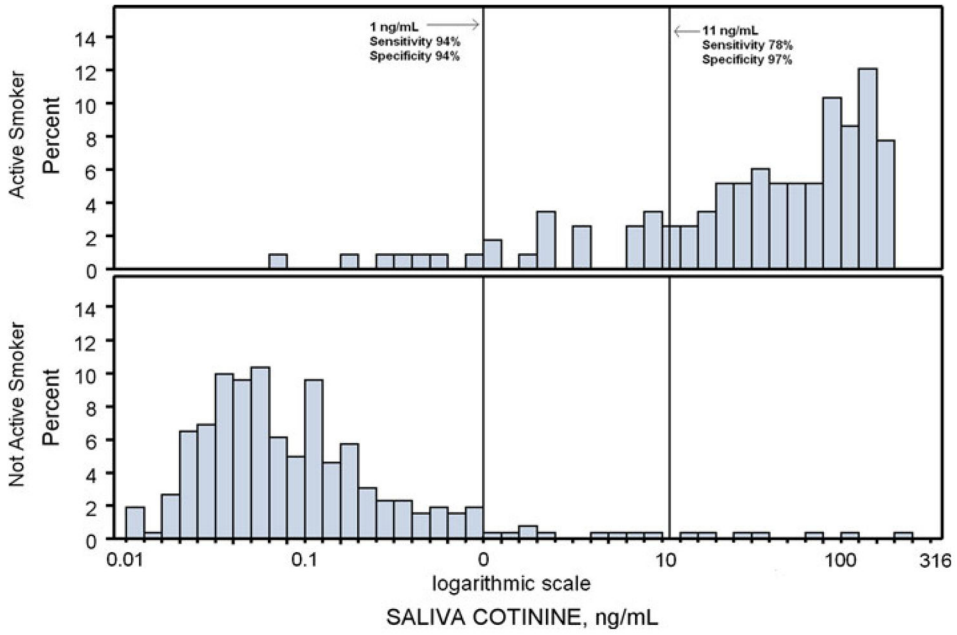

Fig. 3.

Distribution (n = 377) of saliva cotinine concentrations for active smokers (*upper histogram*) and not active smokers (*lower histogram*). Active smokers reported smoking in the last 7 days. *Reference lines* are included for the optimal ROC cutoff for AN pregnant women (1 ng/mL) and a cutoff recommended for White pregnant women (11 ng/mL, Boyd et al. 1998). Between the two *reference lines* on the *upper histogram* is percent of active smokers misclassified as not active smokers with a cutoff of 11 ng/mL, while on the *lower histogram*, this is percent of not active smokers misclassified as active smokers with a cutoff of 1 ng/mL

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Table 1

Descriptive statistics by tobacco exposure status

n = 377	**Non-smoker no SHS[a] exposure**		**Non-smoker SHS[a] exposure**		**Active Smoker no SHS[a] exposure**		**Active Smoker SHS[a] exposure**		***p*-value[b]**
Total sample (missing n = 1)	n = 124	(33 %)	n = 136	(6 %)	n = 27	(7 %)	n = 89	(24 %)	n/a
Age[c] (missing n = 1)	$\bar{x}$=26.9	*s* = 5.3	$\bar{x}$=24.1	*s* = 5.0	$\bar{x}$=25.8	*s* = 4.6	$\bar{x}$=25.7	*s* = 5.6	$p_H < 0.001$
Trimester of first visit with cotinine measured (missing n = 1)									$p_{x^2} = 0.189$
First trimester	n = 34	(27 %)	n = 34	(25 %)	n = 5	(19 %)	n = 30	(34 %)	
Second trimester	n = 43	(35 %)	n = 48	(35 %)	n = 13	(48 %)	n = 38	(42 %)	
Third trimester	n = 47	(38 %)	n = 54	(40 %)	n = 9	(33 %)	n = 21	(24 %)	
Ever smoker[d] (missing n = 2)	n = 67	(54 %)	n = 86	(64 %)	na	na	na	na	$p_{x^2} = 0.132$
Smoking when discovered pregnancy (missing n = 2)	n = 17	(14 %)	n = 40	(29 %)	n = 24	(89 %)	n = 85	(97 %)	$p_{x^2} < 0.001$
Had a prior full term pregnancy (missing n = 1)	n = 68	(55 %)	n = 71	(52 %)	n = 22	(81 %)	n = 57	(64 %)	$p_{x^2} = 0.020$
Number of prior full term pregnancies (missing n = 1)	$\bar{x}$=1.0	*s* = 1.2	$\bar{x}$=1.2	*s* = 1.5	$\bar{x}$=1.9	*s* = 1.4	$\bar{x}$=1.6	*s* = 1.7	$p_H = 0.004$
Has a husband or partner living in the home (missing n = 1)	n = 104	(84 %)	n = 93	(68 %)	n = 16	(59 %)	n = 55	(62 %)	$p_{x^2} = 0.001$
Number of other adults living in the home (missing n = 1)	$\bar{x}$=1.8	*s* = 1.2	$\bar{x}$=2.0	*s* = 1.3	$\bar{x}$=2.3	*s* = 1.5	$\bar{x}$=2.1	*s* = 1.4	$p_H = 0.027$
Average CPD[e] in past 7 days (missing n = 1)	na	na	na	na	$\bar{x}$=4.3	*s* = 4.0	$p_{x^2} = 7.1$	*s* = 12.2	$p_H = 0.658$
Median saliva cotinine, ng/mL (missing n = 1)	median = 0.1	IQR = 0.1	median = 0.1	IQR = 0.2	median = 47.7	IQR = 130.2	median = 48.7	IQR = 82.1	$p_H < 0.001$

[a] Second-hand smoke

[b] *p*-value for $\chi 2$-test of proportions for categorical variables or the Kruskal–Wallis (H) test for continuous variables

[c] Age in years as of the baby's due date

[d] Smoked at least 100 cigarettes in lifetime. 100 % of "Active" smokers are "Ever" smokers and were not included in test

[e] Cigarettes per day. All non-smokers had average CPD of 0 and were not included in test

Table 2

Regression model with logarithm of cotinine concentration values as dependent variable

n = 370 (7 missing) Adjusted R^2 = 0.662 Dependent variables	**Regression estimates**		
	Estimate	**Standard deviation**	***p*-value**
Intercept	−0.389	0.671	0.563
CPD[a] (natural logarithm) in past 7 days	2.680	0.115	< 0.001
SHS[b] exposure	0.651	0.200	0.001
Mom's age (at due date, years)	−0.066	0.021	0.002
Trimester of first visit with cotinine measured	−0.196	0.121	0.104
Number of prior full term pregnancies	0.206	0.074	0.006
Husband or partner lives in the home	−0.267	0.227	0.239
Number of other adults living in the home	0.101	0.077	0.189

[a] Cigarettes per day

[b] Second-hand smoke