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Author manuscript

*Ann Epidemiol.* Author manuscript; available in PMC 2016 January 15.

Published in final edited form as:

*Ann Epidemiol.* 2014 March ; 24(3): 236–239. doi:10.1016/j.annepidem.2013.12.008.

## Accuracy of prenatal smoking data from Washington State birth certificates in a population-based sample with cotinine measurements

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### Abstract

**Purpose**—To assess the accuracy of smoking data in contemporary U.S. birth certificates.

**Methods**—We compared data on prenatal smoking as reported on Washington State birth certificates to cotinine measured in archived newborn screening dried blood spots for 200 infants born in 2007 (100 randomly selected from births to self-reported non-smokers and 100 born to self-reported smokers). We estimated the sensitivity of the birth certificate data to identify prenatal smokers, and the precision with which self-identified third trimester smokers report smoking levels.

**Results**—Infants born to 2 (2%) mothers who reported they did not smoke during the pregnancy had whole blood cotinine concentrations consistent with active smoking by the mother (sensitivity 85%). Sensitivity of the birth certificate to identify reported smokers who continued to smoke throughout pregnancy was similar (89%). Among self-identified third trimester smokers whose infants' specimens were collected shortly after delivery, Spearman's rho between infant cotinine and maternal-reported cigarettes/day in the third trimester was 0.54.

**Conclusions**—Birth certificates may represent a viable option for assessing prenatal smoking status, and possibly smoking cessation and dose among smokers, in epidemiologic studies sufficiently powered to overcome a moderate amount of exposure measurement error.

### MeSH key words

Bias (Epidemiology); Birth Certificates; Cotinine; Pregnancy; Sensitivity and Specificity; Smoking; Smoking Cessation

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## Introduction

Prenatal smoking is associated with several adverse infant outcomes [1], but it remains unclear whether it increases the risk of longer term outcomes, such as childhood cancer [2, 3]. For uncommon outcomes that typically necessitate a retrospective study, public knowledge of smoking's adverse effects may exacerbate the potential for selection bias [4] and differential reporting [5] of prenatal smoking in epidemiologic studies. Birth certificate prenatal smoking data may circumvent these biases. Although generally obtained prior to disease onset or identification (e.g., in studies with linked death or cancer registry data), smoking is still self-reported, and is generally underreported [6-18]. This too may bias results [19,20], but generally in a predictable, conservative manner.

To ascertain the magnitude of such bias, we compared birth certificate smoking data for 200 infants born in Washington State in 2007 to cotinine levels in their newborn screening dried blood spots (DBS). Neonatal and maternal plasma cotinine are almost perfectly correlated [21] and techniques for assessing cotinine in DBS have been validated [22, 23]. To date, relatively few studies [6,15,16] have attempted to validate data collected since the U.S. National Standard for birth records was revised to include smoking level by trimester [24] (Osterman 2011), and only a clinic-based study [17] used a biologic measure of smoking to validate (older) birth certificate data. Therefore, we conducted a population-based study to examine the accuracy of contemporary U.S. birth certificate data using a biologic measure of maternal prenatal smoking. Specifically, we assessed the nicotine metabolite cotinine in blood collected from these mothers' infants shortly after birth.

## Methods

### Identification of participants

All participants were live-born singleton infants with complete birth certificate smoking data and who provided blood for universal neonatal screening after a hospital delivery in 2007 in Washington State. Typically, six 14mm DBS are collected on a single card prior to discharge, and the card is archived at the Washington State Department of Health after partial use for newborn screening. We required that at least two unused, fully saturated DBS be available: one to remain in the archives and one to assess cotinine. To ensure the quality of this gold standard, we applied the following inclusion criteria: 1) absence of maternal/child blood transfusion during the hospitalization; 2) delivery on the day of admission (to exclude mothers unable to smoke shortly before delivery, as the half-life of cotinine is as low as 8.8 hours among pregnant women [25]); and 3) initial blood collection < 48 hours of birth (the half-life of cotinine is 16.3 hours in newborns [26]). From birth records with complete data on smoking we randomly selected 100 infants whose birth certificate indicated no maternal prenatal smoking, and 25 infants from each of four maternal smoking groups: low (<10), medium (10 -<20), high (20 -<30), very high (≥ 30) mean cigarettes/day across each of the three trimesters.

### Assessment of cotinine in dried blood spots

We punched 2 6.35 millimeter (mm) circles from the most saturated areas of each DBS, methanol-rinsing the punch between specimens. The Environmental Health Laboratory and Trace Organics Analysis Center at the University of Washington (Seattle, WA) assessed cotinine levels blinded to maternal-reported smoking. Assays were conducted in 6 batches, with 3 negative controls and 2 positive controls in each batch. Twenty-three (12%) of samples were split and assayed in duplicate (intraclass correlation = 0.9999). Cotinine levels were corrected for reagent blank values and spike recovery efficiency (92.5-101.2%). Samples below the reporting limit (0.009-0.02 nanograms [ng] cotinine) were assigned half the limit for that batch. We reassayed one batch (18% specimens) using two less saturated punches from the same DBS; agreement was very good (Spearman's  $\rho=0.93$ ; 100% concordance when classifying mothers as smokers/non-smokers).

To estimate the cotinine concentration, we assumed each pair of punches contained 12.32 microliters ( $\mu\text{L}$ ) of serum [27] and 28  $\mu\text{L}$  (0.028 milliliters (mL)) of whole blood (12.32  $\mu\text{L}$ / (1-0.56), where 0.56 is the portion estimated hematocrit [28] and clotting factors in capillary blood from a term neonate 1-3 days old). The latter is similar to that used previously on adult DBS (12  $\mu\text{L}$  for one 6.35 mm punch [22]). We present cotinine concentrations as ng/mL whole blood for comparability to the one prior study measuring cotinine in neonatal DBS [23].

### Statistical analysis

We classified a mother as a true smoker if she reported having smoked any number of cigarettes in any trimester or if her infant's DBS contained cotinine  $>5$  ng/mL. We used this cut point because in adult DBS cotinine 1-5 ng/mL can indicate high exposure to environmental tobacco smoke [22], and is nearly identical to the optimum cut point of 6 ng/mL determined in a recent study assessing cotinine in neonatal DBS [29]. We then identified how many of the 100 self-reported non-smokers were true smokers, and estimated the sensitivity of the birth certificate to identify true smokers. We estimated sensitivity as  $11/(11 + \text{number of self-reported non-smokers who were true smokers})$ . In the present context, sensitivity is defined as the number of smoking mothers who reported that they smoked divided by the total number of smokers. Here we estimate the numerator as 11 because in 2007, 10% of Washington State birth certificates indicated prenatal smoking, and therefore given 100 self-reported non-smokers (as included here) there would be approximately 11 self-reported smokers ( $11/111 = 10\%$ ).

Among reported smokers, we identified those who reportedly quit by the third trimester, but continued to smoke. Finally, among mothers who reported still smoking in the third trimester, we estimated the precision with which they reported smoking level by calculating Spearman's rho [30] between cotinine (continuous) and reported third trimester cigarettes/day (continuous).

## Protection of Human Subjects

Work was conducted after receipt of approvals from the Washington State and Fred Hutchinson Cancer Research Center Institutional Review Boards. Prior to release, specimens were anonymized by archive staff using a previously described protocol [31].

## Results

### Characteristics of participants

Approximately half (48%) of reported non-smokers were non-Hispanic Caucasian; 30% were Hispanic (Table 1). The majority (82%) of reported smokers were non-Hispanic Caucasian. The mean elapsed time between infant birth and blood collection was <24 hours. Among self-reported smokers, mean cigarettes/day declined as the pregnancy progressed, but 76% said they still smoked during the third trimester. They consumed a mean of 14.7 cigarettes/day (standard deviation 10.9, Table 1; median 10, range 2-40 cigarettes/day, data not shown).

### Cotinine and reported smoking status

Cotinine ranged from below the reporting limit (estimated 0.17 ng/mL) to 169 ng/mL (Table 2). Mean, median, interquartile range and maximum cotinine levels were markedly greater in infants whose mothers reported smoking during the third trimester (median 36.6, mean 45.7 ng/mL) than in infants whose mothers reported smoking only earlier in pregnancy (median 0.82, mean 9.95 ng/mL) (Wilcoxon rank sum  $p < 0.0001$ ). Both had markedly greater cotinine than infants whose mothers reported that they did not smoke during pregnancy (median 0.38, mean 1.37 ng/mL) (both  $p < 0.0008$ ).

Two (2%) of the 100 self-reported non-smokers had infants with cotinine >5 mg/mL (Table 2, 22.2-66.0 ng/mL, data not shown), indicating a sensitivity of approximately 85% of the birth certificate data to identify prenatal smoking. Of the 100 reported smokers, 9/24 (38%) of those who reportedly stopped smoking before the third trimester had smoked in the days before birth (Table 2); among self-reported smokers, the sensitivity of the birth certificate data to identify mothers who continued smoking during the third trimester was 89%.

### Cotinine and reported level of smoking

Among infants of reported third trimester smokers, median cotinine was not associated with smoking level (low=35.5, medium=36.7, high=35.9, very high=37.1, in ng/mL, Spearman's  $\rho = 0.04$ , data not shown). However, when we focused on the 15 infants whose blood was collected within 16 hours of birth (the mean cotinine half life in neonates), Spearman's  $\rho$  was 0.54 ( $p = 0.04$ ).

## Discussion

To our knowledge this is the first population-based U.S. sample in which the accuracy of smoking data on birth certificates was assessed using a biologic measure of smoking. Among 100 reported non-smokers, 2 (2%) appeared to be smokers, suggesting that birth certificates identify 85% of prenatal smokers who provide complete birth certificate data on

smoking. These estimates are similar to a recent population-based study of nearly 3,000 pregnant women in Norway [32]. Moreover, cotinine concentrations by smoking group were very consistent with those measured in DBS from other U.S. neonates [23]. Our estimate for sensitivity is markedly greater than that in the single other U.S. study comparing birth certificate-reported smoking status to cotinine levels among mothers at publicly funded clinics [17], or in a study of mothers in Estonia [11]. However, ours is probably more generalizable to the U.S. population, as demographic factors are associated with maternal reporting of prenatal smoking [33]. Given our modest sample size we were unable to explore whether this reporting differed by race or ethnicity in this sample.

In addition, 5% of smokers in our study had cotinine levels of non-smokers, so we cannot rule out missing true smokers. This might have occurred if mothers were unable to smoke prior to delivering, or if infants' blood was collected too long after delivery. We attempted to avoid issues related to cotinine clearance by excluding women hospitalized for >1 day before delivery, and infants whose blood was collected >48 hours after birth. If nonetheless we missed 1 smoker among the reported non-smokers, sensitivity would drop to 79%. If we missed 2, sensitivity would be 73%, which is close to the sensitivity that can be estimated from Allen et al. [6]. Conversely, we could have underestimated the sensitivity of the birth certificates if we observed false positives as previously in a study using neonatal DBS [29]. However, that study used different laboratory methods, and we observed relatively high cotinine (22.2-66.0 ng/mL) in the self-reported non-smokers.

With sensitivities ranging from 73-85%, near perfect specificity (99%), non-differential exposure measurement error, and typical prevalence of prenatal smoking in the non-diseased (10%-30%), sometimes odds ratios (ORs) would be noticeably attenuated (Table 3). For example, at 79% sensitivity and 20% prevalence of smoking, an OR of 5 would be attenuated to 4. Although this represents an attenuation of 20%, the OR remains well above null. The effect on a true OR much closer to the null would be less perceptible. For example, a true OR 1.20 would be only attenuated to 1.17-1.18. These calculations demonstrate the general direction and magnitude of changes to the OR in an idealized scenario. In practice, for example when there also may be misclassification of the outcome – in some instances also likely from the birth certificate – then the effect on ORs may be more complex [34].

More than a third of mothers who said they had quit smoking by the third trimester had not quit. This is more than estimated by England et al. [19] (22%), perhaps because we oversampled mothers who smoked the most, and greater cigarettes/day indicates greater nicotine dependence [35]. Despite the substantial overreporting of cessation among self-reported smokers, sensitivity of the birth certificate data to identify those who continued to smoke throughout pregnancy remained good (89%).

We observed a moderate positive relationship ( $\rho=0.54$ ) between infant cotinine and the mother's reported cigarettes/day in the third trimester when we focused on infants born to self-reported third trimester smokers and whose blood was collected close to delivery. This too is very similar to the results ( $\rho=0.51$ ) of Kvalvik et al. [32], and a recent study confirms that restricting to DBS prepared close to delivery would be important in our analysis [29]. Although these precision estimates are above the minimum acceptable for dietary data [36],

this degree of measurement error would have substantial effects. In a hypothetical study of the development of childhood asthma in relation to the number of cigarettes in the third trimester (excluding zero), a true OR of 1.20 for each pack/day would be observable as only 1.05 (1.2 to the power of  $(0.54)^2$ ), assuming non-differential measurement error, according to the attenuation equation [30]. In a study between smoking and birth weight as a continuous outcome, the effect per pack/day would be estimated at less than one-third its true level ( $(0.54)^2$ ). While these estimates indicate that the cigarettes/day variable should be used with care to estimate smoking level, we likely underestimated precision. Greater smoking could be associated with greater cotinine clearance [37], and as noted above, some women's smoking may have been hampered by labor and hospitalization.

Although self-reported smoking data must be used with some caution, especially when the timing of the smoking is important [38], our results are generally encouraging. Birth certificate data collected prior to the child's diagnosis may reduce selection and information bias, and may be a cost-effective way to assess prenatal smoking exposure in epidemiologic studies.

## Acknowledgments

This research was supported by grant R03 CA141487 from the National Cancer Institute of the National Institutes of Health. We thank the Washington State Department of Health for data access, and Sheila Weiss of the Newborn Screening Program; Jacqui Ahmad of the Environmental Health Laboratory and Trace Organics Analysis Center, University of Washington; and William O'Brien of the University of Washington for data management.

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## Abbreviations

<b>DBS</b>	Dried blood spot
<b>mm</b>	Millimeter
<b>mL</b>	Milliliter
<b>ng</b>	Nanogram
<b>OR</b>	Odds ratio
<b>RL</b>	Reporting limit
<b>µL</b>	Microliter



**Table 1**  
**Maternal and infant characteristics and smoking, by maternal prenatal smoking status on the birth certificate, Washington State 2007**

	Did not smoke during pregnancy N=100 <sup>b</sup>	Smoked during pregnancy <sup>a</sup> N=100 <sup>b</sup>
	<u>n (%)</u>	<u>n (%)</u>
Mother's race/ethnicity		
Caucasian	46 (48)	81 (82)
Hispanic	29 (30)	7 (7)
Asian/Pacific Islander	13 (14)	3 (3)
African American	5 (5)	3 (3)
Native American	3 (3)	5 (5)
Male infant	53 (53)	56 (56)
Preterm (<37 weeks)	3 (3)	5 (5)
Low birth weight (<2500 grams)	1 (1)	3 (3)
	<b>Mean (SD)<sup>c</sup></b>	<b>Mean (SD)<sup>c</sup></b>
Birth to blood collection (hours)	23.2 (8.8)	23.4 (8.3)
Cigarettes smoked/day <sup>d</sup>		
Before pregnancy <sup>e</sup>	12.0 (11.3)	21.3 (14.6)
1 <sup>st</sup> trimester	n/a	20.5 (14.9)
2 <sup>nd</sup> trimester	n/a	17.9 (14.6)
3 <sup>rd</sup> trimester	n/a	14.7 (10.9)

<sup>a</sup>25 infants from each of four maternal smoking levels (low (<10), medium (10 -<20), high (20 -<30), very high (≥30) cigarettes/day)

<sup>b</sup>May not add to totals due to missing data; percent among those with complete data

<sup>c</sup>Standard deviation

<sup>d</sup>Among those smoking during the specified period: 2 prenatal non-smokers and 97 prenatal smokers who smoked prior to pregnancy; and 98 prenatal smokers who smoked during the 1<sup>st</sup> trimester, 82 during the 2<sup>nd</sup> trimester and 76 during the 3<sup>rd</sup> trimester

<sup>e</sup>3 months prior to conception

**Table 2**  
**Cotinine (ng/mL) in newborn screening dried blood spots, by birth certificate-reported maternal prenatal smoking, Washington State 2007**

	Did not smoke during the pregnancy N=100	Quit smoking before the 3 <sup>rd</sup> trimester N=24	Smoked during the 3 <sup>rd</sup> trimester N=76
Mean <sup>d</sup>	1.37	9.95	45.74
Standard deviation <sup>d</sup>	6.90	15.91	31.93
Minimum	<RL <sup>b</sup>	<RL <sup>b</sup>	<RL <sup>b</sup>
25 <sup>th</sup> percentile	<RL <sup>b</sup>	0.38	23.24
Median	0.38	0.82	36.60
75 <sup>th</sup> percentile	0.71	14.82	60.19
Maximum	66.01	53.29	169.12
n (%) 1-5 ng/mL (passive smoker)	11 (11)	2 (8)	1 (1)
n (%) >5 ng/mL (active smoker)	2 (2)	9 (38)	72 (95)

<sup>a</sup> Non-detects assigned one half of the reporting limit for the batch

<sup>b</sup> Below the reporting limit (0.32-0.71 ng/mL)

**Table 3**  
**Observable odds ratio (OR)<sup>a</sup>, by sensitivity of birth certificate to identify prenatal smoking, the proportion of non-diseased who smoke, and true OR**

Sensitivity	Proportion non-diseased		True disease-smoking odds ratio				
	who smoke		1.2	1.5	2.0	3.0	5.0
85%	0.10		1.18	1.44	1.87	2.72	4.33
	0.20		1.18	1.45	1.89	2.71	4.21
	0.30		1.18	1.44	1.86	2.63	3.93
79%	0.10		1.17	1.43	1.86	2.67	4.20
	0.20		1.18	1.44	1.86	2.64	4.00
	0.30		1.18	1.43	1.82	2.52	3.66
73%	0.10		1.17	1.42	1.84	2.63	4.08
	0.20		1.17	1.43	1.83	2.57	3.82
	0.30		1.17	1.41	1.78	2.43	3.44

<sup>a</sup> According to the attenuation equation [30]. Assumes non-differential exposure measurement error (sensitivity equal in diseased and non-diseased, specificity = 99% in both diseased and non-diseased), and no error in outcome ascertainment.