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Urine and toenail cadmium levels in pregnant women: a reliability study

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Abstract

Background—Cadmium, as measured in human tissue, has been associated with numerous health outcomes. However, few studies have evaluated the reliability of cadmium measurements across different biologic samples. We evaluated toenail cadmium levels over time and compared toenail cadmium to urinary cadmium. We also evaluate the relationship between biomarker concentrations and cigarette smoking, a known source of cadmium exposure.

Methods—Cadmium was assessed in urine and toenail samples collected from 1,338 pregnant women participating in the New Hampshire Birth Cohort Study. Each participant was asked to provide a urine and a toenail sample at enrollment (between 24–28 weeks gestation) and another toenail sample 2–8 weeks postpartum. Cadmium concentrations were determined using inductively-coupled plasma mass spectrometry. Spearman correlations were assessed for cadmium in the toenails across the two-time points and comparing toenail and urine levels. Smoking status was evaluated as a predictor of cadmium levels.

Results—Toenail cadmium assessed during pregnancy and postpartum were modestly correlated ($R=0.3$, $p<0.0001$). However, urine and toenail cadmium levels were unrelated ($R=-0.03$, $p=0.46$). Both toenail and urinary cadmium levels were associated with women's smoking status.

Conclusion—Our findings suggest that both toenail and urinary cadmium concentrations reflect the major source of exposure – cigarette smoking. Toenail cadmium concentrations are modestly

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reproducible pre- and postpartum; but do not appear to be related to urinary cadmium and thus likely represent different windows and chronicity of exposure among pregnant women.

Keywords

cadmium; pregnancy; urine; toenail; reliability; biomarker

Introduction

Cadmium is a toxic and persistent heavy metal and is ubiquitous in the environment due to both industrial and agricultural activities ¹. The general population is exposed to cadmium predominately through the use of tobacco products and contamination in their diet ². Dietary cadmium intake has been recently estimated to exceed recommended thresholds for kidney damage ³. Women may be particularly susceptible to cadmium exposure, as they are more likely to be iron deficient ⁴ and lower iron body store levels may result in increased cadmium absorption ^{5,6}. Higher cadmium exposure has been associated with a number of health outcomes including elevated blood pressure ^{7,8}, cardiovascular disease ⁹, diabetes ^{8,10}, chronic kidney disease ⁸, osteoporosis ¹¹ and possibly breast cancer ¹². In pregnant women, cadmium levels have been related to risk of preeclampsia ¹³ and reduced offspring birth weight ¹⁴.

Cadmium sources (e.g. dietary intake, smoking, air pollution) ¹ are varied and difficult to quantify, and thus representative biomarkers are critical to studying this exposure. Epidemiologic studies of the health effects of cadmium often rely on urinary cadmium levels as biomarkers of individual exposure ¹⁵. Cadmium is known to accumulate in the kidney with a long half-life (10–30 years) ¹, meaning that urinary levels are hypothesized to reflect long-term exposure ¹⁶. Urinary measures of cadmium have been highly correlated with cadmium measured in the kidney cortex ¹⁷ and are hypothesized to reflect cadmium body burden better than estimated dietary intake, a major exposure source ¹⁸. On the other hand, cadmium is potentially nephrotoxic and may affect kidney function (including creatinine production and specific gravity), and thereby could impact the relationship between measured levels and true exposure ¹⁹. Thus, even urine cadmium measures that are standardized for urine dilution are difficult to define and compare. It has also recently been noted that urinary cadmium levels may vary depending on urinary flow, urine collection protocol and recent exposure ²⁰. Additionally, situations may arise where recent exposure levels are more relevant for the health outcome of interest or when other biologic samples are too difficult or expensive to obtain. Toenail cadmium levels have been used as an alternative biomarker. They are relatively simple and inexpensive to obtain and easy to store. Toenails have been estimated to grow about 2mm/month ²¹. By measuring toenail cadmium levels in all five digits, the measurement is estimated to integrate exposure from a 4–6 month window of time that occurred approximately 6–12 months prior to nail collection ^{21–23}. Samples are standardized by weight and are therefore easy to compare across individuals.

In light of the paucity of data on the reliability of cadmium biomarkers, we assessed the reproducibility of toenail cadmium among pregnancy women measured both pre- and postpartum, and tested the reliability of toenail versus urinary cadmium concentrations. We

also examined whether smoking, a major source of cadmium exposure, was associated with toenail and urinary cadmium in this population.

Methods

We examined urine and toenail cadmium levels in samples collected from 1732 pregnant women participating in the New Hampshire Birth Cohort Study (2009–2016). Each participant was asked to provide a spot urine sample at enrollment (between approximately 24–28 weeks gestation) and two toenail samples – one at enrollment and the other from about 2 to 8 weeks postpartum^{24,25}. Participants provided informed consent, and the study was approved of by the Committee for the Protection of Human Subjects at Dartmouth College.

As described previously, study participants were provided with a prelabeled, acid-washed, screw-top 120-mL urine specimen container that contained 30ul of 10mM diammonium diethyldithiocarbamate²⁶. Spot urine samples were stored upright in a Styrofoam container at 4°C and within 24 hours were sent via courier to Dartmouth Hitchcock Medical Center for processing. Samples were aliquoted and stored at –80°C.

As described previously²⁵, toenails were washed with acetone and deionized water and then dried and acid-digested. They were then analyzed using inductively-coupled plasma mass spectrometry (ICP-MS, Santa Clara, CA). Urinary cadmium levels were also analyzed using ICP-MS, after 10-fold dilution with 1% HNO₃. Samples below the limit of detection (LOD) were given values of LOD/ 2. Urine sample LODs were batch-specific (range: 0.001–0.02 µg/g). The average nail sample weight available for digestion was 40 mg with a minimum of about 5 mg needed. Using this sample mass and the ICP-MS instrument detection limit (0.005 µl/l) we calculated a method detection limit of 0.0012 ng/g. Quality control included continuing calibration verification, using analytic duplicates and spikes (1 quality control sample per 20 samples), and digestion of fortified blanks and certified reference materials (NIES#13, hair). Average recovery of the hair CRM was 91 ±7% and average recovery of the analysis spikes was 100 ±6%. We adjusted for batch effects for each group of samples separately using a random effects model to estimate the batch-specific intercept and then standardizing across batches by subtracting that estimate from each value in the batch. We adjusted urine samples for specific gravity using covariate-adjusted standardization²⁷. All values were log-transformed so that the distributions appeared normal.

We first examined correlations between cadmium levels measured in toenails collected at the two time points using Spearman correlation coefficients. We also estimated the correlations between cadmium levels measured in urine and toenails collected at enrollment and as a secondary analysis considered the correlation between urine at enrollment and toenails collected postpartum. When comparing the urine and toenail correlations, we also considered multivariable-adjusted analyses by including age, BMI, race/ethnicity and smoking status as covariates. If needed, we assessed non-linearity by predicting model fit using restricted cubic splines (knots at the 5th, 35th, 65th, and 95th percentiles). We also examined whether the samples collected during gestation were associated with self-reported cigarette smoking when not pregnant (categorized as never, sometimes, everyday) or with

cigarette smoking specifically during second trimester when the urine sample was collected (categorized as yes, no). This was done using either analysis of variance (ANOVA; >2 categories) or a t-test (2 smoking categories) to compare differences in cadmium levels across categories. An alpha level of 0.05 was used to determine statistical significance. The statistical software used for these analyses was R²⁸.

Results

Of the initial 1732 participants, 1,338 provided at least one cadmium measure (Table 1). A total of 1,125 women had toenail cadmium measured at ~24–28 weeks gestation, and 1,049 women had toenail cadmium measured at ~2–8 weeks postpartum. A total of 639 women had urinary cadmium measured at ~24–28 weeks gestation available at the time of this analysis. Study participants were 31 years of age at enrollment, on average, and the majority were non-Hispanic white (97%). Average pre-pregnancy BMI was 25.9 kg/m². Overall, 13% of women reported ever smoking cigarettes, with a smaller proportion reporting smoking just before or during pregnancy (11%, 6% and 4% for the 3 months prior to pregnancy, first trimester, and second trimester, respectively). Women who provided biospecimens were slightly less likely to be smokers, but were otherwise similar to the original cohort (Supplementary Table).

Cadmium levels were below the LOD for 182 (16%), 132 (13%) and 26 (4%) women for prenatal toenails, postnatal toenails and urinary cadmium, respectively. Information on both pre- and postpartum toenail cadmium was available for 915 women. Mean cadmium levels were nearly identical (geometric mean = 0.005 µg/g for both sets of samples), and moderately correlated (Spearman R=0.3, p<0.0001; Figure 1). Pre-natal toenail and urine enrollment cadmium measurements were available from 489 women. Overall, cadmium concentrations in the urine and pre-natal toenails were unrelated (Spearman R= -0.03, p=0.46; Figure 2). Higher toenail cadmium levels were associated with a slight decrease in urinary cadmium levels ($\beta = -0.03$ in log urinary cadmium per 1 unit increase in log toenail cadmium; 95% confidence interval: -0.12, 0.06), with similar results seen after adjustment for age, BMI, race/ethnicity and smoking status or with restriction to never smokers. Results of the spline model showed minimal deviation from linearity with no evidence that the correlation changed for different values of urine or toenail cadmium (Supplementary Figure). Likewise, we observed no correlation between prenatal urinary cadmium and postpartum toenail cadmium (R=0.002, p=0.96).

Both baseline toenail and urinary cadmium levels were associated with self-reported, usual cigarette smoking while not pregnant (ANOVA p=0.01 for toenail and p=0.001 for urine), with statistically significant differences seen between never-smokers and everyday-smokers in post-hoc comparisons (Tukey's method). Baseline toenail and urine cadmium levels were also both associated with self-reported smoking in the second trimester (p=0.009 for toenail and p=0.002 for urine). Results were similar when comparing postnatal toenail levels and cigarette smoking status. In the multivariate models, both BMI and age were associated with urinary cadmium whereas only age was associated with toenail cadmium.

Discussion

In this population of pregnant women, we observed a modest correlation between toenail cadmium levels measured in samples collected at 28 weeks of pregnancy and those measured in samples collected at approximately 6 weeks postpartum in the same woman. When we compared these levels to cadmium measured in urine collected at 28 weeks of pregnancy, we found little to no evidence of a correlation. However, both urine and toenail cadmium were associated with self-reported smoking status when not pregnant and self-reported smoking status during the second trimester.

While other research studies have included multiple types cadmium biomarkers^{29–35}, we only identified one study comparing urine and toenail cadmium levels directly, and this was within an occupationally-exposed population of 239 farm workers in Qatar³⁵. Here, no associations were observed between urine and toenail metal concentrations for a panel of metals, including cadmium.³⁵

In our study, both toenails and urinary cadmium were associated with smoking exposure, the primary source of cadmium in the general population³⁶. Cadmium concentrations in the urine have been previously associated with lifetime pack-years of smoking and long-term exposure to environmental tobacco smoke^{36–39}, and our findings here confirm that association. While urinary cadmium is considered a long-term biomarker of exposure, toenails are thought to reflect exposure in the previous 6–12 months^{22,23}. Thus, the lack of correlation between toenail and urine despite the association with smoking status measures is likely because these biomarkers are capturing different timing and accumulation of exposure. Alternatively, they could be measuring different sources of cadmium exposure; however, evidence of this lacking and hence will need to be determined in future work.

The relationship between toenail and urinary measures of other trace metals varies by metal. Previous studies have reported that toenail arsenic is well correlated with urine arsenic^{40–43}. Studies of other trace metals in toenails compared to urinary levels are limited; mercury levels in urine and toenails have also been shown to be strongly correlated ($r=0.79$; $p<0.01$)⁴⁴ while manganese concentrations were not in a prior study of 46 occupationally-exposed welders⁴⁵.

Consistent with our findings here, other studies have suggested that toenail metal levels are moderately correlated when considering samples taken years apart, although these studies have not included cadmium^{42,46,47}. In a study of adult women ($n=221$) with a family history of breast cancer within the Sister Study cohort, cadmium levels in toenails were similarly moderately correlated ($R=0.38$) in two toenail samples taken 4–10 years apart⁴⁸. It is conceivable that the correlation observed in women during and after pregnancy could be influenced by metabolic or dietary changes during pregnancy or varying cadmium accumulation in the placenta during gestation²⁴. It would be useful to compare our results with future studies of toenail samples collected pre- and postpartum.

Although many studies have utilized toenails as biomarkers of trace metal exposure^{49–55}, the reliability has not yet been well established for many metals^{35,51}. The strengths of this study include the ability to compare two toenail cadmium samples (pre- and postpartum), as

well as to consider the correlation between toenail and urinary cadmium levels. We cannot rule out the possibility that these findings are not influenced by pregnancy and thus not generalizable to studies of non-pregnant populations. As mentioned, it is possible that the altered metabolism of pregnancy may have influenced cadmium uptake and storage in the body⁵⁶. There were also very few smokers in this population, which is to be expected given they were all pregnant. This made it difficult to consider time since quitting or other more detailed smoking variables in relation to cadmium biomarkers. Cadmium exposure occurs from multiple sources, including diet, which are challenging to adequately capture¹⁸. Thus, it is difficult to determine the validity of biomarkers of cadmium and crucial to consider the reliability of alternative biomarkers. Further research is needed to evaluate the reliability of toenail cadmium levels in other populations

We did not consider blood cadmium levels as these measurements were not available in this study population, but it would be of interest to consider correlations across all three biomarkers. Another limitation of this study of note is the number of values below the detection limit for our toenail samples (13–16%). This may be due to a low level of cadmium exposure in the population and low nail sample masses that made it difficult to detect cadmium.

In conclusion, maternal toenail and urinary cadmium concentrations appear to reflect exposure via tobacco smoke, although these matrices represent different exposure windows and exposure accumulation. Other epidemiologic investigations of cadmium in relation to health outcomes can use these results to guide the determination of the optimal biomarker of exposure for their study population and research question of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cadmium is a toxic metal that has been associated with several health outcomes
- Cadmium can be measured in the toenails, which are easily collected and stored
- Toenail cadmium assessed during pregnancy and postpartum were modestly correlated.
- Toenail and urinary cadmium were not correlated
- Toenail and urine cadmium may represent different windows or chronicity of exposure

Figure 1.
Comparison of toenail cadmium levels: 24–28 weeks gestation versus 2–8 weeks postpartum
(n=915 with both measured)

Figure 2.
Comparison of toenail cadmium levels (24–28 weeks gestation) versus specific gravity-adjusted urinary cadmium levels (24–28 weeks gestation); n=489 with both measured

Table 1

Descriptive characteristics of 1338 mothers from the New Hampshire Birth Cohort Study (2009–2016) with at least one cadmium measurement

Participant Characteristics	
Age at enrollment (years); mean (std)	31.3 (4.9)
Non-Hispanic, White; n (%)	1295 (97)
Gestational age at delivery (weeks); mean (std)	39.3 (1.8)
Pregnancy Number; n (%)	
1	1241 (94)
2	78 (6)
3	6 (0)
missing	13
Pre-pregnancy BMI (kg/m²); mean (std)	25.9 (5.6)
missing	38
Smoking when not pregnant; n (%)	
Never	1077 (87)
Sometimes	62 (5)
Every Day	96 (8)
missing	103
Smoking	
Smoked in three months before pregnancy; n (%)	141 (11)
missing	106
Smoked first trimester; n (%)	76 (6)
missing	107
Smoked second trimester; n (%)	54 (4)
missing	106
Toenail cadmium level^a, 24–28 weeks gestation; geometric mean (IQR)	0.005 (0.002–0.01) ^c
Not available	213
Toenail cadmium level^a, 2–8 weeks post- partum; geometric mean (IQR)	0.005 (0.002–0.01) ^d
Not available	289
Urinary cadmium level 24–28 weeks gestation^{a,b}; geometric mean (IQR)	0.07 (0.03–0.15) ^e
Not available	699

^a Adjusted for batch using a random effects model

^b Adjusted for specific gravity using covariate-adjusted standardization

^c 182 women (16%) had values below limit of detection (LOD; 0.0012 µg/g); imputed as 0.0012/ 2 = 0.00849 µg/g.

^d 132 women (13%) had values below LOD; imputed as 0.0012/ 2 = 0.00849 µg/g.

^e 26 women (4%) had values below the batch-specific LOD; imputed as LOD/ 2