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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 evaluated 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 1338 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 and 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 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.

1. Introduction

Cadmium is a toxic and persistent heavy metal and is ubiquitous in the environment due to both industrial and agricultural activities (Järup and Åkesson, 2009). The general population is exposed to cadmium predominately through the use of tobacco products and contamination in their diet (Benavides et al., 2005). Dietary cadmium intake has been recently estimated to exceed recommended thresholds for kidney damage (Satarug et al., 2017a). Women may be particularly susceptible to cadmium exposure, as they are more likely to be iron deficient (Looker et al., 1997) and lower iron body store levels may result in increased cadmium absorption (Gallagher et al., 2011; Julin et al., 2011). Higher cadmium exposure has been associated with a number of health outcomes including elevated blood pressure (Gallagher and Meliker, 2010; Satarug et al., 2017b), cardiovascular disease (Tellez-Plaza et al., 2013), diabetes (Satarug et al., 2017b; Tinkov et al., 2017), chronic kidney disease (Satarug et al., 2017b), osteoporosis (James and Meliker, 2013) and possibly breast cancer (Larsson et al., 2015). In pregnant women, cadmium levels have been related to risk of preeclampsia (Laine et al., 2015) and reduced offspring birth weight (Vidal et al., 2015).

Cadmium sources (e.g. dietary intake, smoking, air pollution) (Järup and Åkesson, 2009) 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 (Adams and Newcomb, 2013). Cadmium is known to accumulate in the kidney with a long half-life (10–30 years) (Järup and Åkesson, 2009), meaning that urinary levels are hypothesized to reflect long-term exposure (Nawrot et al., 2010). Urinary measures of cadmium have been highly correlated with cadmium measured in the kidney cortex (Akerstrom et al., 2013) and are hypothesized to reflect cadmium body burden better than

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estimated dietary intake, a major exposure source (Satarug et al., 2017c). 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 (Madden and Fowler, 2000). 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 (Bernard, 2016). 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 2 mm/month (Yaemsiri et al., 2010). 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 (Yaemsiri et al., 2010; Slotnick and Nriagu, 2006; Grashow et al., 2014a). 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.

2. 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 (Punshon et al., 2015; Davis et al., 2014). 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 10 mM diammonium diethyldithiocarbamate (Gilbert-Diamond et al., 2011). Spot urine samples were stored upright in a Styrofoam container at 4 °C and within 24 h were sent via courier to Dartmouth Hitchcock Medical Center for processing. Samples were aliquoted and stored at −80 °C.

As described previously (Davis et al., 2014), 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% HNO_3. 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 standardization (O'Brien et al., 2016). 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 R (R Core Team, 2013).

3. Results

Of the initial 1732 participants, 1338 provided at least one cadmium measure (Table 1). A total of 1125 women had toenail cadmium measured at ~24–28 weeks gestation, and 1049 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/m^2. 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, $p < 0.0001$; Fig. 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; Fig. 2). Higher toenail cadmium levels were associated with a slight decrease in urinary cadmium levels (β = −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

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