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PRINCIPAL INVESTIGATOR: Rudolph Rull, Ph.D.

CONTRACTING ORGANIZATION:

Cancer Prevention Institute of California

Fremont, CA 94538

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14. ABSTRACT This proposed study will examine whether exposure to cadmium (Cd) from dietary or environmental sources increases the risk of breast cancer. We will examine this hypothesis using information collected from the California Teachers Study (CTS) cohort, a group of approximately 130,000 female school employees living in California followed for breast cancer since 1995. Information collected by questionnaire includes residential addresses, exposure to tobacco smoke, and food and beverage consumption. We will assess levels of dietary and environmental exposure by linking these collected data with available information on Cd residue levels in foods and beverages and environmental sources of Cd pollution near women's residences. In addition, we will estimate total Cd exposure by using existing urine samples provided by 304 women in the CTS to determine the relative contributions of dietary and environmental sources to the level of urinary Cd, which is considered a good measure of cumulative lifetime exposure. We will then evaluate whether dietary, environmental, and total exposure to Cd increase the risk of breast cancer. We made substantial progress in the second year of the study. We created the analytic datasets and completed the initial dietary and environmental exposure assessments. In addition, we identified predictors of urinary Cd concentrations among participants in the exposure validation sub-study. We are preparing our first manuscript and will initiate the breast cancer risk analyses.					
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INTRODUCTION

This proposed study will examine whether exposure to cadmium (Cd) from dietary or environmental sources increases the risk of breast cancer. We will examine this hypothesis using information collected from the California Teachers Study (CTS) cohort, a group of approximately 130,000 female school employees living in California followed for breast cancer since 1995. Information collected by questionnaire includes residential addresses, exposure to tobacco smoke, and food and beverage consumption. We will assess levels of dietary and environmental exposure by linking these collected data with available information on Cd residue levels in foods and beverages and environmental sources of Cd pollution near women's residences. In addition, we will estimate total Cd exposure by using existing urine samples provided by 304 women in the CTS to determine the relative contributions of dietary and environmental sources to the level of urinary Cd, which is considered a good measure of cumulative lifetime exposure. We will then evaluate whether dietary, environmental, and total exposure to Cd increase the risk of breast cancer.

This annual report documents the progress made in the second year of the project.

BODY

In the second year of this project, we made substantial progress on Tasks 3-6 listed in the Statement of Work. These tasks and their progress are documented in this section.

Task 3 (Months 7–15): Link the CTS food frequency questionnaire (FFQ) with the Total Diet Study database. Estimate dietary exposure to Cd for 111,526 subjects in the CTS cohort.

- a. Estimate the mean Cd concentrations and standard errors for 103 food and beverage items listed in the CTS baseline FFQ, based on the assumption that contaminant levels in foods follow a log-normal distribution.
- b. Add estimated Cd concentrations to the CTS nutrient database.
- c. For each subject, estimate the average daily Cd intake ($\mu\text{g/day}$) based on the frequency and portion size of each food or beverage consumed as reported in the baseline FFQ.
- d. For each subject, estimate total dietary Cd intake from all consumed foods and beverages as reported in the baseline FFQ.

Progress: This task is complete, except for the estimation of total dietary Cd intake for all subjects in the CTS cohort. We have completed an assessment of dietary exposures for subjects enrolled in the exposure validation sub-study, and are completing this assessment for the entire CTS cohort. As described in the previous annual report, we used data from the USDA Total Diet Study (TDS) to enter data on the Cd content of foods into our nutrient database. The mean values reported in the TDS were used. We have written programs to convert the nutrient-specific data into individual-level exposure data based on the reported frequency and portion size of each of the consumed foods or food groups included in our study's food-frequency questionnaires. Table 1 lists each food item's Cd concentration in μg per 100g of food. Table 2 lists those food items that made the largest contributions to total Cd intake among participants in the sub-study. The largest contributors to daily Cd intake among these subjects were lettuce or tossed salad, spinach, potatoes, and fiber cereals. In this sub-study population, the mean daily dietary Cd intake was $10.44\mu\text{g}$, with a standard deviation of $4.05\mu\text{g}$. These values ranged between $2.31\text{--}26.53\mu\text{g}$, with a median of $10.00\mu\text{g}$. We are now completing the assessment for the entire CTS cohort and expect a similar distribution of daily Cd intake.

Task 4 (Months 7–15): Link CTS residential addresses with databases of environmental pollutants using a geographic information system (GIS). Estimate environmental exposures to Cd for all subjects in the CTS cohort.

- a. Review accuracy and update residential address geocoding.
- b. Link addresses with environmental pollutant databases (HAPs, ATEDS, AADT) using a GIS.
- c. Estimate average exposure to Cd from environmental sources for 1995 - 2003 for all subjects in the CTS cohort.

Progress: This task is complete, except for the estimation of exposures using the 1995 ATEDS (Air Toxics Emission Data System) dataset. We are reviewing the geocoding accuracy of the 1,010 identified industrial Cd emission sources and expect to complete this task in October 2010. Table 3 lists the distributions for the entire CTS cohort of traffic density within 300 meters of the residence derived from average annual daily traffic (AADT) counts and Cd concentrations in ambient air in the residential census tract derived from the Hazardous Air Pollutants (HAPs) database obtained from the US Environmental Protection Agency. The mean traffic density in the CTS was 9,868 vehicle km traveled (VKT) per km^2 within 300 meters with a standard deviation of 17,760 VKT per km^2 and median of 17,760 VKT per km^2 . The mean Cd concentration in

ambient air was $0.28\mu\text{g}/\text{m}^3$ with a standard deviation of $0.28\mu\text{g}/\text{m}^3$ and a median of $0.23\mu\text{g}/\text{m}^3$. We are evaluating the distributions of these estimated exposures to determine the appropriate cutoff points for categorical analyses.

Task 5 (Months 16–19): Create the analytic dataset. Generate descriptive statistics.

- a. Merge the datasets of dietary CD intake (entire CTS), environmental CD exposure (entire CTS), case-control status and relevant covariate information (entire CTS), and urinary Cd concentrations (validation sub-study) into a single analytic file.
- b. Conduct preliminary descriptive analyses, evaluate variable distributions, and determine variable cut-points.

Progress: This task is complete, as we have created an initial analytic dataset, but expect to make modifications to this dataset as necessary. We are in the process of completing the descriptive analyses, evaluating variable distributions for categorical analyses, and identifying potential confounders. These descriptive analyses as well as modifications to the analytic dataset will be informed by the results from the mixed-effects models in Task 6.

Task 6 (Months 20–24): Evaluate the contribution from dietary and environmental sources to total Cd exposure based on urinary Cd concentrations.

- a. Develop mixed-effects models.
- b. Run these models with urinary Cd concentration as the dependent variable to calibrate exposures from dietary and environmental sources and other covariates in the validation sub-study population.
- c. Conduct formal evaluation of effect modification with stratified models or models with interaction terms.
- d. Evaluate model precision using iterative cross-validation.

Progress: This task is mostly complete, as we are currently conducting stratified analyses and testing for effect modification. The distributions of demographic, environmental, dietary, and biological variables among subjects in the exposure validation sub-study are listed in Table 4. Because the distribution of U-CD concentrations was skewed, we used a natural log transformation to normalize the distribution.

To date, we employed mixed effects models to identify significant determinants of urinary Cd concentrations and to determine the within-person correlation for repeated measurements in the exposure validation sub-study population. In addition, we calculated the coefficient of determination (R^2 -value) and estimated the amount of variability in measured concentrations explained by each model. In addition, we used generalized estimating equations with robust inference to confirm our findings. Table 5 lists the intraclass correlation coefficients and between-person and within-person variance estimates for repeated urinary measurements of Cd, creatinine, and creatinine-corrected in the sub-study. For unadjusted Cd, the intraclass correlation was 0.49 while the correlation for creatinine-adjusted Cd was 0.41. This observation suggests that a single measure of U-Cd does not accurately assess lifetime exposure.

Table 6 lists the parameter estimates (β) from three mixed-effects linear regression models for log-Cd concentration. In these models, we used the unadjusted Cd log-concentration as the dependent variable and included creatinine log-concentration as a predictor variable in our models because it produced a better fit than those using creatinine-adjusted urinary levels as previously recommended (Barr et al., 2005). The first model included creatinine, age, total smoking history, total births, alcohol intake, total breastfeeding history, and dietary Cd intake, as well as the environmental Cd exposure estimates for ambient air, industrial emissions, and traffic density around the residence as predictor variables. In this model, only creatinine, age, total smoking (a major source of Cd exposure), total births, and total breastfeeding history were associated with urinary Cd concentration (p for all variables <0.001). No association was observed for the environmental and dietary Cd exposure variables with urinary Cd concentration. The second model excluded the environmental and dietary variables; parameter estimates for the remaining variables did not appear from those in the first model. The third model included only creatinine and age as predictor variables. Comparing the first two models, it appeared that the second model with fewer predictors was able to explain the same amount of variability as the first model ($R^2 = 0.42$). We also analyzed the environmental and dietary Cd exposures as categorical variables, but none of these transformed variables were associated with urinary Cd concentration. We considered including additional predictors such as body mass index, body surface area, waist-to-height ratio, waist-to-hip ratio, urban/rural residence, history of oral contraceptive use, and history of hormone replacement therapy, but none were associated with urinary Cd concentration.

Table 7 lists the creatinine-adjusted Cd concentrations from the first urine specimen by categories of age, smoking history, alcohol consumption, and by subjects' categorical characteristics. These trends further demonstrate the positive associations of age and

smoking with urinary Cd and the negative associations with alcohol consumption and total live births.

We are currently developing a manuscript of our findings and currently conducting additional mixed-effects analyses, with a particular focus on non-smokers and the contributions of specific food items with high levels of Cd (e.g., spinach). The positive associations of age and smoking with urinary Cd concentration have been previously demonstrated (Ikeda et al., 2005; McElroy et al., 2007). We did not find a relationship between estimated dietary intake of Cd and urinary concentration, but such an association has only been observed in populations consuming Cd-contaminated food (Ikeda et al., 2006; Yamagami et al., 2006). We observed a negative relationship between parity and Cd concentration, unlike a previous study (McElroy et al., 2007). An association between reduced body burden levels and number of pregnancies is consistent with other studies of persistent pollutants (Wolff et al., 2005; Verner et al., 2008). We also observed a negative association between urinary Cd concentrations and average daily alcohol consumption, which was observed in a previous study (McElroy et al., 2007). However, we did not observe a negative association between body size (body mass index or body surface area) and urinary Cd concentrations that was observed in previous studies (McElroy et al., 2007; Dhooge et al., 2010).

Future Tasks: These tasks will be completed in the third year of the project, as indicated by the scheduled months:

Task 7 (Months 24–26): Generate estimates of total Cd exposure for all subjects in the CTS cohort.

- a. Apply β 's estimated from mixed-effects models as weights for the dietary and environmental exposure estimates for all subjects in the CTS.
- b. Estimate total Cd exposure for all CTS subjects.

Progress: Because of the largely null associations between urinary Cd concentrations and estimated dietary and environmental Cd exposures, it may not be feasible to estimate total exposure in the entire CTS cohort that is informed by relative contributions to urinary Cd concentrations in the exposure validation sub-study and parameter estimates from the mixed-effects models. However, we will still be able to use these environmental and dietary Cd exposure variables to predict risk of breast cancer.

Task 8 (Months 27–32): Estimate the effects of total, dietary, and environmental exposure to Cd on breast cancer incidence in the CTS from 1996 to 2005.

- a. Develop Cox proportional hazards models for estimating effects of exposure to Cd on breast cancer risk in the CTS.
- b. Estimate hazard ratios for Cd exposure from specific sources and from all sources.
- c. Conduct formal evaluation of effect modification.

Progress: We will be initiating these analyses in November 2010.

Task 9 (Months 33–36): Prepare final reports, finalize manuscripts and present findings.

- a. Discuss and interpret study findings and their implications.
- b. Prepare final reports.
- c. Write manuscripts.
- d. Present findings at scientific meetings.

Progress: We are currently writing our first manuscript on the comparison of urinary Cd concentrations with dietary and environmental Cd exposures in the exposure validation sub-study.

KEY RESEARCH ACCOMPLISHMENTS, YEAR 2

- Completion of preliminary assessments of environmental Cd exposure and dietary Cd intake in the CTS cohort.
- Creation of the initial analytic dataset.
- Identification of predictors of urinary Cd concentrations in the exposure validation sub-study.
- Presentation of initial study findings at an environmental epidemiology and exposure assessment conference (see below).

REPORTABLE OUTCOMES

On August 29, 2010, we presented a poster of our findings from Tasks 3-6 at the Joint Conference of International Society of Exposure Science & International Society for Environmental Epidemiology in Seoul, Korea. The poster, titled “Urinary Cadmium Concentrations among Female Teachers from Northern California”, described the results from our mixed-effects models (see Appendix 1 for abstract).

In May 2010, we received a grant from the National Institutes of Health (Grant No. 1R01ES018841) to examine the effects of dietary and environmental exposures to Cd on the risk of endometrial cancer (see Appendix 2 for project summary/abstract). This application was motivated by our current study of Cd and breast cancer funded by USAMRMC and a recent report of an elevated risk of endometrial cancer associated with higher dietary intake of Cd among postmenopausal women enrolled in the Swedish Mammography Cohort (Akesson et al., 2008).

CONCLUSION

We made substantial progress on all of the tasks scheduled for completion in the second year of this study and have already initiated the first manuscript of our study results. The completion of the assessment of dietary intake and environmental exposure and the analyses estimating the effects of these exposures on the risk of breast cancer in the third year of the study will contribute to the growing body of evidence regarding the carcinogenicity of Cd.

REFERENCES

- Akesson, A. , Julin, B. , Wolk, A. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. *Cancer Res*, 2008, 68:6435-41.
- Barr, D. B. , Wilder, L. C. , Caudill, S. P. , Gonzalez, A. J. , Needham, L. L. , Pirkle, J. L. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environ Health Perspect*, 2005, 113:192-200.
- Dhooge, W. , Den Hond, E. , Koppen, G. , Bruckers, L. , Nelen, V. , Van De Mieroop, E. , Bilau, M. , Croes, K. , Baeyens, W. , Schoeters, G. , Van Larebeke, N. Internal exposure to pollutants and body size in Flemish adolescents and adults: associations and dose-response relationships. *Environ Int*, 2010, 36:330-7.
- Ikeda, M. , Moriguchi, J. , Ezaki, T. , Fukui, Y. , Ukai, H. , Okamoto, S. , Shimbo, S. , Sakurai, H. Smoking-induced increase in urinary cadmium levels among Japanese women. *Int Arch Occup Environ Health*, 2005, 78:533-40.
- Ikeda M. , Shimbo S. , Watanabe T. , Yamagami T. Correlation among cadmium levels in river sediment, in rice, in daily foods and in urine of residents in 11 prefectures in Japan. *Int Arch Occup Environ Health*. 2006, 79:365-70.
- McElroy, J. A. , Shafer, M. M. , Hampton, J. M. , Newcomb, P. A. Predictors of urinary cadmium levels in adult females. *Sci Total Environ*, 2007, 382:214-23.
- Verner M. A. , Charbonneau M. , López-Carrillo L. , Haddad S. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: a new tool in breast cancer epidemiologic studies. *Environ Health Perspect*, 2008, 116:886-92.
- Wolff M. S. , Deych E. , Ojo F. , Berkowitz G. S. Predictors of organochlorines in New York City pregnant women, 1998-2001. *Environ Res*, 2005, 97:170-7.
- Yamagami, T. , Ezaki, T. , Moriguchi, J. , Fukui, Y. , Okamoto, S. , Ukai, H. , Sakurai, H. , Aoshima, K. , Ikeda, M. Low-level cadmium exposure in Toyama City and its surroundings in Toyama prefecture, Japan, with references to possible contribution of shellfish intake to increase urinary cadmium levels. *Sci Total Environ*, 2006, 362:56-67.

SUPPORTING DATA

Table 1. List of each food item's cadmium concentration (μg per 100g of food).

Table 2. List of food items that made the largest proportional contributions to total cadmium intake among participants in the exposure validation sub-study.

Table 3. Distributions of traffic density within 300 meters of the residence and Cd concentrations in ambient air in the residential census tract for all geocoded residences in the CTS cohort.

Table 4. Distributions of demographic, environmental, dietary, and biological variables among subjects in the exposure validation sub-study.

Table 5. Intraclass correlation coefficients and variance estimates for repeated urinary measurements in the exposure validation sub-study (n=141).

Table 6. Parameter estimates (β) from mixed-effects linear regression models for urinary log-concentration of Cd (n=296).

Table 7. Creatinine-adjusted cadmium concentrations from the first urine specimen by subjects' categorical characteristics (n=296).

Table 1. List of each food item's cadmium concentration (µg per 100g of food).

Food	Cadmium (µg) per 100g
Spinach	14.400
Lettuce or Tossed Salad (not spinach salad)	6.520
French Fries or Tator Tots	3.900
Fiber Cereals, Other Cold Cereals	3.765
Potatoes (either baked, boiled or mashed)	3.342
Chocolate Candy	2.834
Salty snacks, like potato chips, corn chips, popco	2.308
Carrots	2.050
Dark bread, such as whole wheat, rye, pumpernickel	2.050
Bagels, english muffins, hamburger buns	1.904
Mustard Greens, Turnip Greens & Collards (CTS)	1.896
Tuna, tuna salad, tuna casserole	1.702
Pizza, combination (meat & veggie), regular crust	1.600
Salsa, ketchup, taco sauce	1.580
Beef stew or pot pie with carrots or other vegetab	1.500
Macaroni & Cheese	1.500
Spaghetti, Pasta with Tomato Sauce (sometimes with	1.403
Biscuits, Muffins	1.400
Cookies or cake, never lowfat or fat free	1.376
Pasta salad, other pasta without tomato sauce	1.363
Tomatoes, Tomato Juice	1.300
Burritos or Tacos with meat or beans	1.236
Broccoli	1.200
Hamburgers & Cheeseburgers	1.198
Doughnuts, Pastry	1.160
Tortillas, both flour and corn (BC60)	1.100
Other Vegetables	1.060
Fried Fish or fish sandwich	1.050
Hot Dog, regular or meat	0.916
Cantaloupe	0.900
Sweet Potatoes or Yams (CTS)	0.828
Cookies or Cake, sometime lowfat or fat-free	0.813
Cornbread, corn muffins	0.800
Pancakes, Waffles or French Toast	0.772
Chili (composite)	0.750
Strawberries, Other Berries (in season)	0.600
Pumpkin pie, sweet potato pie	0.600
Other Soups, Vegetable-Based	0.540
Chicken stew or mixed dish with chicken (CTS)	0.500

Mayonnaise or Salad Dressing (always lowfat or fat	0.452
Cabbage or Coleslaw	0.442
Shell fish (shrimp, crab, lobster, etc.)	0.425
Other Soups, bean (includes lentil)	0.400
Cauliflower or Brussel Sprouts (CTS)	0.400
Hot Cereal	0.385
Mayonnaise or Salad Dressing (sometimes lowfat or	0.356
Other Soups, like chicken noodle, mushroom, Cup-A-	0.334
Fried Chicken	0.300
Fried Chicken without skin	0.300
Fried Chicken with skin	0.300
Ham, bologna, other lunch meats (regular or made w	0.283
Breakfast bars, granola bars, power bars	0.275
Other Pies (CTS)	0.260
Mayonnaise or Salad Dressing (never lowfat or fat-	0.260
Cookies or cake, Always lowfat or fat-free	0.250
Beans, Lentils, Baked Beans or Chili with beans	0.233
Sausage or Bacon, regular meat	0.200
Peaches, Apricots (Canned or Dried)	0.200
Peaches, Apricots (Fresh, in season)	0.200
Peas	0.200
Rice or dishes made with rice	0.180
Other Cereals (CTS), Corn Flakes & Cheerios	0.115
Butter on bread or rolls	0.100
Butter or Margarine	0.100
Butter or Margarine for cooking	0.100
Cream (real) or Half-n-Half in coffee or tea	0.100
Margarine on bread or rolls	0.100
Non-Dairy creamer in coffee or tea	0.100
Watermelon (CTS)	0.100
String Beans, Green Beans (CTS)	0.078
Other cheeses and cheese spreads, always lowfat or	0.075
Other Cheeses and cheese spreads, never lowfat or	0.075
Other cheeses and cheese spreads, sometimes lowfat	0.075
Apples & Applesauce (CTS)	0.050
Prunes or Prune Juice	0.050
Sugar or Honey in coffee or tea or on cereal (CTS)	0.050
Apple Juice and Grape Juice	0.040
Other Fruit incl. kiwi, fruit cocktail, grapes, ra	0.040
Coffee or Tea	0.030
Chicken or Turkey (roasted or broiled, including o	0.025
Chicken or Turkey without skin	0.025
Chicken or Turkey with skin	0.025

Other Candy or Jelly	0.020
Regular Soda	0.010
Alfalfa Sprouts, including on sandwiches	0.000
Bananas	0.000
Beer (regular and lite versions)	0.000
Breakfast Shakes, Diet Shakes	0.000
Milk on cereal, Lowfat (1%)	0.000
Milk on cereal, Reduced Fat (2% milk fat)	0.000
Milk on cereal, Whole (3.3%)	0.000
Corn	0.000
CHEESE,COTTAGE,LOWFAT,2% MILKFAT	0.000
Eggs	0.000
Egg Substitutes, Egg Beaters and Egg Whites	0.000
Grapefruit (not including juice)	0.000
Kool-Aid, Hi-C or other drinks with added vitamin	0.000
Ice Cream, Always Lowfat or Fat-Free	0.000
Ice Cream, Never Lowfat or Fat-Free	0.000
Ice Cream, Sometimes Lowfat or Fat-Free	0.000
Mixed Drinks	0.000
Liver, including chicken liver	0.000
Milk, Skim milk, 1% milk not including on cereal	0.000
Milk, Reduced Fat (2% milk fat)	0.000
Milk in coffee or tea	0.000
Milk, Whole (3.3%)	0.000
Meat Substitutes made from soy	0.000
Snacks like nachos with cheese, potato skins with	0.000
Oranges (not including juice)	0.000
Orange Juice or Grapefruit Juice	0.000
Other fish (broiled or baked)	0.000
Oysters	0.000
Peanuts or Peanut Butter (SF80)	0.000
Pork, including chops, roasts	0.000
Pork, including chops, roasts with fat	0.000
Pork, including chops, roasts without fat	0.000
Snapple, Calistoga, sweetened bottled waters or ic	0.000
Beef roasts, steaks and sandwiches	0.000
Beef roasts, steaks and sandwiches with fat	0.000
Beef roasts, steaks and sandwiches without fat	0.000
Sweet Cereals, Other Cold Cereals	0.000
Tofu or Tempeh	0.000
White bread, french or italian bread, including sa	0.000
Wine, General	0.000
Yogurt, Frozen Yogurt, Always lowfat or fat-free	0.000

Table 2. List of food items that made the largest proportional contributions to total cadmium intake among participants in the exposure validation sub-study.

Food	Proportion
Lettuce or Tossed Salad (not spinach salad)	23.2%
Spinach	7.4%
Potatoes (either baked, boiled or mashed)	7.1%
Fiber Cereals, Other Cold Cereals	5.5%
Spaghetti, Pasta with Tomato Sauce (sometimes with	4.8%
Other Vegetables	4.5%
Tomatoes, Tomato Juice	4.3%
Carrots	3.6%
Dark bread, such as whole wheat, rye, pumpernickel	3.6%
Bagels, english muffins, hamburger buns	2.4%
Pizza, combination (meat & veggie), regular crust	2.2%
Burritos or Tacos with meat or beans	2.1%
Salty snacks, like potato chips, corn chips, popco	2.0%
Broccoli	2.0%
Chocolate Candy	1.8%
Hot Cereal	1.6%
Macaroni & Cheese	1.5%
Chicken stew or mixed dish with chicken (CTS)	1.3%
French Fries or Tator Tots	1.2%
Tuna, tuna salad, tuna casserole	1.2%
Biscuits, Muffins	1.1%
Beef stew or pot pie with carrots or other vegetab	1.1%
Cookies or cake, never lowfat or fat free	1.1%
Other Soups, Vegetable-Based	1.1%
Hamburgers & Cheeseburgers	1.0%

Table 3. Distributions of traffic density within 300 meters of the residence and Cd concentrations in ambient air in the residential census tract for all geocoded residences in the CTS cohort.

Variable (units)	No. of subjects	Mean	SD	Median	25 th percentile	75 th percentile
Traffic density (daily vehicle km traveled per km ² within 300 m)	119,829	9,698	17,760	4,236	497	11,567
Ambient air concentration (µg/m ³)	120,394	0.28	0.28	0.23	0.17	0.31

Table 4. Distributions of demographic, environmental, dietary, and biological variables among subjects in the exposure validation sub-study.

Variable (units)	N	Mean	SD	Median	25 th percentile	75 th percentile
Age (years)	296	55	12	54	47	62
Body mass index (kg/m ²)	293	27	5.9	25	23	29
Total full-term births (number)	291	1.7	1.4	2	0	3
Lifetime cigarette smoking (pack-years)	296	3.9	10	0	0	1
Industrial emissions (inverse-distance-weighted: kg/km)	296	4.7	31	0	0	0.001
Ambient Cd concentration (µg/m ³)	296	0.20	0.13	0.15	0.09	0.28
Traffic density (vehicle km traveled/km ² within 300 m)	296	6,199	12,542	845	0	7,276
Dietary intake (µg/day)	287	10.4	4.1	10.0	7.6	12.7
Urinary measurements (1 st specimen)						
Urinary Cd (µg/L)	296	0.3	0.2	0.3	0.2	0.4
Urinary creatinine (g/L)	296	0.8	0.4	0.7	0.5	1.0
Creatinine-adjusted Cd (µg/g)	296	0.4	0.2	0.4	0.3	0.5

Table 5. Intraclass correlation coefficients and variance estimates for repeated urinary measurements in the exposure validation sub-study (n=141).

Variable (natural log)	Between-person variance (σ^2_b)	Within-person variance (σ^2_w)	Intraclass correlation coefficient (ρ_w)
Cd ($\mu\text{g/L}$)	0.21	0.22	0.49
Creatinine (g/L)	0.12	0.08	0.60
Creatinine-adjusted Cd ($\mu\text{g/g}$)	0.14	0.20	0.41

Table 6. Parameter estimates (β) from mixed-effects linear regression models for urinary log-concentration of Cd (n=296).

Variable (units)	Model 1 β (SE)	Model 2 β (SE)	Model 3 β (SE)
Intercept	-2.18 (0.14)	-2.27 (0.10)	-2.44 (0.09)
Creatinine (g/L)	0.92 (0.07)	0.94 (0.07)	0.94 (0.07)
Age (year; centered at 31 years)	0.015 (0.003)	0.015 (0.003)	0.016 (0.002)
Total smoking (pack-years)	0.01 (0.003)	0.01 (0.003)	
Total births (number)	-0.07 (0.02)	-0.07 (0.02)	
Alcohol intake (ordinal: none vs. < 20 g/day vs. > 20 g/day)	-0.17 (0.05)	-0.16 (0.05)	
Total breastfeeding (months)	0.006 (0.003)	0.007 (0.003)	
Estimated cadmium level in air ($\mu\text{g}/\text{m}^3$)	0.03 (0.24)		
Industrial emissions (inverse-distance weighted: 1,000 kg/km)	0.14 (0.42)		
Residential traffic density (100,000 VMT/mi ²)	-0.03 (0.03)		
Dietary cadmium (10 mg/day)	-0.03 (0.08)		
AIC (model fit, smaller is better)	667	688	712
R ² (amount of variability explained)	0.42	0.42	0.35
Q _w (within-person correlation)	0.27	0.28	0.34

Table 7. Creatinine-adjusted cadmium concentrations from the first urine specimen by subjects' categorical characteristics (n=296).

Characteristic	n	%	Mean ($\mu\text{g/g}$)	Kruskal-Wallis p- value	p-value for trend
Age					
30 – 39	30	10%	0.32	<0.0001	<0.0001
40 – 49	63	21%	0.36		
50 – 59	114	39%	0.44		
60 – 84	89	30%	0.52		
Smoking history					
Never	200	68%	0.40	0.001	0.002
Former	85	29%	0.49		
Current	10	3%	0.62		
Alcohol consumption					
None	96	32%	0.50	0.0006	0.0001
< 20 g/day	174	59%	0.41		
> 20 g/day	26	9%	0.35		
Total live births					
0	75	26%	0.46	0.39	0.0002
1 – 2	143	49%	0.43		
3	43	15%	0.42		
> 3	30	10%	0.41		

APPENDIX 1

Poster Abstract, "Urinary Cadmium Concentrations among Female Teachers from Northern California"

Urinary Cadmium Concentrations among Female Teachers from Northern California
Authors: Robert Gunier, Rudy Rull, Andrew Hertz, Pamela Horn-Ross, Peggy Reynolds

Background: Cadmium is a toxic metal associated with kidney disease and increased mortality. It has been classified as a probable human carcinogen, demonstrated to have estrogenic properties, and associated with breast cancer in previous case-control studies. Exposure to cadmium occurs from smoking, diet and inhalation of air polluted from combustion, mining, and manufacturing. Excretion of cadmium in urine is widely considered a biomarker of lifetime exposure. Urinary cadmium concentration has been associated with age, smoking status, body surface area, parity and household income in previous studies. Our objectives were to identify predictors of urinary cadmium concentrations and determine the within-person correlation among repeat samples.

Methods: We collected a 24-hour urine sample from 298 women enrolled in the California Teachers Study in 2000 and a second 24-hour sample from 141 participants approximately three, six, or nine months later. Urinary cadmium concentrations ($\mu\text{g/L}$) were determined by ICP/MS. Age, body mass index, smoking status, diet, alcohol consumption, and parity and other reproductive characteristics were obtained from interview data. Environmental cadmium exposure from traffic, industrial and commercial emission sources as well as modeled outdoor air concentrations were estimated using a geographic information system. We used mixed-effects models to estimate the within-person correlation between repeat measurements and identify predictors of urinary cadmium levels.

Results: The arithmetic mean creatinine-adjusted cadmium concentration was 0.43 (standard deviation = $0.24 \mu\text{g/g}$) and the range was 0.1 to $1.5 \mu\text{g/g}$. The within-person correlation among repeat samples was 0.49. Urinary cadmium levels increased with age and lifetime pack-years of smoking and decreased with greater alcohol consumption and number of previous pregnancies. These factors explained 38% of the variability in urinary cadmium concentrations.

Conclusion: These preliminary results suggest that a single measurement of urinary cadmium does not accurately assess lifetime exposure. Additional analyses will evaluate the role of dietary, environmental, and other potential predictors.

APPENDIX 2

Project Summary/Abstract, “Dietary & Environmental Exposure to Cadmium & the Risk of Endometrial Cancer” (NIH/NIEHS 1R01ES018841)

PROJECT SUMMARY/ABSTRACT

Exposure to high levels of circulating estrogens unopposed by progestins is the primary cause of endometrial cancer. However, little is known about whether environmental contaminants that mimic the effects of estrogen increase the risk of this disease. Cadmium is a trace metal released into air and soil as a byproduct of industrial processes and is perhaps the most potent of these estrogenic contaminants with respect to endometrial cancer etiology. Major sources of non-occupational exposure to Cd include cigarette smoke, diet, and inhalation of ambient air contaminated by industrial processes and combustion of fossil fuels. This proposed study will test the emerging hypothesis that greater levels of Cd exposure increase endometrial cancer risk by utilizing existing data on dietary intake, residence, smoking history, and other risk factors and urine specimens from 356 women diagnosed with endometrial cancer and 683 matched controls enrolled in the Nutrition, Estrogens and Endometrial Cancer in Teachers (NEET) study, a nested case-control study within the California Teachers Study (CTS) cohort. The availability of these data, urine specimens for the measurement of Cd concentration—a classic measure of chronic exposure, and existing databases of environmental and dietary sources of Cd, will allow us to conduct a comprehensive assessment of exposure that incorporates a myriad of sources and evaluates the relative contribution of each source. This will also allow us to assess whether any observed elevations in risk are heterogeneous across exposure sources. The specific aims of this study will be to: 1) characterize exposure to Cd from dietary and environmental sources for all cases and controls in the NEET study; 2) evaluate the contributions of dietary intake and exposure from environmental sources on Cd concentrations measured in urine; and 3) estimate the effects of dietary, environmental, and total Cd exposure on the risk of endometrial cancer.

The emerging evidence that Cd is a potential risk factor for endometrial cancer suggests a future direction for minimizing dietary and environmental exposures to this toxic metal. This study offers a unique and timely opportunity to improve our understanding of whether Cd plays an etiologic role in the development of this cancer and identify important, and potentially modifiable, sources of exposure to this metal.