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REFERENCES

1. Takahashi H, Ohira T, Yasumura S, et al. Re: Thyroid cancer among young people in Fukushima. *Epidemiology*. 2016;27:e21.
2. Tsuda T, Tokinobu A, Yamamoto E, Suzuki E. Thyroid cancer detection by ultrasound among residents ages 18 years and younger in Fukushima, Japan: 2011 to 2014. *Epidemiology*. 2016;27:316–322.
3. Hamaoka Y. Re: Re: Thyroid cancer among young people in Fukushima. *Epidemiology* 2016;28:e4–e5.

Urinary Cadmium and Mammographic Density

To the Editor:

Women whose mammograms show high mammographic density have approximately three-fold risk of breast cancer compared with women with low mammographic density.[1] The etiologic relationship between mammographic density and breast cancer remains unclear, but high density shares risk factors with breast cancer, including hormone therapy and reproductive history.[1]

Nonoccupational exposure to cadmium occurs through tobacco smoke or contaminated foods.[2] Cadmium accumulates primarily in kidneys, but is also present in breast tissue, and urinary cadmium reflects long-term exposure.[2] In vitro and in vivo, cadmium displays estrogenic activity,[3] and epidemiologic evidence suggests that cadmium exposure is associated with increased breast cancer risk.[4] A previous study in a smaller sample of premenopausal women found equivocal evidence that urinary cadmium was associated with higher mammographic density.[5] Thus, we sought to further study the relationship of cadmium exposure with mammographic density.

Women ages 40–65 years with no history of breast cancer or breast surgery were recruited online through the Dr. Susan Love Foundation (www.armyofwomen.org). Of 1,004 eligible women, 790 consented, completed the study questionnaire, and returned a urine sample and a mammography report from the previous 18 months. The study protocol was approved by the Institutional Review Board of University of Wisconsin (Madison). Sixty-five reports had no or ambiguous breast density descriptions. Hence, 725 women were included in our study. Mammographic density was assessed on the Breast Imaging - Reporting and Data System (BI-RADS, 4th edition) semiquantitative scale.[6] Urine collection containers were sterile, acid-washed polypropylene bottles with screw-top lids, a method previously used without evidence of contamination.[4] Urinary cadmium was quantified using high-resolution inductively-coupled plasma mass spectroscopy. Urinary creatinine was measured using standard colorimetric techniques. Creatinine-normalized urinary cadmium (μg/g-cr) was calculated for each woman by dividing urinary cadmium by creatinine.

Median urinary cadmium was 0.268 μg/g (interquartile range 0.152–0.452 μg/g-cr). Geometric mean urinary cadmium was elevated in older women (ages 40–45 years: 0.146 μg/g-cr, ages 61–65 years: 0.403 μg/g-cr) and ever-smokers (0.249 μg/g-cr) compared with never-smokers (0.210 μg/g-cr). After least-squares

TABLE. ORs and 95% CIs of Higher Mammographic Density Compared with Lower Mammographic Density Associated with Creatinine-normalized Urinary Cadmium Concentration

	Mammographic Density		
	Low (BI-RADS 1,2)	High (BI-RADS 3,4)	
	N = 252	N = 473	OR[a] (95% CI)
Cadmium tertile (range, μg/g-cr)			
All women			
1st (0.001, 0.185)	75	166	1 (reference)
2nd (0.186, 0.369)	85	157	0.96 (0.63, 1.5)
3rd (0.370, 2.192)	92	150	0.95 (0.61, 1.5)
			P (trend): 0.81
Per two-fold higher cadmium			1.0 (0.88, 1.2)
Never-smokers	N=164	N=328	
1st (0.001, 0.185)	50	124	1 (reference)
2nd (0.186, 0.369)	62	113	0.78 (0.47, 1.3)
3rd (0.370, 2.192)	52	91	0.84 (0.48, 1.5)
			P (trend): 0.54
Postmenopausal women	N = 290	N = 194	
1st (0.001, 0.185)	73	47	1 (reference)
2nd (0.186, 0.369)	102	63	1.1 (0.64, 1.9)
3rd (0.370, 2.192)	115	84	0.94 (0.55, 1.6)
			P (trend): 0.74

[a]Adjusted for age, body mass index, alcohol consumption, parity, postmenopausal hormone use, smoking status, and menopausal status.

BI-RADS indicates Breast Imaging – Reporting and Data System (4th edition); CI, confidence intervals; OR, odds ratios.

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adjustment for age and smoking, urinary cadmium was higher in women of higher parity (nulliparous: 0.227 μg/g-cr; ≥3 children: 0.261 μg/g-cr), and in postmenopausal (0.254 μg/g-cr) compared with premenopausal (0.233 μg/g-cr) women.

In contrast to a previous report,[5] no association was observed between urinary cadmium tertile and BI-RADS category, comparing BI-RADS 3 or 4 to 1 or 2 (Table). Results were similar when analysis was restricted to never-smokers (*P* interaction: 0.75) or postmenopausal women (*P* interaction: 0.34); when repeated with women with >1 μg/g-creatinine as the highest exposure group; and when BI-RADS 3 and 4 were analyzed separately.

The women in this study were recruited through the "Army of Women,"[7] a nationwide pool of breast cancer study volunteers. Therefore, participating women may not be representative of US women, and our study sample differs from the earlier study.[5] The range of urinary cadmium we observed was comparable with representative samples of US women,[8] while the prevalence of high mammographic density was higher than reported for similarly aged US women.[9] Overall, our study included an adequate range of both urinary cadmium and mammographic density to have detected an etiologic relationship, if present.

We used BI-RADS ratings recorded in routine mammography reports from participant's community mammogram providers, a feasible approach for epidemiologic studies compared with obtaining mammogram images and measuring percent mammographic density. Moreover, good correlations between BI-RADS and percent mammographic density, and in BI-RADS assignment between readers, have been demonstrated.[10] Thus, we expect that misclassification of BI-RADS may have modestly biased our results toward a null finding.

In summary, although cadmium is a putative "metallohormone,"[3] we did not find evidence that cadmium exposure as measured in urine was associated with breast density. If cadmium is a risk factor for breast cancer, our findings might imply that this relationship is independent of breast density.

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REFERENCES

1. Vachon CM, Brandt KR, Ghosh K, et al. Mammographic breast density as a general marker of breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2007;16:43–49.
2. Järup L, Akesson A. Current status of cadmium as an environmental health problem. *Toxicol Appl Pharmacol*. 2009;238:201–208.
3. Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB. Cadmium–a metallohormone? *Toxicol Appl Pharmacol*. 2009;238:266–271.
4. McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, Newcomb PA. Cadmium exposure and breast cancer risk. *J Natl Cancer Inst*. 2006;98:869–873.
5. Adams SV, Newcomb PA, Shafer MM, et al. Urinary cadmium and mammographic density in premenopausal women. *Breast Cancer Res Treat*. 2011;128:837–844.
6. American College of Radiology. *Breast Imaging and Reporting Data System® (BI-RADS®)*. 4th ed. Reston, VA: American College of Radiology; 2003.
7. Army of Women®, Dr. Susan Love Research Foundation. Available at:https://www.drsusanloveresearch.org/army-of-women. Accessed September 30, 2016.
8. Paschal DC, Burt V, Caudill SP, et al. Exposure of the U.S. population aged 6 years and older to cadmium: 1988-1994. *Arch Environ Contam Toxicol*. 2000;38:377–383.
9. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106:dju255.
10. Garrido-Estepa M, Ruiz-Perales F, Miranda J, et al.; DDM-Spain. Evaluation of mammographic density patterns: reproducibility and concordance among scales. *BMC Cancer*. 2010;10:485.

Joint Association of Long-term Exposure to Both O_3 and NO_2 with Children's Respiratory Health

To the Editor:

Recent studies have suggested associations between long-term exposure to ozone and respiratory health.[1,2] These studies have generally characterized

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