In summary, Lubin *et al.* (2) examined the dose–response trend of thyroid-cancer incidence, which is highly susceptible to the screening effort. Their conclusions and claims are deeply flawed. They sustain unwarranted fear of radiation-induced cancer, which seriously impedes very important applications of low doses of radiation in medical diagnostics and treatments.

Finally, an error is apparent in the letter by Leung, Methods section, which states that the Lubin *et al.* study comprised 252 cases among irradiated individuals with >2.5 million person-years of follow-up and 142 cases among non-irradiated individuals with >1.8 million person-years of follow-up. In table 1 of the article by Lubin *et al.*, it is clear that the person-years of follow-up apply to the 61,155 exposed and the 46,439 non-exposed individuals, not to the 252 and 142 thyroid cancer cases, respectively.

Author Disclosure Statement

Drs. Cuttler, Mortazavi, Welsh and Doss are members of Scientists for Accurate Radiation Information (SARI), Dr. Doss serves as president and Dr. Cuttler as vice president of the XLNT Foundation, organizations that focus on potential biological effects of low doses of ionizing radiation (LDIR).

References

1. Leung AM 2017 Low-dose childhood radiation effects to the thyroid follow a linear dose–response trend and persist even 45+ years after exposure. *Clin Thyroidol* **29**:235–236.
2. Lubin JH, Adams MJ, Shore R, Holmberg E, Schneider AB, Hawkins MM, Robison LL, Inskip PD, Lundell M, Johansson R, Kleinerman RA, de Vathaire F, Damber L, Sadedtzi S, Tucker M, Sakata R, Veiga LHS 2017 Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts. *J Clin Endocrinol Metab* **102**:2575–2583.
3. Ahn HS, Kim HJ, Welch HG 2014 Korea's thyroid-cancer "epidemic"—screening and overdiagnosis. *New Engl J Med* **371**:1765–1767.
4. Cuttler JM, Pollycove M 2009 Nuclear energy and health: and the benefits of low-dose radiation hormesis. *Dose Response* **7**:52–89.
5. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P 1999 Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* **353**:2111–2115.

Address correspondence to:
 Jerry Cuttler, DSc
 Cuttler & Associates, Inc.
 1104 - 11 Townsgate Drive
 Vaughan
 Ontario, L4J 8G4
 Canada

E-mail: jerrycuttler@rogers.com

DOI: 10.1089/thy.2018.0185

Response to Cuttler *et al.* re: “Low-Dose Childhood Radiation Effects to the Thyroid Follow a Linear Dose–Response Trend and Persist Even 45+ Years After Exposure”

Angela M. Leung,^{1,2} Jay H. Lubin,³ and Arthur B. Schneider⁴

Dear Editor:

We thank Cuttler *et al.* for their comments (1) regarding a recent *Clinical Thyroidology* review (2) that summarized the report of nine pooled cohorts that showed a positive association between childhood low-dose radiation exposure and incident thyroid cancer that was consistent with linearity (3). However, they provide no data to support their

objections to our interpretation regarding radiation risks. We appreciate the opportunity to address their concerns and further highlight the potential adverse health effects of low-dose radiation exposure.

Cuttler *et al.* raise three concerns: (i) over-diagnosis of thyroid cancer occurred in both early and recent time periods, which they claim invalidates the demonstration by Lubin *et al.* of temporal consistency of the linear relationship for

¹Division of Endocrinology, Diabetes, and Metabolism; UCLA David Geffen School of Medicine, Los Angeles, California.

²Division of Endocrinology, Diabetes, and Metabolism; VA Greater Los Angeles Healthcare System, Los Angeles, California.

³Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, Maryland.

⁴University of Illinois College of Medicine, Section of Endocrinology, Diabetes, and Metabolism, Chicago, Illinois.

thyroid cancer incidence and low-dose radiation; (ii) over-diagnosis of thyroid cancer, as for example from increased screening, nullifies any assessment of linearity; and (iii) analysis of thyroid cancer incidence “is not clinically significant” and mortality-based analyses are preferable.

First, Cuttler *et al.* provide no scientific evidence supporting their assertion regarding temporal variation of “over-diagnosis” rates. More importantly, they provide no evidence that “over-diagnosis” *per se* is related to dose, and thus provide no basis for their claim that diagnostic patterns confound the observed linear dose–response relationship. Indeed, evidence indicates the opposite. Lubin *et al.* describe secondary analyses indicating that there was no effect of either calendar period or screening on the dose–response, which directly contradicts Cuttler *et al.*’s suggestion of confounding by diagnostic pattern. Second, the reference to a Korean study (4) of changing thyroid cancer diagnostic patterns is irrelevant in relation to radiation dose–response, unless such patterns are associated with radiation dose. The Korean study presented no evidence of such a radiation dose-related association and therefore is uninformative on potential confounding. Third, the letter implies a possible screening bias in the pooled cohort results but again provided no evidence for this assertion. The original publication (3) discusses in detail that although medical screening may have increased the detection of thyroid cancer cases, there was little reason to presuppose that screening was also related to dose and thus confound results. Fourth, Cuttler *et al.* allude to “over-diagnosis” of thyroid cancer in children exposed to ^{131}I following the Chornobyl* accident. However, studies directly contradict their suggestion. Indeed, studies in Ukraine and in Belarus of thyroid cancer in radiation-exposed children only enrolled screened individuals (5,6). Moreover, both studies reported dose–response relationships that were consistent with linearity at low doses. Finally, regarding concern (iii), in the study of disease etiology, which includes analysis of dose–response, incident events are universally preferred whenever possible, since analysis of mortality outcomes is potentially confounded by non-causal factors associated only with differential survival.

The pooled data from the nine studies represent the best available epidemiologic evidence on the potential adverse effects of external low-dose childhood radiation exposure. Those data suggest that incident thyroid cancer rates are

consistent with linearity at low radiation doses, even 45 years later, and thus long-term surveillance would be beneficial toward optimizing health outcomes.

References

1. Cuttler JM, Javad Mortazavi SM, Welsh JS, Doss M 2018 Re: “Low-dose childhood radiation effects to the thyroid follow a linear dose–response trend and persist even 45+ years after exposure” (Clin Thyroidol 2017;29:235–236). Thyroid **28**:679–680.
2. Leung AM 2017 Low-dose childhood radiation effects to the thyroid follow a linear dose–response trend and persist even 45+ years after exposure. Clin Thyroidol **29**:235–236.
3. Lubin JH, Adams MJ, Shore R, Holmberg E, Schneider AB, Hawkins MM, Robison LL, Inskip PD, Lundell M, Johansson R, Kleinerman RA, de Vathaire F, Damber L, Sadetzki S, Tucker M, Sakata R, Veiga LHS 2017 Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts. J Clin Endocrinol Metab **102**:2575–2583.
4. Ahn HS, Kim HJ, Welch HG 2014 Korea’s thyroid-cancer “epidemic”—screening and overdiagnosis. New Engl J Med **371**:1765–1767.
5. Brenner AV, Tronko MD, Hatch M, Bogdanova TI, Oliynik VA, Lubin JH, Zablotska LB, Tereschenko VP, McConnell RJ, Zamotaeva GA, O’Kane P, Likhtarev IA, Bouville AC, Chaykovskaya LV, Greenebaum E, Paster IP, Shpak VM, Ron E 2011 I-131 dose-response for incident thyroid cancers in Ukraine related to the Chornobyl accident. Environ Health Perspect **119**:933–939.
6. Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, Lubin J, Romanov GN, McConnell RJ, O’Kane P, Evseenko VV, Drozdovitch V, Luckyanov N, Bouville A, Masyakin VB 2011 Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. Br J Cancer **104**:181–187.

Address correspondence to:
 Angela M. Leung, MD, MSc
 Division of Endocrinology, Diabetes, and Metabolism (111D)
 VA Greater Los Angeles Healthcare System
 11301 Wilshire Boulevard
 Los Angeles, CA 90073

E-mail: amleung@mednet.ucla.edu

*In compliance with international rules (United Nations Conferences on the Standardization of Geographical Names and the United Nations Group of Experts on Geographical Names), the transliteration of names of settlements is made using the country state language, hence Chornobyl (Ukrainian) instead of Chernobyl (Russian).