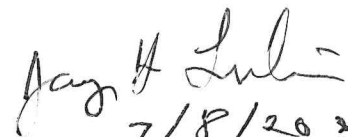


7 August, 2024

Opinion

To the 32nd Civil Division of the Tokyo District Court


7/8/2024
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With reference to Tokyo District Court, Case Nos. 1880 and 22539 of 2022, I am writing to inform you that the defendant Tokyo Electric Power Company Holdings, Inc. has issued a critique against me regarding my publication, "Thyroid Cancer Following Childhood Low-Dose Radiation Exposure: A Pooled Analysis of Nine Cohorts" (Journal Clin Endocrin Metabolism 2017:102(7);2575-2583; doi.org/10.1210/jc.2016-3529), of which I am the first author, as specified from (1) - (3) below.

My response to the defendant's criticisms are as follows:

- (1) *This is contrary to international consensus that the Epidemiological Survey (LSS) of atomic bomb survivors has not confirmed that exposure below 100 mSv increases the risk of cancer.*

MY RESPONSE:

The Lubin et al paper (Journal Clin Endocrin Metabolism 2017:102(7);2575-2583; doi.org/10.1210/jc.2016-3529) was a pooled analysis of nine epidemiologic

studies. This pooled analysis derived from a subset of the data from a larger analysis of 12 epidemiologic studies (see Veiga et al Radiat Res 2016:185(5); doi: 10.1667/RR14213.1). The 12 studies represented all available epidemiologic studies of thyroid cancer in children who were externally exposed to low LET radiation for which there were detailed information on exposure. These data included those from the LSS. Thus, information from the LSS pertaining to thyroid cancer incidence from exposure to external radiation is embedded in these results. Moreover, we found that no single study had an inordinate impact on overall results (Figure 3). While one would expect results in low dose radiation studies (<0.2 Gy and/or <0.1 Gy) to vary due to limited exposure ranges and thus limited statistical power, overall results were clear and supported a significant radiation effect on thyroid cancer incidence. The results supported our final conclusion, namely: *“analyses reaffirmed linearity of the dose response as the most plausible relationship for ‘as low as reasonably achievable’ assessments for pediatric low-dose radiation associated thyroid cancer risk.”*

(2) *The Lubin paper is a meta-analysis of epidemiological studies on medical exposure, but there is a possibility of confounding bias in epidemiological studies on medical exposure. In meta-analyses, the credibility of the epidemiological papers targeted is extremely important. The results of the epidemiological survey covered by the Lubin paper are subject to confounding bias and require careful consideration.*

MY RESPONSE:

First, there is some ambiguity in the definition of the term “meta-analysis”. In its most common usage, meta-analysis refers to the abstracting and combining of results from previously published articles, and not the analysis of original data. Any assessment of potential confounding thus depends entirely on what the authors make available in the published articles. We did not conduct a meta-analysis. In contrast, our results derived from the pooling of original data from the 12 studies. All observational epidemiologic studies are potentially subject to some (unknown) degree of residual confounding. Nonetheless, pooled analyses allow better homogenization of variables across studies (e.g., common categorization, adjustment for age and other factors, etc.), simultaneous evaluation of variables and consequently a more in-depth exploration of potential confounders.

Our pooled data included studies of diagnostic, therapeutic and environmental

radiation exposures. The data, including the LSS, involved external radiation exposure. However, there is little evidence that thyroid cancer risk from external radiation exposures differs appreciable from risk incurred from internally deposited exposures, as for example from children exposed to I-131 as a result of the Chernobyl accident.

(3) *Even after the Lubin paper was published, ICRP and UNSCEAR's opinion that "exposures below 100 mSv have no direct evidence of cancer risk" has not changed.*

MY RESPONSE:

Our analyses of all available epidemiologic studies of external childhood radiation exposure and thyroid cancer incidence found statistically significant dose-response relationships for exposures <0.2 Gy and <0.1 Gy, with estimates of the excess relative risk and 95% CIs at one Gy of 11.1 (6.6, 19.7) and 9.6 (3.7, 17.0), respectively (Table 2). Further, there was no evidence for a departure from a linear dose-response relationship for thyroid cancer.

(4) *In Table 1 of the Lubin paper, the 95% confidence interval for the relative risk of developing thyroid cancer includes 1 for 1 to 4 mGy, 5 to 20 mGy, 20 to 30 mGy, and 60 to 80 mGy; Not significant.*

MY RESPONSE:

This information on category-specific RRs (relative risks) carries no probative value. Any specific categorization is entirely arbitrary for the evaluation of the nature of a relationship between a continuous exposure and a disease outcome. An analyst may choose to combine categories or split categories, which of course impacts CIs (confidence intervals). The relevant features concern whether the relationship conforms to the observed pattern of category-specific RRs and whether as in our case the absence of any significant departure from a simple linear excess RR association (in conjunction with our defined class of alternative model forms, namely, a broad class of linear-exponential models).

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