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Safety of the Use of Radioactive Iodine in Patients With Hyperthyroidism-Reply

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We appreciate the opportunity to respond to the letters from Peacock et al.[1] and Grady et al.[2]

The aim of our study was to investigate the *dose-response relationship* between estimated organ doses and cancer mortality risks in patients treated with RAI for hyperthyroidism.[3] This was the major strength of our study compared to earlier analyses of this and other similar cohorts, which relied on the cruder approach of comparing risks in *exposed and unexposed patients*. Dose-response relationships are less likely to be explained by confounding and, thus, provide stronger evidence in support of a causal relationship.[4] They also quantify the risk per unit dose, which can be translated into estimated absolute risks. In the paper, we emphasized that the magnitude of the risk associated with current typical treatment doses is small (20–30 lifetime excess cancer deaths per 1,000 RAI-treated patients).

In response to Peacock et al.,[1] any uncertainties in the dosimetry were mainly expected to have biased our dose-response estimates toward the null, and statistical tests showed that the linear dose-response model provided the best fit for the mortality data. We disagree with the authors of both letters[1,2] that multiple testing or the size of the cohort were probable explanations for the findings in our *hypothesis-driven* study. On the contrary, those problems were much more likely in the previous *exploratory* analysis of this cohort by Ron et al., referenced in the two letters,[1,2] which involved many more tests of exposed versus unexposed patients. Their approach was also more susceptible to confounding by indication. Indeed, Ron et al. explained that the drug-only group included a high proportion of patients with a history of cancer at baseline, leading to a biased estimate of cancer mortality; this risk was no longer elevated after patients with a cancer history were excluded. Peacock et al. and Grady et al. overlooked this important bias when asserting that anti-thyroid drugs were more strongly associated with cancer mortality compared with RAI. We agree that further research is needed on the risks from surgery and anti-thyroid drugs. However, our cohort cannot be used to answer these questions because of dramatic changes in anti-thyroid drug formulations since the 1940s-60s—the era of treatment for this cohort—and lack of information on specific drug types.[5]

Evidence-based medicine relies on high-quality randomized and non-randomized studies to continuously evaluate after-market adverse events and to quantify any associated risks. Our findings had not been observed previously because our study was the first to evaluate

dose-response for site-specific cancer deaths using estimates of organ dose. Our results should not be altogether surprising, as ionizing radiation is an established carcinogen and our findings were consistent with other high-quality radiation epidemiologic studies.[6]

Nowhere in our paper did we state or imply the need to change current hyperthyroidism treatment guidelines based on results of a single observational study. Additional studies are needed to more rigorously assess the full spectrum of risks and benefits for each major treatment option for hyperthyroidism. Nonetheless, our findings can contribute to more informed discussions between patients and their providers about the risks of RAI.

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