

Commentary/Perspective/Editorial –

There is No Association of Radioactive Iodine Treatment with Cancer Mortality in Patients with Hyperthyroidism

The appropriate use of radioactive iodine therapy in hyperthyroidism has been undermined by the recent paper of Kitahara, et al. in JAMA Internal Medicine, published online on July 1, 2019 (1). The paper is flawed in many ways, and we are writing to refute the claims made by Kitahara et al. This paper uses the same hyperthyroid patient cohort of the original paper by Saenger et al. in 1968 (2), and the follow up paper by Ron et al. in 1998 (3). These two papers (2,3) reviewed the use of I-131 therapy (RAI [radioactive iodine]) for treatment of hyperthyroidism and compared RAI to treatment with antithyroid drugs (ATDs) and thyroid surgery. The current paper by Kitahara et al. follows this patient cohort for another 24 years and investigates a dose-risk relationship for these hyperthyroid patients; however, the authors did not compare risk of cancer mortality with RAI to risk of ATD therapy or thyroid surgery. There was no appropriate control group, a basic methodological error. Also, there was no correction for other more significant risk factors for cancer, especially smoking, which are known to have significant causal relationships with cancer risk, as acknowledged by the authors.

Saenger et al. and Ron et al. (2, 3) both concluded that RAI was a safe treatment for hyperthyroidism and neither found any increase in cancer mortality compared to ATDs and thyroid surgery. In the paper by Ron et al. there was a significant increase in cancer mortality from ATDs compared to RAI (3).

One of the most important issues, the known increase in cancer incidence and cancer mortality in patients with hyperthyroidism (4,5), especially Graves' Disease, was not considered in the Kitahara paper. Hyperthyroidism itself has a known positive association with an increased risk of thyroid and breast cancer (4), leukemia (2), and colon, lung, prostate, and breast malignancy (5). Saenger et al. reported that the risk of leukemia in hyperthyroid patients was 50% greater than in the US population (2), yet Kitahara et al. calculated no dose-response relationship at all for leukemia in these patients. This is because they used assumptive model-based calculations that are likely incorrect and additionally because the causative factor of hyperthyroidism overwhelms the assumed low-dose contribution to the leukemia risk. Ryodi et al. (6) in a comparison of RAI therapy and thyroid surgery found that "the increased cancer risk in hyperthyroid patients is attributable to hyperthyroidism and shared risk factors, not the treatment modality."

Much more importantly, a very recent publication (7) by two of the coauthors of Kitahara et al. is now contradicting their findings: "The overall perception of death from cancer risk associated with I-131 is inflated and not supported by evidence. As co-authors of this article, we offer previously unpublished data and analysis that 1) disputes clinical significance of the associated risk from I-131 and 2) shows, again, that antithyroid drugs carry a statistically significant and a much more obvious cancer death risk." And "In conclusion, the Kitahara et al. publication provides a numerical estimate of excess cancer deaths after RAIT using assumptive model-based calculations. No excess cancer deaths were actually observed after I-131 treatment relative to that predicted in contemporaneous population (using SMR analyses). In contrast, ATD treatment is strongly associated with the excess cancer deaths in TTFUS [Cooperative Thyrotoxicosis Follow Up Study (Saenger (2))]. Due to the article's sole focus on the hypothetical and very doubtful I-131-associated cancer risks, it completely missed the highly statistically and clinically significant ATD-associated cancer risks that begs for immediate attention."

There is no effect at all below an exposure of 0.1 Gy (10 rad), as shown in their own graph (Figure B). Results above 0.1 Gy to 0.5 Gy (10-50 rad) show no dose response. It is reported that an exposure to the stomach of 0.17 Gy (17 [+/- 18] rad) causes an increase in all solid cancer mortality, but that inexplicably exposure to the esophagus of 1.60 Gy (160 [+/- 150] rad), 10 times as much, does not cause an increase in solid cancer mortality. Interestingly, there is no statistically significant increase in leukemia. The incidence of cancer mortality noted in the patients treated with RAI, 15.3%, is actually substantially less than that in the general US population of 20-25% (8). In light of the known increased cancer mortality due to hyperthyroidism, this result of only 15.3% is notable in being so small. As stated by Giovanella and Verburg, "In fact, as in spite of nearly 8 decades of radioiodine therapy, no study has yet been able to prove the latter hypothesis" [a relationship between radioiodine therapy for hyperthyroidism and cancer mortality] (9,10).

Dose modeling was used instead of actual dose assessment, and these dose estimates have very large error bars. Using these dose estimates to correlate with patient risk, estimated using an assumed, but not supported, linear model is problematic. The linear no-threshold dose-risk model is simply assumed; this is known to be inaccurate (11) and is not even supported by the reported data. As mentioned above, the data shown in Figure 1B in this paper do not indicate a linear dose-response relationship for breast cancer, even though this relationship is reported to be statistically significant. Thus, the authors have attempted to find a dose-risk relationship even though both the assumed doses and risks are likely highly inaccurate. Therefore, the authors' assumption that association is related to causation and other conclusions have little basis in reality (12).

Most of the doses reported in this paper are very low and have not been previously shown to cause an increase in cancer mortality. The breast exposure of 15 rad would not be expected to cause an increase in cancer incidence or mortality.

The conclusion of the Kitahara paper, "In RAI-treated patients with hyperthyroidism, greater absorbed doses appeared to be modestly positively associated with risk of death from solid cancer, including breast cancer" is not justified by the data, as indicated by Tulchinsky (7). This lack of justification is further supported by the findings of a previous article by the Kitahara group analyzing a different cohort of individuals (13) as noted by Giovanella and Verburg (10), that indicate increased breast cancer mortality in women with hyperthyroidism over 60 years of age, but no effect of RAI on this association.

In summary, major flaws of this paper include: 1) poorly characterized dose estimates that were not directly measured and therefore have enormous and unknown uncertainties; 2) an analysis that does not even support the paper's conclusion that there is an association between RAI therapy and increased cancer mortality - there is no effect below 0.1 Gy (10 rad), and no dose response up to 0.5 Gy (50 rad); 3) the estimated doses are too low to expect increased cancer incidence or mortality; 4) since the relative risks are likely inaccurate, comparing them to the assumed and not directly measured doses is meaningless, especially since there are other known causative factors that are much more important contributors to cancer risk; 5) the known increase in cancer mortality associated with hyperthyroidism was not considered, 6) **the greater cancer mortality of ATD therapy compared to I-131 therapy was ignored**, and 7) the assumption that a mild association indicates causation is unsupported.

The real harm of this paper is that clinicians may decline to use I-131 therapy for the treatment of hyperthyroidism, in the belief that they are protecting their patients from cancer. In reality, aside from the fact that no evidence is presented of cancer risk at low doses, the use of ATDs will actually increase

cancer incidence and mortality, in addition to the other problems with ATDs, including hepatic toxicity and agranulocytosis.

Based on the major flaws discussed above, and the major harm to clinical practice we anticipate, we suggest the readers submit a rebuttal paper to JAMA Internal Medicine.

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