Associating radioiodine therapy in hyperthyroidism with cancer mortality: robust or random results of a statistical analysis?

Dear Editor,

Recently, Kitahara et al. (2019) published an article in JAMA Internal Medicine entitled "Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism". This publication was based on organ dosimetry calculations from 18,805 patients with hyperthyroidism treated with radioiodine treatment (RAI) followed for nearly 7 decades. The results of the work suggest that solid cancer mortality increases in hyperthyroid patients treated with RAI, with greater absorbed doses to exposed organs being associated with increased risk of death [1]. As expected, these -undoubtedly interesting- findings have raised serious concerns in both physicians and patients regarding the safety profile of RAI. Driven by this, we aim to critically read the article and highlight some of the limitations of the study.

First of all, the authors provide data on the association of RAI with cancer mortality and not with cancer incidence, which may be an interesting approach, but constitutes at the same time a weakness of the study. The authors' choice to investigate RAI as a progression and not as an actual risk factor for the onset of malignancies in hyperthyroid patients may be interpreted as an inability to document a causal relationship between them. It would be methodologically more correct either to examine as confounders -among others- cancer stage, patients' age and other co-morbidities, previous treatment administered, or to declare the absence of these data as a major limitation of the conducted analysis.

Moreover, the negligence of the role of thyroid hormone levels is another fundamental limitation of this analysis, since a large body of the literature has documented the association of increased thyroid hormone levels with carcinogenicity [2-6].

In their introduction, the authors state that RAI has declined in favor of antithyroid drugs (ATD). This trend is attempted to be explained by the "increased awareness" of an association between RAI and Graves ophthalmopathy exacerbation as well as radiation-induced secondary malignancies. This argument has however little supporting evidence, since several studies demonstrate that ATD remain the least commonly used agents through the last decades. Moreover, the authors neglect that ATD carry a statistically significant and more obvious cancer death risk than RAI. On the other hand, the use of RAI as index therapy has been doubled through the decades, influenced by several causes including patient-, disease-, physician- and health system- related factors and, of course, not only patients' and physicians' "increased awareness" [7]. In addition, concerns are raised regarding organ dosimetry calculations with large uncertainties introduced in the analysis due to reported errors in measured thyroid uptake and mass as well as same model parameters used for patients with different thyroid entities[8]. As Tulchinsky and Bertrand Brill -the Nuclear Medicine physician coauthors of the JAMA paper- state, 'the Kitahara et al. (2019) publication provides a numerical estimate of excess cancer deaths after RAI using assumptive model-based calculations' but 'no excess cancer deaths were actually observed after RAI relative to that predicted in contemporaneous population (using standardized mortality ratio analyses)' [8].

Further, the authors report that "Malignancy was the primary cause for 2,366 deaths (15.3%)" without mentioning other causes of death. However, it would be appropriate to provide some data at least on cardiovascular disease (CVD)-related mortality given that thyrotoxicosis has been associated with CVD by a large number of studies [9].

Some other methodological limitations include the lack of more appropriate control groups for comparison, such as hyperthyroid patients treated with other treatments (surgery, ATD or both), hyperthyroid patients without treatment, as well as euthyroid patients. Finally, the lack of multivariate analyses for all the aforementioned confounders as well as the lack of detailed description of "Other risk factors (x)" in the applied model: "$background\ (a,\ s,\ b,\ x)[1+\beta d*f(y)]$" constitute methodological drawbacks of the analysis.

The key-point of the analysis-thankfully mentioned by the authors- is summarized by the phrase: "some results may be because of chance; therefore, the results should be interpreted with caution." And we could not agree more.

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