Joint Statement from the Society for Endocrinology and the British Thyroid Association regarding "Association of Radioactive Iodine Treatment With Cancer Mortality in Patients With Hyperthyroidism"

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We are aware of the substantial interest shown in the recent publication in JAMA internal medicine by Kitahara et al[1]. This retrospective analysis of data from the large multicentre Cooperative Thyrotoxicosis Therapy Follow-up study (CTTFUS) suggests a modest increase in potential risk of death from cancer in people who receive radioiodine therapy for hyperthyroidism. These findings have obviously raised considerable concern as radioiodine is one of the key treatment options in hyperthyroidism, particularly in those who relapse or have disease that is difficult to control. Experience with radioiodine is longstanding and it is a widely used treatment modality for hyperthyroidism. The conclusion in this paper that "in RAI-treated patients with hyperthyroidism, greater organ-absorbed doses appeared to be modestly positively associated with risk of death from solid cancer, including breast cancer" has naturally caused anxiety for both patients and clinicians. Whilst the work in the study is innovative and detailed, the Society for Endocrinology (SFE) and the British Thyroid Association (BTA) are concerned that the conclusion will need to be interpreted cautiously for the following reasons.

1) **There was no control cohort with hyperthyroidism in this study.** This is a substantial limitation of the study. It is not clear why patients with hyperthyroidism who did not receive radioiodine were not used as controls since this data is available in the CTTFUS cohort. The lack of a hyperthyroidism control group makes it difficult to ascertain if the increase in cancer risk is a consequence of hyperthyroidism and poor disease control or of radioiodine per se. This is important, as a previous analyses of the CTTFUS dataset which included a control group did not find increased risk of cancer mortality from radioiodine[2]. Furthermore a further analysis of the CTTFUS dataset by two of the study co-authors has shown no excess cancer mortality attributable to radioiodine whereas an increased risk of solid cancer deaths was

observed in hyperthyroid patients who were not treated with radioiodine or surgery[3]. This discrepancy with findings of the original study is a cause for concern and calls for a more detailed evaluation of cancer risks in the entire CTTFUS cohort.

2) **The model used to calculate the absorbed radioiodine dose is novel but not validated.** A complex mathematical model has been used to estimate the absorbed radioiodine dose, based on a series of assumptions on thyroid gland weight and radioiodine uptake in a small preliminary sample of patients. These assumptions leave significant uncertainties in organ dose exposure and whilst impressive, will need to be replicated further and validated.

3) **In the analysis, important confounders such as smoking and obesity have not been considered.** The analysis did not correct for a number of important confounders for cancer risk including smoking, obesity, alcohol intake, and biochemical disease severity. This is likely due to the nature of the dataset used, but it remains an important limitation which should warrant further caution in the interpretation of data and conclusions.

4) **Excess solid cancer risk is not seen following administration of substantially higher doses of radioiodine to patients with thyroid cancer.** Studies in radioiodine-treated thyroid cancer patients show development of secondary cancers only when doses in excess of 10 GBq are administered and the most commonly observed malignancies are haematological cancers such as leukaemia[4]. A causative role for radioiodine in the study findings thus seems unlikely given that excess risk was only observed for solid malignancies, and the administered radioiodine doses were well below the expected threshold for cancer risk.

5) **Whilst statistically significant, the magnitude of observed effects in this study are modest**. The risks observed were marginal, with an estimated relative risk of 1.06, 95% Confidence Interval, 1.02—1.10, for total solid cancer mortality. Thus, given the uncertainties in the radioiodine dose estimates, the potential for unexplored confounding influences, and the lack of patient control groups, these marginal risks will need to be interpreted with caution.

Recent observations have shown the importance of achieving good control of hyperthyroidism in a timely fashion to improve long-term cardiovascular and mortality outcomes[5,6]. In this context, it would be unfortunate if patients were deprived of the option of rapid, effective control of their hyperthyroidism with radioiodine, due to concerns of cancer risk. Overall, on the basis that current evidence shows no excess cancer risk, it would be reasonable to continue with current approaches to the management of hyperthyroidism, whilst further, appropriately controlled studies are undertaken. We believe that long term monitoring of outcomes, including cancer mortality risk, is essential for patients who have undergone radioiodine therapy . We endorse and would actively support efforts to construct large national databases of radioiodine-treated hyperthyroid patients to assess such outcomes.

References

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