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Mini-Review

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Does Radioactive Iodine Therapy for Hyperthyroidism Cause Cancer?

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Abbreviations: CTTFUS, Cooperative Thyrotoxicosis Therapy Follow-up Study; RAI, radioactive iodine; SMR, standardized mortality ratio; TNG, toxic nodular goiter.

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Abstract

Radioactive iodine has been considered a safe and effective therapeutic option for hyperthyroidism secondary to Graves disease and autonomously functioning thyroid nodules since the mid-20th century. The question of whether I-131 at the doses used for hyperthyroidism might increase the risk of cancer has been investigated in a number of observational cohort studies over the years, with the preponderance of evidence being reassuring as to its safety. In particular, the 1998 Cooperative Thyrotoxicosis Therapy Follow-up Study (CTTFUS) has been widely cited as compelling evidence that I-131 is safe in hyperthyroidism therapy with respect to carcinogenesis. However, in 2019, a study by Kitahara and colleagues re-analyzed the CTTFUS cohort, extending the follow-up time and applying a novel dosimetric model for estimating tissue absorbed doses of radiation. This new analysis concluded that radioactive iodine was associated with an increased risk for mortality from overall cancer, breast cancer, and non-breast solid cancers. Reaction to this study was vociferous and particularly negative in the nuclear medicine literature. This mini-review was inspired by the 2019 CTTFUS controversy, and it is intended to provide the necessary context for clinicians to provide nuanced advice to their patients on the subject. To that end, the pre-2019 literature is surveyed, the 2019 CTTFUS study and a 2020 follow-up are discussed, and lessons from the literature and critical commentaries are considered.

Key Words: hyperthyroidism, radioactive iodine, cancer

Radioactive iodine (RAI) has been considered a safe and effective therapeutic option for hyperthyroidism secondary to Graves disease and autonomously functioning thyroid nodules since the mid-20th century (1, 2). While still the leading treatment modality in the United States, survey data from the American Thyroid Association,

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Endocrine Society, and American Association of Clinical Endocrinologists indicate that I-131 has slowly been declining in popularity over the past 3 decades in competition with antithyroid thionamide drugs, which have long been more popular in Europe and Asia (3-5). This trend likely reflects persistent concerns that RAI may increase the risk for Graves orbitopathy, as well as the accumulation of favorable data regarding the long-term use of thionamides. Anxiety related to potential radiation carcinogenesis may also be a deterring factor, though expert opinion has largely been reassuring on this issue following the publication of the landmark 1998 Cooperative Thyrotoxicosis Therapy Follow-up Study (CTTFUS), which reported no increased risk of cancer mortality comparing RAI-treated hyperthyroid patients with general population controls (1). The consensus view that RAI therapy for hyperthyroidism is safe for adult patients with respect to carcinogenesis is reflected in recent society guidelines from both the American Thyroid Association (2016) and the National Institute for Health and Care Excellence (United Kingdom, 2019), with neither document suggesting that cancer risk is a significant decision-making factor for choice of therapy (6, 7).

However, in 2019, a highly polemical debate over the safety of RAI therapy for hyperthyroidism erupted following the publication of a new study of the CTTFUS cohort by Kitahara and colleagues (8). This further extension and re-analysis of the CTTFUS cohort reported a modest positive association between higher estimated organ-absorbed doses of I-131 and the risk of death from solid cancers, including breast cancer. The authors wrote: "For every 1000 patients with hyperthyroidism receiving typical doses to the stomach (150 to 250 mGy), an estimated lifetime excess of 19 (95% CIs, 3-40) to 32 (95% CIs, 5-66) solid cancer deaths could occur." This conclusion triggered considerable critical reaction in the medical press, particularly in the nuclear medicine journals. Inspired by this debate, the purpose of this mini-review is to put the newer data in context with the prior literature in order to help clinicians provide nuanced advice on the subject to their patients.

In preparation of this mini-review, a PubMed search was performed for review articles and studies of RAI and hyperthyroidism that examined cancer risk from 1980-2020. The references of the primary studies identified were examined to identify other relevant publications. Guidelines of national endocrinology societies were reviewed, as was one meta-analysis (9). Letters, articles in the medical press, and commentaries relating to the 2019 CTTFUS study were identified via Google search.

Why Worry About RAI Carcinogenesis at Doses Used for Hyperthyroidism?

I-131 emits ionizing radiation in the form of gamma rays and beta particles. Current expert opinion, as summarized in the *National Research Council report on Biological Effects of Ionizing Radiation VII* (2006), holds that there is a linear dose-response relationship between ionizing radiation and the development of cancer (10, 11). Quantifying the cancer risk associated with lower radiation exposures is nontrivial for reasons relating both to the physics of different types of radiation as well as to variable patient- and tissue-susceptibilities. That being said, the question to be addressed is not really whether I-131 can cause cancer, but instead whether the exposures seen with hyperthyroidism therapy have a large enough carcinogenic effect to be deemed clinically relevant.

A few concepts from the radiation effects literature are particularly relevant for this mini-review, starting with the idea that establishing a dose-response is vital for establishing causation. For RAI therapy in hyperthyroidism, no definitive study exists in this regard. A point of reference for higher administered I-131 doses exists in the thyroid cancer literature, although dose-response data are scarce (12). Evidence exists for an increased risk for persistent chromosomal abnormalities in circulating lymphocytes following RAI for thyroid cancer (13), Meta-analyses of the thyroid cancer literature by Sawka and colleagues have suggested that there may be an increased risk of solid cancers and leukemia with administered doses greater than 100 mCi in post-thyroidectomy patients; some dose-response data for leukemia exists if one considers accumulated dose (14, 15). Extrapolating these data to the lower administered doses used for hyperthyroidism though is nontrivial since subjects with thyroid cancer may have innate risk factors for other cancers not shared by hyperthyroid patients. At the same time, the overactive thyroid gland itself becomes a source of radiation during RAI, increasing the exposure of other tissues at a given administered dose as compared to postthyroidectomy subjects. Note that RAI-induced thyroid cancer is therefore discussed as a special case in the following literature review. In any event, even with the higher administered doses used in thyroid cancer, the absolute risks of secondary primary malignancies have been thought to be small enough that the 2015 American Thyroid Association cancer guidelines state that no additional cancer screening is necessary beyond age-appropriate testing (16).

Another salient concept arising from studies of environmental and occupational radiation exposures is that there may be a latency period of several years before radiation-induced cancers are seen (17). For hematologic malignancies, this latency period is thought to be shorter, perhaps 1

or 2 years. Thus, study designs that do not exclude cases occurring in the first years after RAI therapy may overestimate the risks of cancer. On the other end of the spectrum, it is possible that risks of cancer may remain elevated for some tissues for many years or even decades after exposure, such that that studies with short follow-up times may underestimate risk (18). It should be noted that patient age at the time of exposure is widely accepted as being clinically relevant, with cancer risks for many tissues being higher for children. While clinical data involving RAI in children with hyperthyroidism is scarce, some experts advise against its use in very young children out of an abundance of caution (6).

Survey of the Literature Prior to 2019 CTTFUS

In order to evaluate the debate sparked by the 2019 CTTFUS extension and re-analysis, it is first necessary to survey the preexisting data (Table 1). This literature, which consists entirely of observational cohort studies, is dominated by the CTTFUS cohort. Initiated in 1961, the CTTFUS cohort is both the oldest and the largest of its kind, originally including 36 609 patients who were treated for hyperthyroidism between 1946 and 1964 at 25 centers in the United States and 1 in the United Kingdom (1). Initial publications included a study by Saenger and colleagues showing no increased incidence of leukemia (19), and a study by Dobyns and colleagues reporting no increase incidence or mortality from thyroid cancer with a mean follow-up period of 8.2 years (20). In the early 1980s, Hoffman and colleagues studied cancer risk in RAI-treated hyperthyroid patients at the Mayo Clinic, including their subgroup of CTTFUS subjects, comparing them with thyroidectomized control patients. The results were predominately negative, with no increases in mortality for any nonthyroid tissue and cancer incidence only being increased for a pooled group of "iodine-avid" tissues, none of which individually reached significance (21–23). Similarly, Goldman and colleagues at the Massachusetts General Hospital studied RAI-treated patients including their CTTFUS subgroup as compared with general population controls, reporting no significant increases in cancer incidence or mortality for any tissue, including breast (24, 25). Thus, the early CTTFUS related studies were reassuring in regard to cancer risk.

In contrast, worrisome data emerged from Sweden in the early 1990s, where a series of studies by Hall and Holm and colleagues examined the risk of cancer following RAI for hyperthyroidism in a cohort of 10 522 patients as compared with general population controls using the Swedish Cancer Register (31, 32). With an average follow-up duration of 15.5 years, there was a slightly increased incidence of overall cancer (standardized incidence ratio [SIR] of 1.06; CI, 1.01-1.11), as well as a small increase in mortality from overall cancer (standardized mortality ratio [SMR] of 1.09; CI, 1.03 to 1.16). Considering latency, the investigators focused on patients surviving more than 10 years after RAI, finding increased incidence of stomach, kidney, and brain cancers but not breast cancer. Mortality was increased for stomach, esophageal, and lung cancer, but not the other cancers; thus, only stomach cancer had both increased incidence and mortality in 10-year survivors. These data comprise the most concerning safety results from the pre-2019 literature.

Following the publication of the Swedish studies, and in part spurred by public interest in radiation safety following the 1986 Chernobyl nuclear disaster, the CTTFUS cohort was re-analyzed in 1998 by Ron and colleagues in perhaps the most definitive study of the pre-2019 literature (1). The 1998 CTTFUS study extended the mortality follow-up through 1990, requiring the investigators to assemble a new database from original sources ranging from microfiche to hand-written doctors' notes, a Herculean task that resulted in a final dataset with complete follow-up through the end of 1990 for 28 719 patients. The main mortality analysis compared RAI, thionamide drugs, and surgically treated patients with general population controls based on US national mortality rates. The study design was notable in that it used a relatively simple dosimetric model to estimate tissue-specific exposures and thus tissue-specific cancer risk. In contrast to the Swedish data, and in spite of having a minimum latency period set to only 1 year, the major results were negative: RAI was not linked to total cancer deaths (SMR 1.02; 95% CI, 0.98-1.07) nor to any specific type of nonthyroid cancer, including breast, esophageal, stomach, or lung (1).

As the reconstituted 1998 CTTFUS database is foundational for the 2019 CTTFUS study and a subsequent 2020 study, a few specific observations are worth noting. First, CTTFUS patients treated with antithyroid drugs had a significantly higher incidence of preexisting cancer than the other treatment groups. While mortality was higher for antithyroid drug patients than the population controls (SMR 1.31; 95% CI, 1.06-1.6), the excess was no longer present for any endpoints other than brain cancer when patients with preexisting cancers were excluded from the analysis. Thus, the data do not prove that antithyroid drugs themselves convey a carcinogenic risk, but instead this difference between groups highlights the possibility of confounding by indication, that is, confounding occurring when a clinical indication for selecting the treatment also affects the outcome under study (33). Second, the CTTFUS cohort as a whole had higher mortality rates from breast, lung, and kidney cancers than US population controls, raising the possibility that there could be disease-specific

Table 1. Major epidemiologic studies of RAI for hyperthyroidism, 1982-2020

	Cohort size	Follow-up duration	Outcome	Control group	Latency period	Overall cancer	Breast cancer	Thyroid cancer
2020 CTTFUS Kitahara et al (26)	31 363	26 years (mean)	Mortality: SMR	Hyperthyroid: drugs/surgery	5 years	NS	NS	NS
2020 CTTFUS Kitahara et al (26)	31 363	26 years (mean)	Mortality: HR	Internal: dose-response	5 years	Positive[a]	Positive	NS
2019 CTTFUS Kitahara et al (8)	18 805	26 years (mean)	Mortality: excess RR	Internal: dose-response	5 years	Positive[a]	Positive	NS
2019 Gronich et al, Israel (27)	1664	7.3 years (mean)	Incidence: HR	Hyperthyroid: drugs	1 year	NS	NS	NS
2015 Finland Ryödi et al (28)	6148	10 years (median)	Mortality: HR	Age/gender matched;	3 months	NS	NS	NS
2015 Finland Ryödi et al (28)	6148	10 years (median)	Incidence: HR	Hyperthyroid: surgery	3 months	NS	NS	NS
2007 Finland Metso et al (29)	2793	9.8 years	Incidence: rate ratio	Age/gender matched	1 year	Positive[b]	Positive	NS
1999 Franklyn et al, UK (30)	7209	Not indicated	Incidence, Mortality	General population	None	Lower[c]	NS	Positive
1998 CTTFUS Ron et al (1)	35 593	23 years (mean)	Mortality: SMR	General population	Variable	NS	NS	Positive
1992 Sweden Hallet al (31)	10 552	15 years (mean)	Mortality: SMR	General population	Variable	Positive[d]	NS	NS
1991 Sweden Holm et al (32)	10 207	15 years (mean)	Incidence: SIR	General population	1 year	Positive[e]	NS	NS
1990 Goldman et al (25)	873	Not indicated	Mortality: SMR	General population	None	NS	NS	NS
1982 Hoffman et al, Mayo (21)	3146	15 years (mean)	Mortality: RR	Hyperthyroid: surgery	Variable	NS	NS	Not indicated
1982 Hoffman et al, Mayo (22)	3146	15 years (mean)	Incidence: RR	Surgical hyperthyroid	1 year	NS	NS	Positive

Abbreviations: HR, hazard ratio; NS, nonsignificant or negative; positive, increased risk of cancer; RR, relative risk; positive, increased risk of cancer; SIR, standardized incidence ratio; positive, increased risk of cancer.

[a]Also positive for solid non-breast.

[b]Also positive for stomach and kidney.

[c]Overall cancer risk lower for RAI-treated; increased risk of small bowel cancer in RAI-treated.

[d]Positive for stomach, esophagus, and lungs after 10 years.

[e]Positive for stomach, kidney, brain after 10 years.

cancer risks related to the underlying hyperthyroidism that might confound the analysis. Third, reflecting the mid-20th century origins of the study, the dataset lacked information on potential cancer confounders such as smoking and reproductive history. Finally, the authors pointed out that in spite of the large number of subjects and long follow-up time, the statistical power of the study was still limited assuming that the absorbed radiation doses and thus expected cancer risk were very low for most tissues. Thus, while the 1998 CTTFUS study is rightfully the most cited trial supporting the safety of RAI in hyperthyroidism, it must be remembered that the above caveats could have biased the results toward the null hypothesis.

One year later, a British study by Franklyn and colleagues provided more reassuring, albeit surprising results (30). This 1999 study examined a cohort of 7417 hyperthyroid patients who had been treated with RAI in the West Midlands region between 1950 and 1991, comparing them with general population controls. In spite of not setting a latency period, the overall incidence and mortality for cancer were actually decreased in the RAI group, a unique result in the literature. None of the specific cancer sites increased in the Swedish data were positive in this study, but increased incidence and mortality for small bowel and thyroid cancers was reported based on a small number of cases.

Two other major studies round out the survey of pre-2019 data, both examining a cohort associated with Tampere University Hospital in Finland with contrasting results. In 2007, Metso and colleagues compared a cohort of 2793 patients treated with RAI between 1965 and 2002 with a control cohort of age- and sex-matched subjects derived from the Finnish Cancer Registry (29). Alarmingly, the RAI-treated patients had an elevated relative risk for incidence of overall cancer (1.25; 95% CI, 1.08-1.46), with positive findings for stomach, kidney, and breast cancers. This was the first statistically significant finding of increased breast cancer risk associated with hyperthyroidism treatment. Lending credence to the findings, the incidence of overall cancer increased with higher RAI dose, and this difference became significant only after a 10-year period consistent with the latency effect. However, the authors themselves later questioned the possibility of confounding from disease-related cancer risk factors, and in a 2015 study led by Ryödi, they attempted to address this issue by adding hyperthyroid controls (28). For this follow-up study, they compared 1814 RAI-treated patients with 4334 surgically treated hyperthyroid subjects as well as to general population controls. With a median of 10 years of follow-up, there was no increase in overall or nonthyroid site-specific cancer incidence or mortality associated with RAI. Considering their experience, the investigators concluded that while the incidence of gastric and respiratory cancers might be increased in Finnish patients with hyperthyroidism, this increased risk was likely related to the underlying disease rather than the treatment modality.

On the Risk of Subsequent Thyroid Cancer

The overactive thyroid gland is a special case in terms of RAI cancer risk, as the absorbed i-131 doses for overactive thyroid tissue are estimated to be several orders of magnitude higher than any other tissue (34). Concern for RAI as a thyroid carcinogen is logical in light of data indicating that nuclear environmental exposures and external radiation for lymphoma both have been posited as thyroid cancer risk factors in children (35, 36). While adult thyroid tissue may have a lower sensitivity to radiation carcinogenesis, several studies in the hyperthyroidism-RAI literature have reported positive findings for thyroid cancer, ironically including both the 1998 CTTFUS and the 1999 West Midlands studies. Of note, in 1998 CTTFUS most of the increased risk was actually seen during the presumed latency period of the first 5 years, raising questions about causality. On the other hand, since ~97% of thyroid cancers are nonfatal, mortality is likely an insensitive endpoint for this tissue as compared to incidence. Ultimately, a key factor that may explain some of the variability between studies is whether or not the absorbed doses were sufficient for thyroid cell killing; after all, if the gland were destroyed by RAI, there would be no substrate for subsequent cancer. As will be discussed below, the most recent studies in the field have not reported any increased risk for thyroid cancer.

Lessons From the Pre-2019 Literature

The findings from the pre-2019 literature are mixed with regards to cancer risk, but the preponderance of evidence is actually reassuring, with the strongest evidence for safety of RAI being the 1998 CTTFUS study. Of note, the Scandinavian studies and the 1998 CTTFUS study included subgroup analyses comparing Graves patients with those with toxic nodular goiter (TNG), and in general, positive findings for cancer were more pronounced in the TNG patients. While the TNG patients did receive higher median doses of I-131 than Graves patients, these etiologic comparisons had reduced statistical power and were likely confounded by of the older ages of the TNG patients. The positive findings of the Swedish data were not consistently recapitulated in other studies, and concern stemming from the earlier Finnish data was ameliorated by the investigators' own later work. The lack of a consistency of the various tissue-specific positive findings raises questions about their significance, or at least suggests these risks may be population-specific. Furthermore, the small case

numbers imply that absolute risks are low. Thus, it is not surprising that recent society guidelines regarding hyperthyroidism do not discuss carcinogenesis risk as a reason to dissuade adult patients from choosing RAI for definitive therapy of hyperthyroidism (6, 7).

At the same time, it must be said that certain methodologic concerns apply to almost all of the studies in this literature, and intellectually it must be acknowledged that these issues could have biased the results toward the null hypothesis. Statistical power was lacking for many of the less common cancers in these studies, even in 1998 CTTFUS. Latency periods were handled very differently across studies, and post hoc latency analysis could create a perception of bias. Follow-up periods were relatively short for many of these studies, a particular problem when mortality was the endpoint for low-fatality cancers. Perhaps most troubling is the possibility that confounding by indication could have biased the cross-modality comparisons, with the choice of comparison group having an outsized impact on the results. While endocrinologists around the world may have had different reasons for selecting a given treatment modality, it is easy to imagine that some of these reasons, such as older age or reproductive history, might also be relevant for cancer risk. Finally, data regarding what are now established cancer risk factors such as smoking history were not registered, a byproduct of the era in which these cohorts were established. Thus, it should probably be said that expert opinion pre-2019 was based on the best available data, rather than any truly definitive study or studies.

The 2019 CTTFUS Study

In 2019, Kitahara and colleagues brought the CTTFUS cohort back into the spotlight, extending the follow-up period by 24 years while also applying a novel, sophisticated dosimetry model to better estimate the absorbed organ doses of I-131 (37). The investigators applied this new model to a subset of dosimetrically well-characterized CTTFUS patients, and then extrapolated the data in order to estimate the absorbed doses for more than 20 organs and tissues for all subjects in the wider cohort. The results were then normalized to a 100 mGy organ dose to facilitate comparison to the literature on external radiation exposures.

In hopes of avoiding confounding by indication, the new study focused solely on the RAI patients, also foregoing any comparison to general population controls. In essence, there would be no confounding by indication since only one indication, RAI, was considered. The conclusions of the study would hinge on the dose-response data, specifically the estimated tissue-specific absorbed doses and cancer mortality responses.

With the mean follow-up time now extended to 26 years for a cohort of 18 805 RAI-treated patients, and with preexisting cancers excluded and latency set to 5 years, the excess relative risks per 100 mGy estimated absorbed dose to specific organs and tissues were found to be elevated for all solid cancers combined, female breast cancer, and all other non-breast solid cancers combined. For female breast cancer, the relative risk at 100-mGy dose to the breast was 1.12 (n = 291; 95% CI, 1.003-1.32; $P = 0.04$). The authors described this as a "modest" risk, being similar in magnitude to estimates of risk from atomic bomb survivors and other patients with environmental exposures to ionizing radiation. At the same time, the investigators extrapolated the relative risk data using current US mortality rates to estimate that with current administered I-131 doses for RAI, between 19 to 32 excess solid cancer deaths per 1000 patients treated at age 40 years might be attributable to I-131. Excluding subjects with TNG did not affect the findings.

Reaction to the 2019 CTTFUS Study

The 2019 CTTFUS study was met with considerable critical reaction, particularly from the nuclear medicine community, with numerous letters, commentaries, and even articles in the medical press questioning the methodology of the study (34, 38-47). Surprisingly, 2 of the nuclear medicine authors of the 2019 CTTFUS study published a dissenting commentary of their own arguing that data regarding the antithyroid drug patients should have been included (43). The Society for Endocrinology and the British Thyroid Association published a joint statement critical of the study, writing "…current evidence shows no excess cancer risk" though also recommending that further research was warranted (46).

Certain points echo through these critical commentaries. Most prominently, almost all questioned the dosimetric model, suggesting it was not validated sufficiently to accept the dose-response results at face value. Lending a degree of substance to this charge, the manuscript describing the model itself describes 8 different potential sources of uncertainty, while stating that a thorough analysis of the potential dosimetric uncertainties "could be envisaged in a second stage" (37). For the critics, rejection of the dose-response methodology invalidated the conclusions of the study. For their part, however, in the discussion of the paper the 2019 CTTFUS authors argued that uncertainties in the model may have actually led to underestimation of the strength of the dose-response.

Another widespread remonstrance was to reject the single therapeutic modality study design as being a valid remedy for confounding by indication. In spite of the earlier observation that the CTTFUS antithyroid drug group had

a higher rate of preexisting cancer compared to the RAI group, many of the critical commentaries suggested that comparison to this hyperthyroid control group would have provided vital perspective, albeit without explaining how confounding by indication might be addressed. The logic of this position hinges on the possibility that the severity of hyperthyroidism might independently influence both the administered dose of I-131 and cancer risk. Several lines of evidence support the idea that hyperthyroidism itself may be a risk factor for carcinogenesis. For example, basic studies have reported that pharmacologic doses of T3 may stimulate proliferation of certain cell types (48). Clinical lines of evidence include a 2009 prospective observational study from Norway which reported low thyrotropin (thyroid-stimulating hormone) being associated with an increased risk of several solid tumors (49), in addition to the Finnish cohort data linking hyperthyroidism itself rather than treatment modality to gastric and respiratory cancers (28). Several studies have suggested that higher thyroid hormone levels may be associated with increased risk for breast cancer (50, 51). While these lines of evidence are not conclusive in terms of establishing the severity of hyperthyroidism as being a confounding factor, in aggregate they do provide a rationale to question whether the dose-response data in 2019 CTTFUS should be considered as sufficient proof of risk on its own.

The third ubiquitous critique in the 2019 CTTFUS commentaries was to point out that the CTTFUS database, even after its revisions, still does not include data regarding smoking, reproductive function, and other cancer risk factors that were established after the original study period in the 1960s. This is unquestionably a salient criticism, yet it must be considered with a sense of irony since the 1998 CTTFUS study and all the other negative studies suffer from the same deficiency. In fact, all of the studies in this literature suffer from this deficiency save for a 2020 study by Gronich and colleagues which examined cancer incidence for 2829 hyperthyroid Israeli patients treated with I-131 as compared with 13 808 controls treated with antithyroid drugs (27). This study utilized the Clalit health care database, which contains data on potential cancer risk factors, including age, sex, and smoking history. With prevalent malignancies being excluded, and after a relatively short mean follow-up time of 7.27 years, no increases in incidence for any cancer were observed, in spite of having only a 1-year latency period. Thus, this contemporary study provided a somewhat reassuring contrast to the 2019 CTTFUS dose-response data.

The 2020 CTTFUS Study

Kitahara and colleagues published a follow-up analysis in 2020, this time including SMR data for all treatment modality groups, in a design recapitulating the 1998 CTTFUS study (26). In addition, the RAI dose-response analysis was repeated using a simple 3-tiered scheme based on administered dose. Reassuringly, cross-modality comparison adjusted for age, sex, and underlying thyroid diagnosis revealed no differences in the hazard ratios for solid cancer death, including for breast cancer. As was seen in 1998, SMRs were only elevated for the antithyroid drugs group when preexisting cancers were not excluded. At the same time, however, the dose-response analysis for the administered dose was positive for solid cancers combined, breast cancer, and non-breast solid cancers. Thus, while the hyperthyroid but nonexposed control comparison offered the hoped-for reassurance, the positive signal for excess risk was not lost when the novel dosimetric model was set aside, lending credence to the 2019 dose-response results. The authors reminded readers of the possibility of residual confounding in the cross-modality comparisons, pointing out, for example, that the drug-only group included a high proportion of patients with baseline comorbidities, including prior cancer diagnoses, raising the possibility that these groups may have had different baseline risks of cancer death for reasons unrelated to the treatment modality.

Clinical Counseling

Is RAI therapy for hyperthyroidism safe for patients with respect to cancer risk? When a clinician is choosing a therapeutic strategy for hyperthyroidism, the choice is not between RAI or nothing, but rather RAI vs surgery or antithyroid drugs. In practical terms, the question then is not whether RAI is intrinsically free of cancer risk, but rather whether it is as safe as the other treatment modalities. Examining the issue from that perspective, the negative cross-modality comparison data from the 1998 and 2020 CTTFUS analyses are perhaps the most clinically relevant findings, and these can serve as the basis to provide reassurance to patients. Furthermore, given that only the earlier Finnish study echoed any warning of risk for breast cancer, it may be premature to alter clinical guidance for breast cancer following the 2019 and 2020 CTTFUS studies. Of note, the 2019 and 2020 CTTFUS studies did not show any increased risk of thyroid cancer, and it is also quite reassuring that none of the studies in the hyperthyroidism-RAI literature have reported any increased risk for leukemia. Thus, it seems entirely reasonable to counsel patients that, while the question is still a subject of active debate, the risk of cancer from RAI is apparently small enough to be indistinguishable as compared with patients treated with antithyroid drugs or surgery. Clinical counseling for I-131 therapy is known to vary widely, with a 2011 survey of RAI providers indicating that only 66% used a written consent form and only 73% of the forms mentioning pregnancy

avoidance even though it is a universal recommendation (52), Thus, it could be said that practitioners must strive to improve the consent process at a fundamental level while also trying to properly convey a nuanced risk analysis as demanded by the 2019 CTTFUS findings.

Future Directions

From a scientific perspective, the findings from the 2019 and 2020 CTTFUS studies constitute a mandate for further research. An even application of the critiques leveled at the 2019 CTTFUS would weaken much of the evidence favoring safety, and this cognitive dissonance calls out for resolution as well. The polemical debate surrounding these studies could ultimately prove particularly beneficial if the appropriate lessons are learned and accounted for in the development of a new cohort study. Some of these general lessons apply to all cancer cohort studies and have long been known but not always heeded, such as the need for large cohorts with long follow-up periods, and the need to prospectively address latency. Clearly, the glaring historical limitation of the literature regarding established cancer risk factors can and must be addressed in a modern cohort study. Electronic records should also facilitate the inclusion of cancer incidence data in addition to mortality data, a critical factor for cancers with low mortality rates.

Specific lessons for the question of RAI in safety in hyperthyroidism must be learned as well, starting with the need to validate the current dosimetric model for RAI. Given the possibility of hyperthyroidism being a risk factor for cancer, an investigational metric for area under the curve of hyperthyroidism exposure would be ideal, and while nontrivial, it would be of hypothetical benefit to assess this both before and after RAI exposure. As CTTFUS was not suited for characterization of the antithyroid drug exposures, the new cohort should have more precise drug usage data. Toxic nodular goiter patients and Graves patients should probably be analyzed separately given the possibility of different innate risks for cancer, though this would effectively reduce the dose range further thus making dose-response studies even more challenging. One wonders if the question of RAI carcinogenesis should first be tackled in thyroid cancer patients, given the wider dose range and possible advantages with regard to the vexing question of how to handle confounding by indication in an observational setting. Another idea would be to study patients whose Graves disease went into remission without RAI as the control group for those who did receive iodine. To have enough control subjects, clearly many centers would have to pool cases, and the cost and effort to accomplish a study addressing all of the lessons of the past would be at the level of a "moon-shot." Let us hope then that an international group of investigators can come together to match or even surpass the efforts of Ron and colleagues in their 1998 reconstitution of CTTFUS to make such a moon-shot study a reality.

Additional Information

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