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IODIDE AND PERCHLORATE BLOCK UPTAKE OF RADIOIODINE TO PREVENT THYROID CANCER, BUT YOUNGER PEOPLE REQUIRE HIGHER DOSES

Hänscheid H, Reiners C, Goulko G, Luster M, Schneider-Ludorff M, Buck AK, Lassmann M. **Facing the nuclear threat: thyroid blocking revisited.** J Clin Endocrinol Metab. August 24, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

Radioiodine-131 is a major fission product released into the atmosphere after a nuclear accident and results in contamination of water and soil. It may be ingested through food and water that is contaminated with 131-iodide. Radioidine-131 from the Chernobyl accident resulted in a dramatic increase of thyroid cancer in children who were exposed to the radiation. To prevent thyroid cancer from thyroid uptake of 131-iodide, the World Health Organization and the U.S. National Research Council have recommended that the potentially exposed population be given tablets containing 100 mg of iodide as potassium iodide to block the uptake of the radioiodide.

The purpose of the present study was to evaluate sodium perchlorate (SP) as a blocking agent, as compared with potassium iodide (KI), and to evaluate the prediction of the effectiveness of this therapy.

METHODS

Twenty-seven healthy euthyroid subjects with a mean age of 25 years participated in 48 studies of ^{123}I kinetics in the thyroid. Patients first had a study of iodine uptake with 0.14 mCi ^{123}I (13.3 hr physical half-life) with uptake measurements at 2, 6, 24, and 48 hours. This was followed by a study of the blocking agent with a dose of 0.7 mCi ^{123}I. The different interventions were tested in subgroups of six or seven volunteers: 100 mg of KI 24 hours before or 2, 8, or 24 hours after ^{123}I exposure; 100 mg of SP 2 hours after exposure; or 1 g of SP 2 or 8 hours after exposure.

RESULTS

The highest mean reduction of thyroid absorbed dose, 88.7%, was found in individuals blocked with 100 mg of KI at 24 hours before exposure. The mean reduction in subjects blocked at 2, 8, and 24 hours after the injection of ^{123}I was reduced to 59.7%, 25.4%, and 2.8%, respectively (P <0.001). The

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reduction by 100-mg and 1000-mg perchlorate at 2 hours was 56.9% and 58.3%, respectively, and the reduction by 1000-mg perchlorate at 8 hours was 7.4%. The effects of perchlorate were not significantly different from the 100-mg dose of KI at similar times.

The time for blockade of further uptake, after the blocking agent was given orally was calculated to be about 15 minutes. Additional thyroid uptake after the intervention did not exceed 2% of the dose. It appeared that the 100-mg dose of perchlorate was slightly less effective at blocking further uptake, but this was probably not significantly different from the other blocking regimens.

Iodine kinetics were significantly faster in subjects younger than 25 years of age, as compared with those older than 25. The time of intervention to achieve a 50% dose reduction was 2.4 hours for the subject with the fastest kinetics and 9.2 hours for the subject with the slowest kinetics.

CONCLUSIONS

Current guidelines for blocking ^{131}I uptake are adequate for older individuals but probably overestimate the efficacy of blocking in young individuals, who have faster kinetics. Perchlorate may be used for thyroid blocking as an alternative for individuals with iodine hypersensitivity or those at risk for thyrotoxicosis.

COMMENTARY

At a time of a nuclear disaster, shielding from radiation by distance, staying indoors, and taking all other measures to avoid exposure to radiation are important. Public authorities must act quickly to distribute iodide tablets to the population who may be exposed in order to prevent thyroid uptake of ^{131}I that has strong beta radiation, which can induce DNA damage and result in thyroid cancer. The data of this paper show that the best blockade occurs when the blocking agent is given before the isotope is administered. The conclusion that thyroid iodine kinetics vary among individuals is not novel, but the point that younger people have faster turnover and may need a larger blocking dose given at an earlier time is important.

In 2002, the American Thyroid Association took the position that KI should be available and distributed to families living within 50 miles of a nuclear plant. In 2004, the National Research Council published Distribution and Administration of Potassium Iodide in the Event of a Nuclear Incident (1). In a quick review of this book, I could not find the amount of iodine in the tablet. A commercial tablet called Iostat contains 130 mg of KI, equivalent to 100 mg of iodide; we may assume that KI tablets contain 100 mg of iodide when the amount is not specified. Surprisingly, the article reviewed here used 100 mg of KI, which would be equivalent to only 77 mg of iodide. It is also surprising that the authors did not refer to the landmark paper of Braverman and colleagues (2), which showed that 130 mg of KI reduced 24-hour uptake of ^{123}I to <1%, data similar to those of the present study. Based largely on Braverman's work, the Food and Drug Administration (FDA) in 2001 recommended that people potentially exposed to radioiodine fallout take potassium iodide tablets that contain 100 mg of iodide per day to block thyroid uptake of the ^{131}I for prevention of thyroid cancer (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080542.pdf). However, the FDA recommended half this dose for people younger than 18 years of age, a dose that may be too low based on the present paper.

Monte Greer and colleagues showed that a dose of 0.5 mg of perchlorate per kilogram per day reduced thyroid uptake of ^{123}I by 67% (3). A cell model developed to test the blocking effect of ^{131}I-induced DNA double-strand breaks by monovalent anions that compete for iodide transport showed that

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perchlorate was sixfold more potent than iodide (4). It is unfortunate that doses of perchlorate lower than 1000 mg were not tested by Hänscheid and colleagues before administration of the radioiodine in order to determine what dose of perchlorate would be as effective as 100 mg of KI when given beforehand. The in vitro cell model also showed that incubation with blocking anions less than 1 hour after incubation of the cells with ^{131}I was much less effective in preventing the DNA damage that is a precursor to cancer (4).

— Jerome M. Hershman, MD

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RESTRATIFICATION OF THYROID CANCER DURING THE FIRST YEAR AFTER TREATMENT GREATLY IMPROVES PROGNOSTIC PRECISION

Castagna MG, Maino F, Cipri C, Belardini V, Theodoropoulou A, Cevenini G, Pacini F. **Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients.** Eur J Endocrinol 2011;165:441-6. Epub July 12, 2011; doi: 10.1530/eje-11-0466.

SUMMARY

BACKGROUND

The strategic approach to the individual treatment of differentiated thyroid cancer (DTC) has greatly evolved in recent times and continues to do so. Recently, the ATA and the ETA have produced guidelines for stratifying the risk of recurrence or persistence of DTCs (ATA: low-, intermediate-, and high-risk categories, ETA: very–low-, low-, and high-risk). This article and others recently published stress the relevance of delayed risk stratification (DRS) during the visits following the initial treatment, since this strategy can greatly change the risk category of an individual patient.

METHODS AND RESULTS

A total of 512 patients treated at the University Center of Sienna were retrospectively evaluated. Their mean (±SD) age was 46±16 years, and 89% presented with papillary and 11% with follicular thyroid cancer. Using the classification according to the AJCC/UICC system (American Joint Cancer Committee/Union Internationale Contre le Cancer), 86% of the patients were categorized as having stage I cancer, 8.4% as stage II, and 5% as stage III. All patients were treated with total thyroidectomy and radioactive iodine. Lymph-node resection in the medial central compartment was done in only 7.4%. The mean follow-up was 5.6 years. Eight patients (1.6%) died of the disease; the overall survival rate at 10 years was 98%. Five patients had recurrent disease and five had distant metastasis. Interestingly, 4 additional patients presented with elevated thyroglobulin levels but no residual lesion could be detected.

After the initial treatment, the patients were classified according to both ETA and ATA guidelines. According to ETA guidelines, tumors of >4 cm, or those extending beyond the capsule and/or with an aggressive histology and lymph-node involvement were considered high risk; all others were considered low risk. According to the ATA guidelines, some cases were classified in the intermediate-risk category (microscopic invasion, cervical lymph nodes, aggressive histology).

Six to 12 months after the initial treatment, the patients were seen again in the clinic for their first posttherapy visit. At that time, DRS was established. Clinical remission was defined as no evidence of recurrence based on either basal thyroglobulin levels or the levels after recombinant thyrotropin (TSH), ultrasound evaluation, and/or ^{131}I whole-body scans. In cases of clinical remission, substitution therapy was reduced to nonsuppressing serum TSH levels, and yearly follow-up was limited to a clinic examination and basal serum thyroglobulin levels. The other patients were considered to have persistent or recurrent disease and were treated accordingly.

The initial risk classification identified 46% (45% for ATA and 48% for ETA) low-risk patients. The ETA high-risk cases represented 55% and the ATA intermediate-risk patients 52%. Following DRS, the majority of the initially low-risk patients (87%) were considered to be in complete remission. In the higher-risk groups, as expected, only 53% were in complete remission and, thus, became low-risk cases. On the other hand, nearly 12% of initially low-risk patients moved into the high-risk category.

The recurrence rate after complete remission was extremely low (2.7%), suggesting that the DRS stratification is associated with an excellent prognosis.

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The comparison of the diagnostic value between the initial stratification and the DRS stratification is a strong argument in favor of adding an evaluation during the first posttherapy visit. For instance, the positive predictive value was very low for both the ATA and ETA classification (39%). Fortunately, however, the negative predictive value was excellent (91%), indicating that few initially severe cases are missed. DRS had a much better predictive value of 73%.

CONCLUSIONS

The data strongly suggest that even though initial stratification by the ETA and ATA guidelines are good and necessary, they need to be readjusted 6 to 12 months after the initial treatment with total thyroidectomy and radioactive iodine ablation. Many initially intermediate- or high-risk patients can be reclassified as low-risk after 1 year. However, this does not exclude an unfavorable evolution, which was observed in 12% of low risk patients.

COMMENTARY

It is worrisome that even with the updated stratification schemes of the ETA and the ATA, the positive predictive value of the initial stratification is unsatisfactory or even unacceptable. A second look is, therefore, appropriate. In practice, every endocrinologist does it spontaneously without knowing about its prognostic value. This study answers some of these questions and clearly indicates that more than 97% of the patients may be considered to be cured. However, we are missing criteria identifying those patients considered low-risk at the onset, but evolving to high-risk later on. Hopefully, molecular biology might one day be able to fill this gap; at present, several molecular markers, such as BRAF, are being evaluated with this aim in mind, but a final answer is pending.

In view of the cure rate, one may also wonder whether we are still overtreating our patients when using total thyroidectomy and radioactive iodine ablation. This open question will certainly be answered within the next decade.

— Albert G. Burger, MD

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CAN NODULES WITH A BENIGN SONOGRAPHIC APPEARANCE BE LEFT ALONE WITHOUT BIOPSY?

Virmani V, Hammond I. **Sonographic patterns of benign thyroid nodules: verification at our institution.** Am J Roentgenol 2011;196:891-5.

SUMMARY

BACKGROUND

There are several published studies that show that a combination of sonographic features such as solid texture, hypoechogenicity, microcalcifications, macrocalcifications, and intranodular vascularity predict that a nodule is more likely to be malignant (1-3). Additional studies have shown that some sonographic patterns are associated with benign nodules. It is unclear whether these benign sonographic characteristics are sufficient to justify the decision not biopsying a nodule >1 cm. Bonavita et al. (4) demonstrated that a nodule with four characteristic morphologic patterns (spongiform, cyst with colloid clot, "giraffe" pattern, and "white knight" pattern) were 100% specific for benignity. This study tests the reliability of the four sonographic patterns to identify benign thyroid nodules.

METHODS

This was a retrospective review of the pathology records and sonograms of 950 thyroid nodules that underwent ultrasound-guided fine-needle aspiration (FNA) biopsy from July 2005 through July 2009. The nodules were placed into four categories based on the cytology: insufficient, benign, indeterminate, and malignant. All the nodules from the benign and malignant groups were included in the study. Nodules with insufficient biopsy samples were excluded from the study. Indeterminate nodules were categorized and included in the study only after post-surgical pathological determinations of whether they were benign or malignant. The ultrasound images of the remaining 811 nodules from 661 patients (552 female, 109 male) with a mean age of 46.5 years (range, 18 to 88) were examined. The nodules ranged in size from 4.8 to 72 mm. The spongiform pattern was defined as an aggregation of multiple linear microcystic components in a nodule giving a honeycomb appearance or "puff pastry" appearance. The cyst with a colloid clot is a cystic nodule with an avascular hyperechoic colloid clot. The giraffe pattern is rounded or ovoid areas of hyperechogenicity separated by thin linear areas of hypoechogenicity that appear similar to the two-tone block-like coloring of a giraffe. The "white knight" pattern is a homogeneous hyperechoic nodule.

RESULTS

A total of 66 nodules showed a spongiform pattern. Of these nodules, 60 were benign on FNA cytology; the remaining 6 had an indeterminate cytology but proved to be benign after surgical resection. A total of 28 nodules showed the cyst with a colloid clot pattern. Of these nodules, 24 were benign on FNA cytology and 4 were benign on postoperative histologic evaluation; 14 showed the giraffe pattern and 13 had a cytologic diagnosis of Hashimoto's thyroiditis. The remaining giraffe-pattern nodule with an indeterminate cytology was removed surgically and found to be Hashimoto's thyroiditis on postoperative histology. White-knight sonographic changes appeared in 8 nodules, and all were shown to be Hashimoto's thyroiditis on cytologic study. None of the 121 malignant nodules showed any of these four benign sonographic patterns.

CONCLUSIONS

These four sonographic characteristics were seen in 116 (16.1%) of the 690 benign nodules but never in the 121 malignant nodules. Therefore, a nodule with one of these sonographic signs is very likely to be benign. But because these signs were seen in only 16% of benign nodules, the absence of them does not indicate an increased risk of malignancy. The 100% specificity of these four sonographic features for benign thyroid nodule may lead to a reduction in unnecessary thyroid biopsies and subsequent surgery for nodules with an indeterminate cytology.

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COMMENTARY

In the past decade, several guidelines (5, 6), including the 2009 ATA Guidelines for Nodules and Cancer, recommend on the basis of strong evidence that an ultrasound should be used to discriminate which nodules have suspicious characteristics and should be prioritized for biopsy. The ATA Guidelines note that a spongiform appearance is likely to be benign, and recommended biopsy only if the nodule >2.5 cm. This study now provides additional evidence that there are sonographic appearances that strongly suggest that a nodule is benign. It is very likely that future iterations of the ATA Guidelines for Nodules and Cancer will suggest that thyroid nodules with certain benign sonographic signs such as spongiform changes may not need to be biopsied at all. A point of concern for me is that these changes can be subtle. Identification of these sonographic characteristics depends on the experience of the person evaluating the images. In addition, high-quality images may not be provided by sonographic equipment used in endocrinology offices.

— Stephanie L. Lee, M.D., Ph.D.

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PRACTICE WHAT YOU PREACH: THERE IS INCREASING USE OF TOTAL THYROIDECTOMY FOR BENIGN DISEASE IN THE UNITED STATES

Ho TW, Shaheen AA, Dixon E, Harvey A. **Utilization of thyroidectomy for benign disease in the United States: a 15-year population-based study.** Am J Surg 2011;201:570-4.

SUMMARY

BACKGROUND

Determining the extent of thyroidectomy for benign disease hinges on the balance of surgical risk and eliminating the need for reoperation for disease recurrence. Academic centers have advocated the safety of total thyroidectomy in experienced hands and have recommended this procedure for the management of benign goiters. Others have argued that even the small added operative risk of total thyroidectomy is unjustified for benign disease. The purpose of this study was to assess whether the use of total thyroidectomy for benign thyroid disease is increasing as advocated by "experts."

METHODS

The authors extracted data from 119,885 thyroidectomy patients from the Nationwide Inpatient Sample Database for the years 1993 to 2007. Adult patients who underwent total or partial thyroidectomy for benign disease were identified by ICD-9 code. Study variables included year of operation, extent of thyroidectomy, hospital type and volume, morbidity, mortality, hospital charges, and length of stay. Analysis was performed by multivariate logistic regression or multiple linear regression.

RESULTS

There was a trend for increased performance of total thyroidectomy over the study period: 17% (1993 to 1997), 26% (1998 to 2002), and 40% (2003 to 2007). In addition, teaching hospitals and high-volume hospitals (>100 cases per year) performed total thyroidectomy more frequently with better outcomes than nonteaching institutions and low-volume hospitals (<10 cases per year). Postoperative complications—such as hypocalcemia, bleeding, and recurrent laryngeal nerve injury—length of stay, and total hospital charges were higher after total thyroidectomy.

CONCUSIONS

This study confirms the increased use of total thyroidectomy for benign disease in the United States over the 15-year period studied.

COMMENTARY

Although the performance of total thyroidectomy is on the rise, the majority of patients still undergo partial thyroidectomy for benign disease in the United States. Moreover, these data suggest that high-volume and teaching hospitals more often perform total thyroidectomy for benign disease with apparently better outcomes. This supports the notion that we are practicing what we preach (or publish).

The authors analyzed outcomes such as postoperative hypoparathyroidism and recurrent laryngeal-nerve injury, but such data from an administrative database can be unreliable because of poor patient follow-up and inaccurate coding. I would be hesitant to draw strong conclusions from this report, although the number of patients studied is certainly impressive.

This report reveals a trend in our surgical management over the past two decades, but it should not be misconstrued as a treatment algorithm. Certainly, total thyroidectomy will mitigate the need for reoperation in a patient with asymmetric goiter, whereas partial thyroidectomy is sufficient for a patient with a hot nodule. This study does not detail the specific pathology for each patient, so we cannot

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be sure which types of patients are increasingly being treated with total thyroidectomy. Presumably, patients with benign goiters are undergoing total thyroidectomy more often, since recurrence is a rationale for this approach. Regardless, the approach to every patient with benign thyroid disease should still be individualized and based on multiple factors, including operative risk, type of thyroid pathology, and patient preference.

— Mark P. Sawicki, MD, FACS
Chief, General Surgery
VA Greater Los Angeles Healthcare System
Los Angeles, CA

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THE BRAF V600E MUTATION DOES NOT MAKE PAPILLARY THYROID CANCERS MORE VASCULAR OR EXPRESS MORE VEGF-A OR VEGF RECEPTORS

Durante C, Tallini G, Puxeddu E, Sponziello M, Moretti S, Ligorio C, Cavaliere A, Rhoden KJ, Verrienti A, Maranghi M, Giacomelli L, Russo D, Filetti S. **BRAFV600E mutation and expression of proangiogenic molecular markers in papillary thyroid carcinomas.** Eur J Endocrinol 2011;165;455-63. Epub June 8, 2011; doi: 10.1530/EJE-11-0283.

SUMMARY

BACKGROUND

If a papillary thyroid cancer (PTC) has invaded the lymphatic nodes or blood vessels, the patient's risk of having a recurrence, of distant metastases, and of death is increased. Therefore, it would be important to learn what factors are involved in lymphovascular growth in PTCs. Vascular endothelial growth factors (VEGFs) and platelet-derived growth factors (PDGFs) act via tyrosine kinase receptors to promote growth of lymph and blood vessels. Certain tyrosine kinase inhibitors (TKIs) are known to inhibit tumor vascularity and growth, but the mechanisms involved remain unclear. Some TKIs that block VEGF and PDGF receptors (VEGFRs, PDGFRs) also inhibit the serine/threonine kinase BRAF. The most common point mutation in thyroid cancers is BRAF (V600E), which is present in about 40% of all PTCs, and can be twice as common in some geographic regions. This mutation constitutively activates the downstream MEK/ERK pathway and can cause cell transformation. The authors of this paper studied a collection of PTCs previously obtained from several Italian centers to address whether the V600E mutation is associated with tumors that are more vascular; that express higher levels of VEGF-A, VEGFRs 1–3, or PDGFR-β mRNAs; or have histologic or clinical features associated with increased risk of tumor spread or recurrence.

METHODS

The levels of mRNAs encoding VEGF-A, VEGFRs 1–3, the co-receptor neuropilin-1, and PDGFR-β were measured by reverse transcriptase–polymerase chain reaction (RT-PCR) in 55 selected PTCs bearing the V600E mutation and in 35 PTCs without this mutation. Smaller numbers of histologic samples were assayed for VEGF-A and VEGFR, and for microvessel and lymphatic vessel density from the two groups, using a biotin-free horseradish peroxidase detection method for immunostaining. In addition, the V600E mutant was induced/silenced in rat/human cell lines in vitro to study the effects on pro-angiogenic gene expression.

RESULTS

The mRNA levels of the pro-angiogenic factors were actually lower in the PTCs that expressed the V600E mutation. Vessel densities and VEGFR staining intensities were not significantly different between PTCs expressing V600E and those expressing wild-type (wt) BRAF. In both wt and mutant BRAF tumors, lymphatic density was higher outside the tumors, whereas microvascular density was higher within the tumors. In the rat cell line, inducing V600E BRAF caused the level of VEGF-A mRNA to fall, while silencing V600E increased VEGF-A mRNA levels in the human cell line.

CONCLUSIONS

The V600E-containing tumors actually expressed lower levels of VEGF-A, VEGFRs, and PDGFR-β mRNA. Although the vessel densities and VEGFR staining were similar in both V600E-positive and V600E-negative tumors, one probably should not draw any firm conclusions, because of the small number of cases examined in the present study. In contrast, PDGF-β (not the receptor) was reported to be increased in V600E-positive tumors in a Chinese study, while unspecified VEGF isoform(s) were reported to be increased in a Korean study.

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COMMENTARY

A recent meta-analysis of the literature found that PTCs bearing the V600E mutation were more likely to be associated with advanced tumor–node–metastasis (TNM) staging, regardless of the geographic region being studied (1). The association with extrathyroidal invasion, however, was greater in geographic regions where the mutation occurred in less than half the PTC population, and the association with lymph-node metastases was significant only in geographic regions where the mutation occurred in less than half the PTC population. Thus, it might be informative to look for markers that are associated with lymph-node metastases in geographic regions where the V600E mutation occurs in more than half of PTCs.

The decreased tissue expression of VEGF-A, VEGFRs 1–3, and PDGFR-β mRNA levels in V600E expressing PTCs suggests that these tumors have made compensatory responses to the constitutive activation of BRAF, prior to any treatment. Phase 2 trials with several TKIs have shown promising partial responses in PTC, but the low frequency of sustained complete remissions suggests that simply blocking the oncogenic effect of the BRAF mutation—while concurrently inhibiting VEGFR and PDGFR tyrosine kinases—still permits other oncogenic changes in the complex feedback loops that regulate the Ras/BRAF/MAPK/ERK and other pathways (2).

It remains to be established whether the V600E mutation is associated with the circulating levels of other pro-angiogenic cytokines, platelets, and soluble VEGFRs and with the tissue levels of other VEGF family members, other angiogenic factors, other V600 BRAF mutations, BRAF fusion proteins, heterodimer partners or alternatively spliced isoforms, as well as to miRNAs and the BRAF pseudogene.

Clinically, the detection of the V600E mutation appears to improve identification of a PTC preoperatively, and can help in surgical decision-making if a fine-needle aspiration (FNA) biopsy is equivocal, by analyzing fluid obtained by rinsing the FNA needle (3). Postoperatively, if V600E is present in a PTC that is <1 cm in diameter, the risk of lymph-node metastases or tumor recurrence is increased if certain histopathologic features are also present (4).

— Stephen W. Spaulding, MD

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FAMILY HISTORY OF DIFFERENTIATED THYROID CANCER IS ASSOCIATED WITH AN INCREASED RISK OF THYROID CANCER IN FIRST-DEGREE RELATIVES

Xu L, Li G, Wei Q, El-Naggar AK, Sturgis EM. **Family history of cancer and risk of sporadic differentiated thyroid carcinoma. Cancer.** July 28, 2011 [Epub ahead of print]. doi: 10.1002/cncr.26398.

SUMMARY

BACKGROUND

The purpose of this study was to investigate the association of sporadic differentiated thyroid carcinoma (DTC) with a first-degree family history of cancer. Patients with familial DTC, defined as ≥3 first-degree family members (parent, sibling, or child) with the disease, were excluded.

METHODS

The study included subjects at the M.D. Anderson Cancer Center recruited from November 1999 through November 2010 who presented for evaluation of a thyroid-gland mass. Based on final diagnosis, they were divided into a group of 288 subjects with DTC (91% papillary) and another group of 197 with benign thyroid disease. In addition, there was a control group of 591 visitors to the institution who were recruited into a molecular epidemiologic study of head and neck squamous-cell carcinoma during a similar period. The subjects completed a self-administered questionnaire concerning personal and family history relevant to the study.

RESULTS

A family history of cancer in first-degree relatives was reported by 49.0% of the DTC group, 55% of the benign thyroid disease group, and 58% of the controls. There was no significant association with family history of all cancers in first-degree relatives of those with DTC (odds ratio [OR], 1.0; 95% confidence interval [CI], 0.7 to 1.4) or benign thyroid disease (OR, 0.9; 95% CI, 0.7 to 1.3). The patients with DTC were significantly more likely than controls to have a family history of thyroid cancer in first-degree relatives (6.3% vs. 1.4%; OR, 4.1; 95% CI, 1.7 to 9.9). All of those with positive family histories had papillary thyroid cancer (PTC). In those with benign thyroid disease, there was also an increased association with a family history of thyroid cancer (OR, 3.2; 95% CI, 1.2 to 8.7). Multifocal PTC was twice as common in those with a positive family history of thyroid cancer (69%), as compared with those with no family history of thyroid cancer (35%).

CONCLUSIONS

The results indicate that a family history of thyroid cancer in first-degree relatives is associated with an increased risk of sporadic PTC.

COMMENTARY

This study confirms other case–control studies reporting a family history of thyroid cancer in those with "sporadic" DTC (1, 2). This becomes a semantic dilemma; if there are two first-degree relatives with DTC, many would call this familial DTC rather than sporadic PTC. Approximately 5% to 10% of cases of PTC may be familial.

In contrast with familial medullary thyroid cancer, the cause of the familial DTC is unclear. There is a recent review of the genetics of familial DTC (3). Aside from familial adenomatous polyposis and Cowden's syndrome, no genetic loci have yet been established as causes. Because of similar environmental exposure of family members, there is still the possibility that some of the familial cases are due to environmental exposures rather than genetics. Nevertheless, a positive family history of thyroid cancer increases the possibility that a thyroid nodule is malignant, a concept reinforced by the current study.

— Jerome M. Hershman, MD

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PRETERM BIRTH IS ASSOCIATED WITH SUBSEQUENT HYPOTHYROIDISM IN ADULT LIFE

Crump, C, Winkleby MA, Sundquist J, Sundquist K. **Preterm birth and risk of medically treated hypothyroidism in young adulthood.** Clin Endocrinol (Oxf) 2011;75:255-260.

SUMMARY

BACKGROUND

Low birth weight may be a consequence of either delayed fetal growth or preterm birth. Previous studies suggested that low birth weight is associated with thyroid autoimmunity and hypothyroidism in later life, but the potential effect of preterm birth, independent of fetal growth, is unknown. The author's objective was to determine whether preterm birth is independently associated with medically treated hypothyroidism in young adulthood. The previous studies to date were generally small and had insufficient power to examine the specific effect of preterm birth on hypothyroidism in later life. In addition, differences in effect between singletons and twins have not been previously examined. Twins are exposed to a more adverse intrauterine environment, which may potentially modify the risk of autoimmunity developing. To address these gaps in the current knowledge, the authors conducted the largest study to date to examine the potential effect of preterm birth on the risk of medically treated hypothyroidism in young adulthood.

METHODS

The authors identified 648,276 individuals in the Swedish Medical Birth Register who were born from 1973 through 1979. Of this total, the following individuals were excluded: those who were no longer living in Sweden at the time of follow-up (2005–2009); those who had congenital hypothyroidism, hypopituitarism, or significant congenital anomalies; those with missing information on birth weight; those with gestational age <23 weeks; and those with a birth weight >4 SD above or below the mean birth weight for gestational age and sex from a Swedish reference growth curve. A total of 629,806 individuals (97.2% of the original cohort), between 25.5 and 37.0 years of age during the follow-up period, remained for inclusion in the study.

Medication data were obtained using a national pharmacy register maintained by the Swedish National Board of Health and Welfare. This register contains a record of each medication prescribed by a health care provider and dispensed to a patient by any outpatient or inpatient pharmacy in Sweden. The authors obtained all outpatient and inpatient prescriptions for thyroid hormone medications which include both levothyroxine and liothyronine. The outcome was defined as an average of at least one thyroid hormone prescription per year during the follow-up period. The exposure of interest was gestational age at birth, which was based on maternal report of the last menstrual period, obtained from nationwide prenatal and birth records in a national research database (Center for Primary Health Care Research, Lund University, Lund, Sweden). Gestational age at birth was categorized as 23 to 31 weeks, 32 to 36 weeks, 37 to 42 weeks (full-term), and ≥43 weeks.

RESULTS

Of the 629,806 study participants, 27,935 (4.4%) were born prematurely (<37 weeks)—2062 (0.3%) at 23 to 31 weeks and 25,873 (4.1%) at 32 to 36 weeks. Compared to individuals who were born at full-term, those who were born prematurely were more likely to be male and/or a twin, and their mothers were more likely to be either <20 or ≥35 years old at delivery, to be divorced or never married, and to have the lowest educational attainment and/or the lowest family incomes. A total of 11,159 (1.8%) individuals were prescribed at least one thyroid hormone medication per year during the follow-up period. Individuals who were born very preterm (23 to 31 weeks) had a higher prevalence of thyroid hormone prescription than those who were born full-term (P = 0.001). Among individuals born prematurely (<37 weeks), twins had a higher prevalence of thyroid hormone prescription than singletons (2.3%, vs. 1.8%; P = 0.02). Young adults who had been born

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very preterm (23 to 31 weeks) had increased relative odds ratios of thyroid hormone prescription relative to those born at full-term. Adjustment for potential confounders, with or without fetal growth, had only modest effects on the odds ratios. In the fully adjusted model, comparing all individuals born very preterm (23 to 31 weeks) to those born full-term, the odds ratio for thyroid hormone prescription was 1.70 (95% confidence interval [CI], 1.29 to 2.23). Among twins, the association appeared to be stronger than among singletons, and an increased relative odds ratio was observed across the full range of preterm gestational ages. In the fully adjusted model for twins, the odds ratios were 2.62 (95% CI, 1.30 to 5.27) and 1.44 (95% CI, 1.02 to 2.03) for those born at 23 to 31 weeks and 32 to 36 weeks, respectively, relative to full-term births.

CONCLUSIONS

This national cohort study suggests that preterm birth is associated with an increased risk of hypothyroidism that requires medical treatment in young adulthood. This association was independent of fetal growth and appeared stronger among twins than among singletons. Additional studies are needed to confirm these new findings in other populations and to elucidate the mechanisms.

COMMENTARY

The association between low birth weight and hypothyroidism later in life has been reported in series with small number of patients. An earlier study suggested an association between low birth weight and autoimmunity but not with hypothyroidism in women evaluated at 60 to 71 years of age (1). Association with hypothyroidism has also been reported (2). The association between twin pregnancies suggested that in monozygous twin pairs with discordant birth weights, the smaller twin had a higher prevalence of thyroid peroxidase antibodies (3). However, other studies failed to confirm previous findings (4, 5). No studies specifically related to prematurity were available until the present one from Sweden. In the present study, no information was available on maternal thyroid disease during pregnancy; the only information was related to thyroid hormone prescription during the follow-up period. It could be speculated that thyroid autoimmunity was already present in many of the mothers of the patients included in the study by Crump et al., perhaps undiagnosed at the time of their pregnancies. Some of them might have had treated hypothyroidism, but the thyroxine dose was not properly adjusted during their pregnancy. Most of the patients reported were born before the need for an increased dose of thyroid hormone during pregnancy was recognized. The finding in twin pregnancy is fascinating and deserves further study, since twin studies have reported a strong genetic influence on autoimmune thyroid disease (6).

— Jorge H. Mestman, MD

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Clinical THYROIDOLOGY
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OVERT HYPERTHYROIDISM CAUSES 20% INCREASED RISK OF MORTALITY

Brandt F, Green A, Hegedüs L, Brix T. **Is the association between overt hyperthyroidism and mortality causal? Critical review and meta-analysis.** Eur J Endocrinol. July 1, 2011 [Epub ahead of print]. doi: 10.1530/EJE-11-0299.

SUMMARY

BACKGROUND

Overt hyperthyroidism is associated with cardiac arrhythmias, hypercoagulopathy, stroke and pulmonary embolism, which all may increase mortality. Most but not all studies demonstrate an increased mortality in patients with overt hyperthyroidism. This critical review and statistical meta-analysis was conducted to determine whether overt hyperthyroidism is associated with an increased risk of death.

METHODS AND RESULTS

Case–control and cohort studies written in English were selected based on a PubMed search using the terms: hyperthyroidism, thyrotoxicosis, and mortality or survival. Eight studies fulfilled the inclusion criteria (number of subjects >10, inclusion of control group, overall mortality data, thyrotropin and peripheral hormone levels), and six of these studies showed an increased all-cause mortality. One study could not be used in the meta-analysis because it contained only risk estimates and not the number of deaths. Seven studies, with a total of 31,138 patients and 400,000 person-years at risk, were analyzed and subjected to meta-analysis. The relative risk (RR) of overall mortality was 1.21 (95% confidence interval [CI].1.05 to 1.38). After adjusting for setting, treatment, and control for comorbidities, the increased risk of mortality persisted. An increased, but not statistically significant, mortality was found when pooling all studies treating with radioiodine. Four of six studies examining cardiovascular risk found increased mortality with hyperthyroidism. Pooling the six studies showed that there was a higher mortality in patients with hyperthyroidism than in control subjects (RR, 1.19; 95% CI, 1.00 to 1.29).

CONCLUSIONS

Clinically, it is well known that overt hyperthyroidism is associated with significant complications, including structural changes in the heart, dehydration, tachycardia, atrial arrhythmia, muscle weakness, and osteoporosis. But the data proving that hyperthyroidism increases mortality have not been conclusive. The variation in reported mortality risks has been attributed to differences in study design, characteristics of the patients, differences in treatments, or the influence of confounding factors (1). This meta-analysis demonstrates that overt hyperthyroidism is associated with an approximate 20% increased risk of mortality. Future studies including genetic susceptibility will need to address whether the cause of this increased mortality is from the hyperthyroidism or other factors, such as smoking or comorbidities.

COMMENTARY

This meta-analysis shows a 20% increased risk of mortality with overt hyperthyroidism. This is a strong statistical association despite the heterogeneity of the subjects, their treatments, and the different methods of the included studies. Several questions remain unanswered. Is mortality is associated with severity or length of time that hyperthyroidism has been present? Is mortality higher in the different forms of hyperthyroidism when the level of thyroid excess is taken into account? Does treatment such as radioactive iodine increase risk of mortality, as has been reported by Franklyn et al.(2)? Finally, does the risk regress to the level of the control population after the hyperthyroidism is treated? There are still many questions to be answered before we know how this

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study applies to our patients. It makes sense to try to reduce the very high levels of thyroid hormone to the reference range as quickly as possible by one of the usual treatments—antithyroid drugs, radioiodine, or thyroidectomy. The current reason to bring the high thyroid levels to normal may not be to reduce mortality but because our patients feel better and because important morbidities of hyperthyroidism such as tachycardia, atrial arrhythmias, tremor, and accelerated bone loss are reduced by lowering the thyroid hormone levels.

— Stephanie L. Lee, MD, PhD

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SUNITINIB CAUSES HYPOTHYROIDISM BY REGRESSION OF THYROID CAPILLARIES AND ENHANCEMENT OF TYPE 3 DEIODINASE ACTIVITY

Kappers MH, van Esch JH, Smedts FM, de Krijger RR, Eechoute K, Mathijssen RH, Sleijfer S, Leijten F, Danser AH, van den Meiracker AH, Visser TJ. **Sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression.** J Clin Endocrinol Metab. August 3, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

The tyrosine kinase inhibitor, sunitinib (Sutent), approved for treatment of metastatic renal-cell cancer and gastrointestinal stromal tumor, causes hypothyroidism in a high proportion of patients taking it. The drug inhibits multiple kinases, including the vascular endothelial receptors. The mechanism responsible for the hypothyroidism is still unclear. This study aimed to investigate further the incidence, time course, and mechanism of the hypothyroidism.

METHODS

The study consisted of three components: a retrospective clinical study of 83 patients who had thyroid tests based on clinical indications during sunitinib therapy; a prospective study of 15 patients who had thyroid tests before treatment and at the end of the first and second 4-week treatment cycles; a study of rats treated with sunitinib at a dose of 26.7 mg per kilogram per day for 8 days, and suitable controls. At the end of the treatment period, serum thyroid-function tests were measured, thyroid histology was assessed, and deiodinase type 1 (D1) and type 3 (D3) activities were measured in liver tissue.

RESULTS

In the retrospective study, 35 patients (42%) had an elevated serum thyrotropin (TSH) with a mean time to onset of 90 days (range, 14 to 856); the maximum TSH was observed at a mean of 221 days (range, 20 to 1033). A total of 5 of the 35 had a suppressed serum TSH preceding the elevated serum TSH by 117 to 235 days. In the prospective study, the mean serum TSH doubled after the second cycle of therapy. Although serum free thyroxine (T_4), triiodothyronine (T_3), and reverse T_3 were not significantly changed, the ratio of T_3 to reverse T_3 was slightly reduced. Antithyroid peroxidase antibody levels were not affected.

In the rats, serum T_4 and T_3 were slightly reduced by sunitinib, as compared with controls. Sunitinib treatment reduced hepatic D1 and increased hepatic D3 activity, and these changes were reversible after stopping sunitinib. Thyroid histology showed a decrease in the number of capillaries with sunitinib treatment, but no change in larger vessels. When the treatment was stopped, there was a rebound increase of capillary numbers. Treatment with an endothelin receptor antagonist partially prevented the sunitinib-induced reduction of capillaries.

CONCLUSIONS

Sunitinib induces hypothyroidism due to changes in T_4 and T_3 metabolism as well as causing thyroid capillary regression.

COMMENTARY

This is an excellent study of the mechanism responsible for sunitinib-induced hypothyroidism. The retrospective study confirms similar retrospective studies concerning the incidence of hypothyroidism in patients treated with this drug (1, 2). In other studies (3, 4), it has been proposed that destructive thyroiditis is responsible for the hypothyroidism, but the small proportion of patients with suppressed TSH in this study and the very long lag time for development of hypothyroidism make antecedent thyroiditis an unlikely explanation for the hypothyroidism experienced by most patients. In the prospective study, the small change in the ratio of T_3 to reverse T_3 suggests a

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reduction of D1 and increase of D3. Sunitinib therapy is associated with nausea, reduced food intake, and weight loss, raising the issue of changes in thyroid tests similar to those in nonthyroid illness. The studies in rats were more convincing with regard to changes in deiodinase activities. However, the rats were treated with a very high dose of sunitinib and did not gain as much weight as the controls. Although it is possible that the results were slightly affected by altered nutrition, the changes in deiodinase activity were reversible when the drug was stopped for only 11 days. The authors hypothesize that sunitinib may increase hypoxia-induced factor 1 that in turn increases D3 activity, as they reported previously (5), and that this process could be triggered by hypoxia caused by reduction of capillary blood flow.

In patients with hypothyroidism who are taking sunitinib and similar tyrosine kinase inhibitors, there is frequently an increase in the requirement for thyroxine to maintain the target TSH, and this has not been adequately explained. It is possible that the reduction of D1, a pathway producing the active thyroid hormone, and increase of D3, a pathway of T_4 disposal, provide some explanation for the increased thyroxine requirement. I expect that this very productive group in Rotterdam are engaged in studies of this hypothesis, even though they did not comment on it in this paper.

— Jerome M. Hershman, MD

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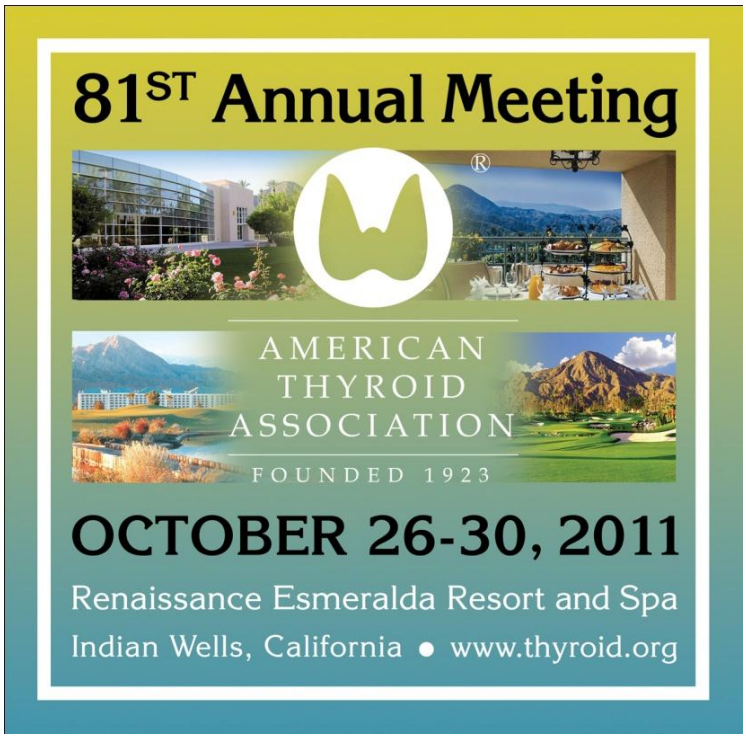

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Call for Proposals – American Thyroid Association (ATA) Research Grants -- Deadline: January 31, 2012

Electronic Submission: Proposals must be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, Thyroid Autoimmunity, Iodine Uptake and Metabolism, Thyroid Cancer, Medullary Thyroid Cancer, Clinical Disorders of Thyroid Function, Thyroid Hormone Action and Metabolism, Thyroid Imaging, Thyroid Nodules and Goiter, Thyroid Development and the Brain. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to $25,000 annually, will be awarded for two year terms based on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (i.e., to the NIH). Interested investigators should submit a brief description of the proposed research by January 31, 2012.

Eligibility of Applicant and Use of Funds Guidelines:

a. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
b. Faculty members (MD and PhD) are eligible; however, those investigators who have reached the rank of associate professor or higher are not eligible.
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d. Students working towards an MD or a PhD are not eligible.
e. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible.
f. Applications are limited to one per individual researcher.
g. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
h. Recipients of ATA grants must be ATA members (submit application online if not already a member). For new members, membership dues for the first year will be waived.

Proposal Requirements (please submit the following documents online):

1. Demographic information: Name /affiliation of applicant, complete work/home contact information – submitted into online system (do not include in grant proposal).
2. Grant Proposal (A **s**hort proposal that should be no longer than 900 words (including selected references) and no more than three double-spaced pages in 12 point type with 1" margins. These space requirements are absolute and nonconformance will preclude review. Do not include letterhead, name, address, institution, etc. This short proposal should include:
   - Title of proposed study
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - Selected References (e.g. Uchino S, et al. World J Surg 2002;26:897-902)

   a. CV (NIH-style CV – up to 4 pages) - including evidence that the applicant is a new investigator with date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. **Note: Without a suitable CV, applications will not be considered.**
3. Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2012 and invited to submit a complete grant application.

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