AMERICAN THYROID ASSOCIATION
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Clinical Thyroidology® for the Public

VOLUME 11 | ISSUE 7 | JULY 2018

Addition of selenium to methimazole does not alter the response to therapy in Graves' hyperthyroidism

The essential trace element selenium is necessary for the normal production and action of thyroid hormone. There is evidence that selenium may also be involved in affecting processes related to thyroid autoimmunity which causes both hypothyroidism and hyperthyroidism. The aim of this study was to determine whether selenium supplementation given to patients with Graves' disease who were starting treatment with methimazole resulted in improved response or remission rates.

Kahaly GJ et al. Double-blind, placebo-controlled, randomized trial of selenium in Graves hyperthyroidism. J Clin Endocrinol Metab 2017;102:4333-41.

Endocrine disrupting chemicals during pregnancy and thyroid function in the mother and the baby

Normal thyroid function is very important for normal brain development of the baby. Endocrine disrupting chemicals (EDC's) are chemicals in the environment that have been shown to affect hormonal systems in humans and animals. A growing body of literature has linked EDC exposure to alterations in thyroid function. This study measured six different EDCs in the blood of both mother and baby and compared levels with measurements of thyroid function.

Preston EV et. 2018 Maternal plasma per- and polyfluoroalkyl substance concentrations in early pregnancy and maternal and neonatal thyroid function in a prospective birth cohort: Project Viva (USA). Environ Health Perspect 126:027013. PMID: 29488882.

Rate of nodule growth on surveillance ultrasound predicts risk of cancer

Thyroid nodules that have benign biopsy results still need to be followed by ultrasound surveillance and nodules that significantly grow need to undergo a 2nd biopsy to ensure the initial biopsy did not miss a cancer. However, nodule growth alone is not very specific to identify a cancer as low-risk thyroid cancers may remain stable for several years. To help sort this out, the current study compared the rate of nodule growth between nodules with benign and cancerous cytology during ultrasound surveillance.

Angell TE et al. Differential growth rates of benign versus malignant thyroid nodules. J Clin Endocrinol Metab. October 12, 2017

Higher TSH level is associated with papillary microcarcinoma growth during active surveillance

While surgery is usually recommended when thyroid cancer is diagnosed, if the nodule/cancer is <1 cm another option is observation, otherwise known as active surveillance. TSH is a growth factor that stimulates thyroid tissue to produce thyroid hormone; also it affects the growth of thyroid cells and thyroid cancer cells. This study describes the association between serum TSH level and growth of PTMC.

Kim HI et al. High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance. J Clin Endocrinol Metab. 2018 Feb 1;103(2):446-451. doi: 10.1210.

Management of thyroid nodules in patients over the age of 70 needs to consider coexistent serious diseases

Thyroid nodules are found in up to 50% of the population over the age of 60. Data on older patients with thyroid nodules are limited, and management should not only be guided by risk of cancer of these nodules, but also by the risks of any intervention. The goal of this study was to present detailed information on the evaluation, treatment and outcome of patients with thyroid nodules who are 70 years of age or older.

Wang Z et al. 2018 Quantitative analysis of the benefits and risk of thyroid nodule evaluation in patients ≥70 years old. Thyroid 28:4764–471. Epub 2018 Apr 2. PMID: 29608439.

Minimal extrathyroidal extension leads to a slight increase in thyroid cancer recurrence, but does not impact survival for thyroid cancer

It is controversial whether minimal extrathyroidal extension (ETE) impacts thyroid cancer recurrence or death. The AJCC thyroid cancer staging took minimal ETE out of staging for survival, but currently it is still part of the ATA guidelines risk of recurrence model that was last updated in 2015. This study wanted to re-examine the role of minimal ETE on recurrence and survival for thyroid cancer.

Diker-Cohen T et al, 2018 Impact of minimal extra-thyroid extension in differentiated thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. Epub 2018 Mar 1. PMID: 29506045.

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Clinical Thyroidology® for the Public

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EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We also provide even faster updates of late-breaking thyroid news through Twitter at @thyroidfriends and on Facebook. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room. Also check out our friends in the **Alliance for Thyroid Patient Education**. The **Alliance** member groups consist of: the *American Thyroid Association, Bite Me Cancer, the Graves' Disease and Thyroid Foundation, the Light of Life Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International.*

We invite all of you to join our **Friends of the ATA** community. It is for you that the American Thyroid Association (ATA) is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer. We thank all of the Friends of the ATA who support our mission and work throughout the year to support us. We invite you to help keep the ATA mission strong by choosing to make a donation that suits you – it takes just one moment to give online at: www.thyroid.org/donate and all donations are put to good work. The ATA is a 501(c)3 nonprofit organization and your gift is tax deductible.

July is Graves' Disease Awareness Month.

In this issue, the studies ask the following questions:

- Does selenium improve the response to therapy in patients with Graves' disease?
- Does exposure to endocrine disrupting chemicals in the environment alter thyroid levels during pregnancy?
- Does the rate of nodule growth predict risk of cancer?
- Does TSH levels affect the growth of small papillary thyroid cancers that are followed by ultrasound instead of surgery?
- Is management of thyroid nodules different in patients >70 years old?
- Does minimal extension of thyroid cancer outside the thyroid affect thyroid cancer recurrence or death?

We welcome your feedback and suggestions. Let us know what you want to see in this publication. I hope you find these summaries interesting and informative.

— Alan P. Farwell, MD, FACE

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GRAVES' DISEASE

Addition of selenium to methimazole does not alter the response to therapy in Graves' hyperthyroidism

BACKGROUND

The essential trace element selenium is necessary for the normal production and action of thyroid hormone. A deficiency of selenium, especially if accompanied by iodine deficiency, decreases the making of thyroid hormone and may decrease thyroid hormone levels. There is evidence that selenium may also be involved in affecting processes related to thyroid autoimmunity which causes both hypothyroidism and hyperthyroidism. Some studies, but not all, have shown that taking selenium reduces the production of thyroid antibodies, reduces postpartum thyroid problems and decreases permanent hypothyroidism.

A small trial done in Croatia showed that patients with Graves' disease who were given methimazole and selenium supplements took less time to normalize thyroid hormone levels. Another trial looked at selenium levels in patients with Graves' disease who discontinued methimazole. Although there were no significant differences, there was a trend for higher selenium levels in patients who were in remission. Other studies done on patients with Graves' disease and looking at symptoms (nervousness, tremor), reported inconsistent results when patient were given selenium supplementation.

The aim of this study was to determine whether selenium supplementation given to patients with Graves' disease who were starting treatment with methimazole resulted in improved response or remission rates.

THE FULL ARTICLE TITLE

Kahaly GJ et al. Double-blind, placebo-controlled, randomized trial of selenium in Graves hyperthyroidism. J Clin Endocrinol Metab 2017;102:4333-41.

SUMMARY OF THE STUDY

This trial was done in Germany and recruited 70 untreated patients with Graves' hyperthyroidism from an endocrinology clinic. All these patients had elevated thyroid hormone levels, suppressed TSH, elevated TSH receptor antibodies and evidence of increased thyroid blood flow on ultrasound. These patients were assigned at random to methimazole, 10 or 20 mg depending on thyroid hormone level, with either selenium 300 mg daily or placebo. Patients were examined by one investigator who was not aware of the assignments. Selenium was continued until week 24, when it was discontinued. Methimazole doses were evaluated and adjusted at weeks 4,12 and 24. Labs were drawn at weeks 4, 12 and 24. There were 35 patients in each group. As it is with thyroid disease, more than 75% of participants in each group were women, and both groups were similar in regards to other characteristics such as height, weight, smoking status or other autoimmune conditions.

At week 24, a total of 25 of 31 selenium-treated patients (80%) and 27 of 33 placebo-treated patients (82%) had normal thyroid hormone levels. At week 36, 11 of 23 selenium-treated patients (48%) and 12 of 27 placebo-treated patients (44%) had relapses of hyperthyroidism. The selenium level was not associated with response or relapse rate. Higher antibody levels at baseline were associated with a lower likelihood of response.

The conclusion of the study was that selenium supplementation did not improve the response rate to methimazole therapy in patients with Graves' hyperthyroidism.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The strength of this study is its design: randomized, placebo-controlled, and well balanced treatment groups. The weakness is the relative short duration, as prior studies have suggested 12-18 months to maximize the rates of remission. The baseline selenium level did not indicate that these patients were deficient, unlike the patients in the Croatian study, who were selenium-deficient.

Since the US population is not considered to be selenium-deficient, based on current data, selenium supplementation is not likely to improve response to methimazole or increase the rate of remission in patients with Graves' disease.

— Jessie Block-Galarza, MD

GRAVES' DISEASE, continued

ATA THYROID BROCHURE LINKS

Graves' Disease: https://www.thyroid.org/graves-disease/

ABBREVIATIONS & DEFINITIONS

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Selenium: a mineral found naturally in various foods that is important for making thyroid hormones and for normal thyroid function. It is needed in small amounts by the body.

Placebo: a pill with no biologic action that is used in clinical trials to determine if an active drug or compound is effective in treating or preventing a disease.

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THYROID AND PREGNANCY

Endocrine disrupting chemicals during pregnancy and thyroid function in the mother and the baby

BACKGROUND

Normal thyroid function is very important for normal development of the baby, especially brain development. A number of studies have shown an association with low thyroid hormone levels and impaired brain development. Endocrine disrupting chemicals (EDC's) are chemicals in the environment that have been shown to affect hormonal systems in humans and animals. A growing body of literature has linked EDC exposure to alterations in thyroid function. Synthetic chemicals known as Per and polyfluoroakyl substances (PFASs) are believed to be endocrine disrupters. PFASs are synthetic chemicals found in the environment where they are commonly used in consumer products such as food packaging and fire-fighting foam. PFASs from environmental exposure are measureable in human blood and have been shown to alter thyroid function. This study measured six different PFASs in the blood of both mother and baby and compared levels with measurements of thyroid function

THE FULL ARTICLE TITLE

Preston EV et. 2018 Maternal plasma per- and polyfluoroalkyl substance concentrations in early pregnancy and maternal and neonatal thyroid function in a prospective birth cohort: Project Viva (USA). *Environ Health Perspect* 126:027013. PMID: 29488882.

SUMMARY OF THE STUDY

These investigators measured the concentrations of six EDC's in mother and newborn blood samples. They measured six PFASs, which are EDC's that humans are typically exposed to in the environment. These PFAS are often used in food packaging, nonstick surfaces and firefighting foam and can be measured in human blood. Higher concentrations in the blood suggest higher exposures. They measured blood concentration of PFASs and thyroid function (TSH, T_4, Free T_4 index) in 732 pregnant women participating in a prospective study in Boston, MA known as Project Viva, at approximately 10 weeks of pregnancy. They also examined thyroid hormone (T_4) levels in the blood from 480 newborn babies as part of the New England neonatal thyroid screening program. Higher levels of 4 of the 6 PFASs measured in the mothers were associated with lower free T_4 index levels in pregnant women and lower thyroid hormone (T_4) levels in male newborn babies. TSH levels in the mother were not affected by PFAS exposure in mothers except those with positive anti-thyroid peroxidase antibodies (a marker of auto-immune thyroid disease). These results indicate that environmental exposure to EDCs, specifically PFASs, during pregnancy can negatively impact thyroid function in both the mother and the newborn.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

These results suggest that exposure to PFASs in the environment can affect thyroid hormone levels in mothers and their babies. Higher measured blood concentrations of PFAS's were associated with lower free T_4 index in mothers and lower thyroid hormone levels in male newborns. This is concerning since thyroid hormone deficiency has been associated with negative effects on brain development. Additional research is needed to determine whether PFAS exposure during pregnancy can cause impairments in brain development of the baby related to alterations in thyroid function.

— Whitney W. Woodmansee MD

ATA THYROID BROCHURE LINKS

Thyroid Disease and Pregnancy: https://www.thyroid.org/thyroid-disease-pregnancy/

Thyroid Function Tests: https://www.thyroid.org/thyroid-function-tests/

THYROID AND PREGNANCY, continued

ABBREVIATIONS & DEFINITIONS

Endocrine Disrupting chemical (EDC): A synthetic compound that can affect the function of the endocrine system of humans or animals when exposed to the substance in the environment.

Thyroxine (T4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

Thyroid Awareness Monthly Campaigns

The ATA will be highlighting a distinct thyroid disorder each month and a portion of the sales for Bravelets™ will be donated to the ATA. The month of **July** is **Graves' Disease Awareness Month** and a bracelet is available through the **ATA Marketplace** to support thyroid cancer awareness and education related to thyroid disease.

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THYROID CANCER

Rate of nodule growth on surveillance ultrasound predicts risk of cancer

BACKGROUND

Thyroid nodules are very common, occurring in up to 50% of individuals in the US. The vast majority of nodules (~95%) are non-cancerous (benign). Nodules are evaluated by ultrasound and, on the basis of nodule size and ultrasound characteristics, are selected for thyroid biopsy. Nodules that have benign biopsy results still need to be followed by ultrasound periodically (ultrasound surveillance) and nodules that significantly grow need to undergo a 2nd biopsy to ensure the initial biopsy did not miss a cancer. That being said, cancer is still rare in growing nodules that have had a prior benign biopsy. However, nodule growth alone is not very specific to identify a cancer as low-risk thyroid cancers may remain stable for several years. Indeed, some studies suggest that certain smaller nodules that are cancerous may not require surgery immediately and can also be followed by ultrasound. To help sort this out, the current study compared the rate of nodule growth between nodules with benign and cancerous cytology during ultrasound surveillance.

THE FULL ARTICLE TITLE

Angell TE et al. Differential growth rates of benign versus malignant thyroid nodules. J Clin Endocrinol Metab. October 12, 2017

SUMMARY OF THE STUDY

This study followed patients who underwent a thyroid nodule biopsy at Brigham and Women's Hospital during the period 1995–2014. Nodules ≥1 cm were included if repeat ultrasound examinations were performed at least 1 year apart for benign nodules and at least 6 months apart for cancerous nodules. Nodules were classified as benign on the basis of cytology results alone, while cancerous nodules were confirmed following surgical removal. Patients with cancerous nodules did not undergo immediate surgery for several possible reasons: (a) a delay between initial ultrasound and biopsy, (b) initial non-diagnostic or indeterminate cytology results that were ultimately repeated with a cancerous result, and (c) other higher-priority medical conditions. Nodule growth was defined as >2 mm/year or according to American Thyroid Association (ATA) criteria (>20% increase in two nodule dimensions or >50% increase in nodule volume). The main outcome was growth rate of the largest nodule dimension compared between benign and malignant nodules.

Of the 1363 benign nodules and 126 cancerous nodules included in the study, the average follow-up between ultrasound examinations was 21.8 months for benign nodules and 20.9 months for cancerous nodules. Patients with benign nodules, as compared with cancerous nodules, were older (52 vs. 49 years) and more likely to be female (90% vs. 84%), but there was no difference in average nodule size (1.7 cm).

Growth of >2 mm/year was observed in 12% of benign nodules and 26% of cancerous nodules. When applying the ATA criteria for significant nodule growth, a >20% increase in at least two dimensions was observed in 14% of benign nodules and 25% of cancerous nodules. Nodule growth >2 mm/year was found to be an independent risk factor for cancer. Importantly, 88% of benign nodules and 74% of cancerous nodules either grew <2 mm/year or did not grow at all.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that cancerous nodules are ~2-fold more likely to grow 2 or more mm/year than benign nodules. It is reasonable to continue with this growth criteria to identify whether a nodule with a prior benign biopsy would be biopsied a 2nd time. More importantly, most nodules, whether they are benign or cancerous, either are stable or grown <2 mm/year. This is helpful in the long term management of thyroid nodules.

— Alan. P. Farwell, MD, FACE

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ATA THYROID BROCHURE LINKS

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/
Fine Needle Aspiration Biopsy of Thyroid Nodules: https://www.thyroid.org/fna-thyroid-nodules/
Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5% are cancerous.

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

Thyroid biopsy: a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

Non-diagnostic thyroid biopsy: this happens when some atypical cells are found but not enough to provide a diagnosis. This occurs in 5-10% of biopsies. This often results in the need to repeat the biopsy.

Indeterminate thyroid biopsy: this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS)) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

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THYROID CANCER

Higher TSH level is associated with papillary microcarcinoma growth during active surveillance

BACKGROUND

Thyroid nodules are present in up to half of all patients that have an imaging study of the neck. Thyroid cancer is present in ~5% of thyroid nodules and is diagnosed by a biopsy of the nodule. While surgery is usually recommended when thyroid cancer is diagnosed, if the nodule/cancer is <1 cm another option is observation, otherwise known as active surveillance. In some long-term prospective clinical trials involving active surveillance, the majority the small papillary thyroid microcarcinomas (PTMC) remain stable over time. In 2015 American Thyroid Association endorsed active surveillance for PTMC as an alternative to surgery. Thyroid-stimulating hormone (TSH) is a growth factor that stimulates thyroid tissue to produce thyroid hormone; also it affects the growth of thyroid cells and thyroid cancer cells. In some patients with thyroid cancer excessive doses of thyroid hormone are used to suppress TSH and consequently to slow down tumor progression. This study describes the association between serum TSH level and growth of PTMC.

THE FULL ARTICLE TITLE

Kim HI et al. High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance. J Clin Endocrinol Metab. 2018 Feb 1;103(2):446-451. doi: 10.1210.

SUMMARY

In this Korean retrospective study 126 patients with 127 PTMC who did not have thyroid cancer surgery were followed over time with serial serum TSH measurements and ultrasonography. Patients were divided into three groups based on their TSH level. Lowest TSH group had average TSH of 1.05 mU/L (0.75-1.33), middle TSH group 2.08 mU/L (1.62-2.38) and highest TSH group 3.11 mU/L (2.4-3.95). Patients on thyroid hormone were not included in the study. During average of 26 months of follow-up about 20% of patients had tumor growth defined as greater than 50% increase of volume compared to baseline. There was significant difference in tumor growth between patients with the lowest TSH and the highest TSH. The cutoff point for the TSH level for PTMC growth was 2.5 mU/L. Continuous elevation of TSH during PTMC active surveillance was associated with tumor growth.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This is the first study describing association between serum TSH levels and tumor growth in patients with PTMC. Higher levels of TSH were associated with cancer growth. TSH levels should be monitored closely in patients who elect to proceed with active surveillance. Patients with PTMC and TSH above 2.5 mU/L may be considered for thyroid suppression therapy. Prospective studies are needed to evaluate the association between TSH levels and tumor growth rates.

—Valentina D. Tarasova, M.D.

ATA WEB BROCHURE LINKS:

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

THYROID CANCER, continued

ABBREVIATIONS AND DEFINITIONS:

Papillary thyroid cancer: the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Papillary microcarcinoma: a papillary thyroid cancer smaller than 1 cm in diameter.

Thyroid hormone therapy: patients with hypothyroidism are most often treated with Levothyroxine in order to return their thyroid hormone levels to normal. *Replacement therapy* means the goal is a TSH in the normal range and is the usual therapy. *Suppressive therapy* means that the goal is a TSH below the normal range and is used in thyroid cancer patients to prevent growth of any remaining cancer cells.

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

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THYROID NODULES

Management of thyroid nodules in patients over the age of 70 needs to consider coexistent serious diseases

BACKGROUND

Thyroid nodules are abnormal growths of thyroid cells that form lumps within the thyroid gland. These are very common as one gets older, with thyroid nodules found in up to 50% of the population over the age of 60. The majority of these nodules prove to be non-cancerous. However, data on older patients with thyroid nodules are limited, and management should not only be guided by risk of cancer of these nodules, but also by the risks of any intervention. The goal of this study was to present detailed information on the evaluation, treatment and outcome of patients with thyroid nodules who are 70 years of age or older.

THE FULL ARTICLE TITLE

Wang Z et al. 2018 Quantitative analysis of the benefits and risk of thyroid nodule evaluation in patients ≥70 years old. Thyroid 28:4764–471. Epub 2018 Apr 2. PMID: 29608439.

SUMMARY OF THE STUDY

The study included all patients ≥70 years old who had a neck ultrasound and thyroid biopsy between 1995 and 2015 at a single academic institution. Clinical, ultrasound and histology data, as well as patient coexistent medical conditions and outcomes were collected. Overall survival was used to assist with risk-to-benefit assessment.

Overall, 1129 patients 70 years of age or older with 2527 thyroid nodules measuring ≥1 cm were evaluated. Thyroid biopsy was found to be safe in all patients. Cytology was benign in 67.3% of patients. However, the results of the biopsy led to surgery in 208 patients, out of which 93 (44.7%) had benign results. Significant-risk thyroid cancer was identified in only 17 (1.5%) of patients following surgery. All of these cancers were identifiable by imaging and/or cytology by biopsy and were responsible for all thyroid cancer-related deaths (10 patients, 0.9%). During the 4-year follow-up of the study, another 160 deaths (14.4%) were identified which were not thyroid cancer-related. Survival analyses of these patients showed that increased risk of death was related to a non-thyroid cancer or heart disease at the time of thyroid nodule evaluation, compared to patients without these coexistent conditions.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that ultrasound and biopsy are safe for patients ≥70 years old with thyroid nodules and can help identify thyroid cancer. The authors suggest that in view of the slow growth of most thyroid cancers, future lifespan of the patient and presence of other medical conditions should all be taken into account when evaluating these patients. Physicians should always weigh the benefits and risks before proceeding with referral to surgery for older patients with low risk nodules. This study recommends that a conservative approach should be favored and strongly considered in these patients, given the significant potential for harm compared to limited benefit. This study provides a guide for counseling and shared decision-making between patients and their treating physicians. However, physicians should be careful not to underestimate the number of additional quality years of life older patients look forward to, while trying to avoid the negative effects of overly aggressive treatment.

— Maria Papaleontiou, MD

ATA THYROID BROCHURE LINKS

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

Thyroid Disease in the Older Patient: https://www.thyroid.org/thyroid-disease-older-patient/

THYROID NODULES, continued

ABBREVIATIONS & DEFINITIONS

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5% are cancerous.

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

Thyroid biopsy: a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

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THYROID CANCER

Minimal extrathyroidal extension leads to a slight increase in thyroid cancer recurrence, but does not impact survival for thyroid cancer

BACKGROUND

Thyroid cancer is the fastest rising cancer in women. Overall, prognosis is excellent and staging and management of thyroid cancer focuses on risk of recurrence rather than risk of death. The first risk assessment in thyroid cancer is done after the initial surgery based on the type of cancer, extension of the cancer outside of the thyroid (extrathyroidal extention, ETE) and spread of the cancer into lymph nodes in the neck. It is controversial whether minimal ETE (cancer extends into or just beyond the thyroid capsule, but not grossly into any muscles or structures in the neck) impacts thyroid cancer recurrence or death. The new pathological society (AJCC) thyroid cancer staging took minimal ETE out of staging for survival, but currently it is still part of the American Thyroid Association (ATA) guidelines risk of recurrence model that was last updated in 2015. This study wanted to re-examine the role of minimal ETE on recurrence and survival for papillary and follicular thyroid cancer.

THE FULL ARTICLE TITLE

Diker-Cohen T et al, 2018 Impact of minimal extra-thyroid extension in differentiated thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. Epub 2018 Mar 1. PMID: 29506045.

SUMMARY OF THE STUDY

The authors looked at all the results in the medical literature (systemic review) and examined the results of the good studies (meta-analysis) that had previously examined the impact of ETE on recurrence and/or survival from thyroid cancer. They also looked at if it made a difference depending on if you had positive (spread of cancer into the lymph node) or negative lymph nodes and if you had very small cancers. A national database study that used SEER and 12 smaller single center studies were included. In patients with very small microcarcinomas, minimal ETE did not affect risk of recurrence or survival, regardless of positive or negative nodes. In other patients, it appeared that minimal ETE increased the recurrence rate a very small amount (about 0.8-1.3%) and it did not impact survival.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Minimal ETE *very* minimally impacts risk of recurrence (but only about 1%) and does not impact survival of thyroid cancer. Therefore, it really shouldn't be taken into account when counseling for treatment or prognostic purposes, especially in patients with microcarcinomas. This is a change from previous recommendations (but are reflected in the new staging system).

— Melanie Goldfarb, MD

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer: the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Papillary microcarcinoma: a papillary thyroid cancer smaller than 1 cm in diameter.

Follicular thyroid cancer: the second most common type of thyroid cancer.

THYROID CANCER, continued

Thyroidectomy: surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a *total thyroidectomy*. When less is removed, such as in removal of a lobe, it is termed a *partial thyroidectomy*.

Lobectomy: surgery to remove one lobe of the thyroid.

Completion thyroidectomy: surgery to remove the remaining thyroid lobe in thyroid cancer patients who initially had a lobectomy.

Total thyroidectomy: surgery to remove the entire thyroid gland.

SEER: Surveillance, Epidemiology and End Results program, a nation-wide anonymous cancer registry generated by the National Cancer Institute that contains information on 26% of the United States population. Website: http://seer.cancer.gov/

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ATA Alliance for Thyroid Patient Education

GOAL

The goal of our organizations is to provide accurate and reliable information for patients about the diagnosis, evaluation and treatment of thyroid diseases.

We look forward to future collaborations and continuing to work together toward the improvement of thyroid education and resources for patients.

WHO WE ARE (in alphabetical order)

AMERICAN THYROID ASSOCIATION
www.thyroid.org
ATA Patient Resources:
http://www.thyroid.org/thyroid-information/
Find a Thyroid Specialist: www.thyroid.org
(Toll-free): 1-800-THYROID
thyroid@thyroid.org

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info@bitemecancer.org

GRAVES' DISEASE AND THYROID FOUNDATION
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LIGHT OF LIFE FOUNDATION
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THYCA: THYROID CANCER SURVIVORS' ASSOCIATION, INC.
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AMERICAN THYROID ASSOCIATION
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GRAVES' DISEASE & THYROID FOUNDATION

Thyroid Federation International

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JOIN US

"The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop for patients and caregivers to find specialists, current clinical trials, general thyroid cancer information, and links to other patient support groups and information."

Mary Catherine Petermann
- Father who was diagnosed with Anaplastic Thyroid Cancer in 2006
- He was treated at Mayo Clinic
- He has clean scans as of October 2016

PLEASE JOIN OUR JOURNEY TO ADVANCED DISCOVERIES AND TREATMENT FOR THYROID DISEASE AND THYROID CANCER

As patients with thyroid disease navigate the challenges to their quality of life and researchers and physicians look for more effective directions, we at the ATA have our own destination– **funding for critical thyroid research, prevention, and treatment.** For 94 years, the ATA has led the way in thyroidology. It's a daily obstacle course to find new drugs, better treatments, advanced surgical methods, and more rapid diagnoses for the 20 million Americans who have some form of thyroid disease.

The ATA has paved the way with management guidelines for clinicians who diagnose and treat thyroid disease. For physicians treating pregnant women diagnosed with thyroid disease, our recent publication presents 97 evidence-based recommendations making sure that best practices are implemented with the latest, most effective treatment.

Through your generous support and donations, research takes the lead and hope is on the horizon. **Will you join us** in our campaign to raise **$1.5 million** for thyroid research, prevention, and treatment? Your compassionate, tax-deductible gift will provide funds for:

- Research grants that pave the way for 1,700 ATA physicians and scientists who have devoted their careers to understanding the biology of and caring for patients affected by thyroid disease.
- Patient education for individuals and families looking for life-changing clinical trials, the best thyroid specialists, and cutting edge treatment and drugs.
- Professional education that offers a wealth of knowledge and leading-edge research for trainees and practitioners.
- A website that is the go-to resource for thyroid information for patients and practitioners alike. In 2016 alone, there were more than 3,700,000 website views of ATA's library of online thyroid information patient brochures.

Donations **of all sizes** will change the future for thyroid patients. You will make a direct impact on patients like Mary Catherine's father as he deals with Anaplastic Thyroid Cancer. You will help scientists like ATA Associate Member Julia Rodiger, Ph.D., a scientist at the National Institutes of Health, as she analyzes thyroid hormones for intestinal stem cell development.

Graves' Disease

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is located in the lower front of the neck. The thyroid makes thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormones help the body use energy, stay warm and keep the brain, heart, muscles, and other organs working appropriately.

WHAT IS GRAVES' DISEASE?

Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (*hyperthyroidism*). It is the most common cause of hyperthyroidism in the United States. It is named after Robert Graves, an Irish physician, who described this form of hyperthyroidism about 150 years ago. It is 7-8 times more common in women than men.

WHAT CAUSES GRAVES' DISEASE?

Graves' disease is triggered by a process in the body's immune system, which normally protects us from foreign invaders such as bacteria and viruses. The immune system destroys foreign invaders with substances called antibodies produced by blood cells known as lymphocytes. Sometimes the immune system can be tricked into making antibodies that cross-react with proteins on our own cells. In many cases these antibodies can cause destruction of those cells. In Graves' disease these antibodies (called the thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulins (TSI) do the opposite – they cause the cells to work overtime. The antibodies in Graves' disease bind to receptors on the surface of thyroid cells and stimulate those cells to overproduce and release thyroid hormones. This results in an overactive thyroid (*hyperthyroidism*).

WHAT ARE THE SYMPTOMS OF GRAVES' DISEASE?

- *Hyperthyroidism*

  The majority of symptoms of Graves' disease are caused by the excessive production of thyroid hormones by the thyroid gland (see *Hyperthyroidism brochure*). These may include, but are not limited to, racing heartbeat, hand tremors, trouble sleeping, weight loss, muscle weakness, neuropsychiatric symptoms and heat intolerance.

- *Eye disease*

  Graves' disease is the only kind of hyperthyroidism that can be associated with inflammation of the eyes, swelling of the tissues around the eyes and bulging of the eyes (called *Graves' ophthalmopathy or orbitopathy*). Overall, a third of patients with Graves' disease develop some signs and symptoms of Graves' eye disease but only 5% have moderate-to-severe inflammation of the eye tissues to cause serious or permanent vision trouble. Patients who have any suggestion of eye symptoms should seek an evaluation with an eye doctor (an ophthalmologist) as well as their endocrinologist.

  Eye symptoms most often begin about six months before or after the diagnosis of Graves' disease has been made. Seldom do eye problems occur long after the disease has been treated. In some patients with eye symptoms, hyperthyroidism never develops and, rarely, patients may be hypothyroid. The severity of the eye symptoms is not related to the severity of the hyperthyroidism.

  Early signs of trouble might be red or inflamed eyes, a bulging of the eyes due to inflammation of the tissues behind the eyeball or double vision. Diminished vision or double vision are rare problems that usually occur later, if at all. We do not know why, but problems with the eyes occur much more often and are more severe in people with Graves' disease who smoke cigarettes.

- *Skin disease*

  Rarely, patients with Graves' disease develop a lumpy reddish thickening of the skin in front of the shins known as pretibial myxedema (called Graves' dermopathy). This skin condition is usually painless and relatively mild, but it can be painful for some. Like the eye trouble of Graves' disease, the skin problem does not necessarily begin precisely when the hyperthyroidism starts. Its severity is not related to the level of thyroid hormone.

Graves' Disease

HOW IS THE DIAGNOSIS OF GRAVES' DISEASE MADE?

The diagnosis of hyperthyroidism is made on the basis of your symptoms and findings during a physical exam and it is confirmed by laboratory tests that measure the amount of thyroid hormones (thyroxine, or T4, and triiodothyronine, or T3) and thyroid-stimulating hormone (TSH) in your blood (see the *Hyperthyroidism brochure*). Clues that your hyperthyroidism is caused by Graves' disease are the presence of Graves' eye disease and/or dermopathy (see above), a symmetrically enlarged thyroid gland and a history of other family members with thyroid or other autoimmune problems, including type 1 diabetes, rheumatoid arthritis, pernicious anemia (due to lack of vitamin B12) or painless white patches on the skin known as vitiligo.

The choice of initial diagnostic testing depends on cost, availability and local expertise. Measurement of antibodies, such as TRAb or TSI, is cost effective and if positive, confirms the diagnosis of Graves' disease without further testing needed. If this test is negative (which can also occur in some patients with Graves' disease), or if this test is not available, then your doctor should refer you to have a radioactive iodine uptake test (RAIU) to confirm the diagnosis.

Also, in some patients, measurement of thyroidal blood flow with ultrasonography may be useful to establish the diagnosis if the above tests are not readily available.

HOW IS GRAVES' DISEASE TREATED?

The treatment of hyperthyroidism is described in detail in the *Hyperthyroidism brochure*. All hyperthyroid patients should be initially treated with beta-blockers. Treatment options to control Graves' disease hyperthyroidism include antithyroid drugs (generally methimazole [Tapazole®], although propylthiouracil [PTU] may be used in rare instances such as the first trimester of pregnancy), radioactive iodine and surgery.

Antithyroid medications are typically preferred in patients who have a high likelihood of remission (women, mild disease, small goiters, negative or low titer of antibodies). These medications do not cure Graves' hyperthyroidism, but when given in adequate doses are effective in controlling the hyperthyroidism.

If methimazole is chosen, it can be continued for 12-18 months and then discontinued if TSH and TRAb levels are normal at that time. If TRAb levels remain elevated, the chances of remission are much lower and prolonging treatment with antithyroid drugs is safe and may increase chances of remission. Long term treatment of hyperthyroidism with antithyroid drugs may be considered in selected cases.

If your hyperthyroidism due to Graves' disease persists after 6 months, then your doctor may recommend definitive treatment with either radioactive iodine or surgery.

If surgery (thyroidectomy) is selected as the treatment modality, the surgery should be performed by a skilled surgeon with expertise in thyroid surgery to reduce the risk of complications.

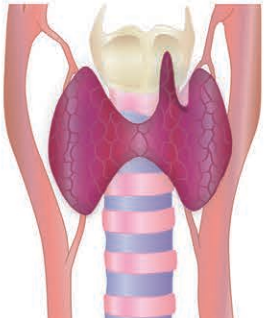
Your doctor should discuss each of the treatment options with you including the logistics, benefits and potential side effects, expected speed of recovery and costs. Although each treatment has its advantages and disadvantages, most patients will find one treatment plan that is right for them. Hyperthyroidism due to Graves' disease is, in general, controllable and safely treated and treatment is almost always successful.

WHAT WILL BE THE OUTCOME OF TREATMENT?

If you receive definitive treatment for your Graves' hyperthyroidism (such as radioactive iodine or surgery), you will eventually develop hypothyroidism (underactive thyroid). Even if you are treated with antithyroid drugs alone, hypothyroidism can still occur. Your doctor will check your *thyroid function tests* frequently to assess thyroid function following treatment. When hypothyroidism occurs, you will need to take a thyroid hormone tablet once a day at the right dose (see *Hypothyroidism brochure*).

OTHER FAMILY MEMBERS AT RISK

Graves' disease is an autoimmune disease and has a genetic predisposition. However, no specific gene has been identified for screening to date.



FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*