

# Nonoccult Differentiated Thyroid Cancer Exhibits Aggressive Behavior in Graves' Disease

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Pellegriti G, Mannarino C, Russo M, Terranova R, Marturano I, Vigneri R, Belfour A. Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. J Clin Endocrinol Metab 2013;98:1014-21. Epub January 24, 2013.

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#### Background

Reports in the medical literature with regard to the aggressiveness of differentiated thyroid cancer (DTC) diagnosed in patients with active Graves' hyperthyroidism are controversial. In previous publications, the authors reported that DTC is more aggressive and has a poorer prognosis in patients with Graves' disease (GD) as compared with DTC in euthyroid patients. The authors speculated that genetic and environmental factors, as well as the lack of appropriate control subjects and/or inadequate patient follow-up, could account for these discrepancies. The objective of this study was to investigate the long-term disease-specific mortality of nonoccult DTCs occurring in patients with GD as compared with DTCs in matched euthyroid control patients.

#### Methods

The authors studied previously described cohorts of nonoccult DTCs occurring in either patients with Graves' hyperthyroidism (DTC-GD, n = 21) or matched euthyroid control patients with DTC who were recruited in the period 1982–1994 at a single

institution (n = 70). The patients were evaluated after follow-up ranging from 50 to 364 months (median, 166) to compare the major clinical end points of persistent/recurrent disease and overall survival. All patients had undergone total thyroidectomy and were followed according to a standardized protocol.

#### Results

Persistent/recurrent disease was more frequent in patients with DTC-GD than in control patients (P = 0.0119). Disease-specific mortality was also significantly higher in patients with DTC-GD (6 of 21, 28.6%) than in euthyroid control patients (2 of 70, 2.9%) (P = 0.0001). At the last visit, the percentage of disease-free patients was 57.1% (12 of 21) in the DTC-GD group versus 87.1% (61 of 70) in the control group (P = 0.0025).

#### **Conclusions**

The authors concluded that non-occult DTCs occurring in patients with GD caused increased disease-specific mortality as compared with DTCs in matched euthyroid patients. These findings emphasize the need for early diagnosis and aggressive treatment of nonoccult DTCs in patients with GD

#### ANALYSIS AND COMMENTARY • • • • • •

The increased risk of mortality in hyperthyroidism is well documented and was recently analyzed by Spaulding in the February issue of Clinical Thyroidology (1). Increased aggressiveness of concomitant DTC in patients with hyperthyroidism should be added to the list of risk factors. In this long-term follow-up study, Pellegriti et al. excluded patients with occult DTCs incidentally found at surgery, because in a previous publication the authors reported good long-term prognosis in patients with occult thyroid tumors (2). Of the 35 DTCs diagnosed among the 550 patients with GD operated on in the period 1982– 1994, a total of 14 cases were incidental occult car*continued on next page* 

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cinomas. In the present study, 21 nonoccult DTCs were compared with 70 DTCs occurring in matched euthyroid patients. All patients with DTCs included in this study underwent total or near-total thyroid-ectomy plus central compartment lymph-node dissection. Serum TSH-receptor antibodies (TSHR-Abs), antimicrosomal antibodies, and/or antithyroglobulin antibodies were obtained before surgery.

After 14 years of patient follow-up, the diseasespecific mortality in patients with Graves' disease is alarming (6 of 21 [28.6%]) as compared with the euthyroid patients (2 of 27 [2.9%]). At the end of the study, the percentage of disease-free patients was 57.1% in the DTC-GD group versus 87.1% in the control group. There was no statistical difference between the groups in age, sex, the papillary histotype, or tumor size. There was a trend toward a higher frequency of high-stage tumors in the DTC-GD group, but the difference did not reach statistical significance. By applying multivariate Cox analysis, the authors found that only two variables, stage and GD, were significantly and independently associated with relapses and with cancer-specific deaths. In patients with stage III-IV cancer, but not in those with stage I-II cancer, relapses were significantly more frequent (P = 0.0062) in patients with GD than in euthyroid control patients.

Circulating TSHR-Abs were present in all patients in whom a recurrence developed, and they persisted as long as signs of disease were evident. Only one patient had a negative titer before surgery. The authors discussed the potential role of TSHR-Abs in thyroid cancer initiation and progression, and the mitogenic and anti-apoptotic effects elicited by both TSH and TSHR-Abs in thyroid follicular cells.

According to the authors, only two other studies have used a control group of euthyroid patients (2, 3). Both these studies did not show a worse outcome of DTCs associated with GD. The authors speculated that the difference between the studies could be due to the inclusion of a large proportion of occult cancers incidentally found at the postsurgical pathology examination and the fact that the authors' study was performed in eastern Sicily, a region including a volcanic area and whose population has a high incidence of thyroid cancer.

This study has important implications for clinicians who care of patients with Graves' disease, among them: (a) performing a careful physical examination to detect the presence of nodules in these patients, and (b) determination of TSHR-Abs before surgery and regularly during postsurgical follow-up.

#### References

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