

The association between serum TSH concentration and thyroid cancer

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Abstract

There is mounting evidence that the serum concentration of TSH is an independent predictor for the diagnosis of thyroid malignancy in patients with nodular thyroid disease. Furthermore, preoperative serum TSH concentrations are higher in patients with more aggressive tumours, suggesting a potential role for TSH in the progression of differentiated thyroid cancer. Based on these observations, patients with higher serum TSH concentrations and borderline cytological results may require more aggressive investigation and treatment when compared with those with lower baseline TSH levels. The mechanisms underlying the finding of higher serum TSH in patients with thyroid cancer remain unexplained. In this issue of *Endocrine-Related Cancer*, Fiore *et al.* have analysed the relationship between serum TSH and diagnosis of papillary thyroid cancer in 10 178 patients with nodular thyroid disease who were investigated by fine-needle aspiration biopsy. They found significantly higher TSH concentrations in patients who were subsequently diagnosed with thyroid cancer compared with those with benign disease. In addition, they found that the development of autonomous thyroid function (TSH < 0.4 μ U/ml) was associated with a reduction in the risk of papillary thyroid carcinoma. In this commentary, the evidence regarding the association between serum TSH and thyroid cancer is discussed placing these new findings into context.

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Introduction

Thyroid cancer is the most common endocrine malignancy and its incidence continues to rise. Between 1973 and 2002, there was a 2.4-fold increase in thyroid cancer and a 2.9-fold rise in papillary thyroid cancer (PTC) diagnoses in the United States (Davies & Welch 2006). Thyroid carcinoma, in most cases, presents clinically as a solitary nodule or as a dominant nodule within a multinodular thyroid gland. In the general population, thyroid nodules are very common with reported prevalences of palpable nodules in 4–7% of adults (Vander *et al.* 1968, Tunbridge *et al.* 1977, Hegedus 2004). Additionally, high resolution ultrasound can detect thyroid nodules in 19–67% of individuals, being most common in women and in the elderly (Marqusee *et al.* 2000, Hegedus *et al.* 2003, Reiners *et al.* 2004). The challenge to clinicians is to identify the minority of thyroid nodules (5–15%) that harbour malignancy from the majority, which can be managed conservatively.

There are a number of well-established predictors of malignancy in thyroid nodules, including the finding of hard and fixed lesions on clinical examination, rapid growth of nodules, associated hoarseness, dysphagia or lymphadenopathy, although all of these symptoms and signs are relatively uncommon at diagnosis (Hegedus *et al.* 2003, Hegedus 2004). Further risk factors include young (<20 years) or old age (>70 years), male gender (Belfiore *et al.* 1992) and history of irradiation exposure (Ron *et al.* 1995). More recently, a number of studies have suggested that higher concentrations of TSH, even within the normal range, are associated with a subsequent diagnosis of thyroid cancer in patients presenting with thyroid nodules (Table 1; Boelaert *et al.* 2006, Jonklaas *et al.* 2008, Polyzos *et al.* 2008). Moreover, higher serum TSH levels have been found associated with advanced stages of thyroid cancer (Haymart *et al.* 2008a). These findings suggest that TSH may play a central role in the development and/or progression of thyroid carcinomas.

Table 1 Summary table of studies investigating the relationship between serum TSH concentration and thyroid cancer

Authors	Journal	No. of patients studied	Country of study	Date of publication	Significant findings
Boelaert <i>et al.</i> (2006)	<i>Journal of Clinical Endocrinology and Metabolism</i>	1500	UK	November 2006	Serum TSH is independent predictor of malignancy in thyroid nodules Risk of malignancy rises in parallel with serum TSH within normal range
Haymart <i>et al.</i> (2008a)	<i>Journal of Clinical Endocrinology and Metabolism</i>	843	US	March 2008	Likelihood of thyroid cancer increases with higher TSH concentration Higher serum TSH associated with advanced stage-differentiated thyroid cancer
Jonklaas <i>et al.</i> (2008)	<i>Thyroid</i>	50	US	September 2008	Higher TSH concentrations are associated with diagnosis of thyroid cancer Patients with thyroid cancer have lower serum total T ₃ concentrations
Polyzos <i>et al.</i> (2008)	<i>Journal of Cancer Research and Clinical Oncology</i>	565	Greece	September 2008	Higher rates of thyroid malignancy in patients with TSH in upper tertile of normal range
Haymart <i>et al.</i> (2008b)	<i>Clinical Endocrinology</i>	1361	US	December 2008 (Epub)	Thyroid cancer incidence correlates with serum TSH independent of age Higher TSH is associated with extra-thyroidal extension of disease
Fiore <i>et al.</i> (2009)	<i>Endocrine-Related Cancer</i>	10 178	Italy	September 2009	Higher TSH in patients with T3–T4 disease and in those with lymph node metastases Autonomously functioning thyroid nodules are less likely to be malignant

TSH is a well-established growth factor for thyroid nodules, and suppression of serum TSH concentrations by administering exogenous thyroid hormone may inhibit the growth of established nodules as well as the development of new thyroid nodules (Papini *et al.* 1998). Moreover, therapy with suppressive doses of thyroxine (T₄) has long been known to positively affect outcomes in differentiated thyroid cancer (Mazzaferrri & Jhiang 1994), and retrospective studies have shown that TSH suppression is an independent predictor of recurrence of differentiated thyroid cancer (Pujol *et al.* 1996). More recently, prospective studies have indicated reductions in thyroid carcinoma-related death and relapse with aggressive TSH suppression, especially in high-risk patients (Jonklaas *et al.* 2006, Hovens *et al.* 2007). Based on these findings, it is plausible that the higher rates of malignancy with increasing serum TSH concentrations reflect a tropic effect of TSH on thyroid tissue promoting neoplasia and carcinogenesis. Iodine deficiency causes a reduction in the level of circulating thyroid hormones associated with a consequent rise in serum TSH

concentrations, and chronic iodine deficiency is a well-established risk factor for the development of goitre and follicular thyroid carcinoma (Belfiore *et al.* 1992, Franceschi 1998, Lind *et al.* 1998, Feldt-Rasmussen 2001, Nagataki & Nystrom 2002). However, a causal role for TSH in the initiation of thyroid cancer has not been conclusively demonstrated and it remains unclear whether serum TSH concentrations are higher as a consequence of the presence of thyroid malignancy.

An alternative explanation is that patients with lower TSH concentrations already have or are progressing towards the development of one or more autonomously functioning thyroid nodules, thyroid autonomy having long been recognised as indicative of benign disease (Mann 1998, Hegedus *et al.* 2003). The relationship between thyroid autoimmunity and thyroid cancer has also been investigated with several studies indicating higher cancer risk in patients with Hashimoto's thyroiditis, which itself is associated with a rising TSH (Okayasu *et al.* 1995, Singh *et al.* 1999, Cipolla *et al.* 2005, Kurukahvecioglu *et al.* 2007).

In this issue of *Endocrine-Related Cancer*, Fiore *et al.* (2009) investigated 10 178 patients presenting with nodular thyroid disease and submitted to fine-needle aspiration biopsy. They report higher TSH concentrations in those with a diagnosis of PTC when compared with those with benign thyroid nodular disease (BTND), both in patients with a clinical diagnosis of multinodular goitre and in those presenting with solitary nodules. Moreover, they observed a significant age-dependent development of thyroid autoimmunity in subjects with BTND, but not in those with PTC. Serum TSH concentrations were significantly higher in PTC patients regardless of the presence of thyroid auto-antibodies and the authors conclude that thyroid autonomy protects against the risk of PTC, while thyroid autoimmunity does not play a significant role. This paper is certainly a very valuable addition to the current literature regarding this topic, although the question regarding a causal role for raised serum TSH concentrations in thyroid carcinogenesis remains unclear. This commentary aims to place the data from Fiore *et al.* in context, taking the available evidence into consideration, and to identify key questions that remain unanswered.

The TSH receptor in benign and malignant thyroid tumours

There are several lines of evidence in favour of an association between TSH and thyroid cancer. Benign and malignant thyroid tumours express functional TSH receptors on the plasma membrane (Ichikawa *et al.* 1976), and *in vitro* studies have indicated that TSH increases adenylate cyclase activity leading to cAMP production and cell growth through stimulation of these receptors (Carayon *et al.* 1980, Chang *et al.* 1988). Differentiated thyroid cancers usually retain responsiveness to TSH, and suppressive doses of L-T₄ administered orally can be used to inhibit the progression of metastatic thyroid cancer (Balme 1954, Simpson *et al.* 1988) as well as to decrease rates of recurrence in patients treated with surgery and radioactive iodine (Mazzaferri & Jhiang 1994, Mazzaferri 1999, Biondi *et al.* 2005). A retrospective study has shown that undetectable TSH values were associated with longer relapse-free survival and that TSH suppression is an independent predictor of recurrence (Pujol *et al.* 1996). Furthermore, suppressive doses of T₄ improve overall survival in high-risk patients (Sanders & Cady 1998). Current clinical management guidelines emphasise the important role for TSH suppression in the management

of patients with differentiated thyroid cancer (Cooper *et al.* 2006, BTA and RCP guidelines 2007).

The role of serum TSH concentrations has also been extensively evaluated in thyroid nodules with a number of studies indicating a reduction in the rate of growth and prevention of new nodule formation in patients undergoing TSH suppression (Papini *et al.* 1998, Zelmanovitz *et al.* 1998, Vermiglio *et al.* 2003, Gharib 2004). In addition, suppressive doses of L-T₄ may induce beneficial cytological changes in thyroid nodules (Vermiglio *et al.* 2003).

Despite these findings, there are a number of arguments to be made against a role for TSH in the development or progression of thyroid cancers. First, TSH receptor mutations in regions functionally associated with increased signal transduction do not commonly occur in thyroid carcinomas (Matsuo *et al.* 1993). Second, *in vitro* studies have shown that other growth factors such as insulin-like growth factor-I (IGF-I) have been shown to be more potent in stimulating thyroid cancer growth (Derwahl *et al.* 1999, Mazzaferri 2000), and TSH requires cooperation with insulin/IGF-1 to exert its proliferative effects (Kimura *et al.* 2001). Third, there is an inverse relationship between TSH receptor mRNA levels and cancer aggressiveness (Shi *et al.* 1993). Fourth, thyroid cancer is known to occur in subjects with a range of TSH concentrations including in the suppressed contralateral lobe of hyperfunctioning nodules (Satta *et al.* 1993). Finally, a recent genome-wide association study has indicated that serum TSH concentrations are lower in patients carrying one of two alleles associated with an increased risk of both papillary and follicular thyroid cancer (Gudmundsson *et al.* 2009). Taken together, these findings suggest that stimulation of the TSH receptor via increased serum TSH concentrations may play a role in the growth of benign and malignant thyroid tumours, although it is unlikely that TSH acts in isolation. It has been proposed that direct thyroid hormone-dependent cellular effects rather than TSH-mediated mechanisms are responsible for the beneficial effects in patients treated with suppressive T₄ therapy (Brabant 2008).

Serum TSH as a biochemical predictor of thyroid cancer

A number of reports have identified baseline serum TSH concentrations as a predictor of the diagnosis of malignancy in patients with thyroid nodules (Table 1). The first study, performed in our group, investigated 1500 euthyroid subjects presenting with thyroid enlargement and undergoing fine-needle aspiration

biopsy. The risk of diagnosis of malignancy rose in parallel with the serum TSH at presentation with significant increases evident in those with TSH > 0.9 mIU/l compared with those with lower TSH concentrations (Boelaert *et al.* 2006). For the first time, we identified serum TSH concentration as an independent predictor of the presence of thyroid malignancy in addition to patients' age and gender as well as the goitre type evident on clinical examination. The lowest risk of malignancy was evident in patients with subclinical hyperthyroidism ($n=182$, TSH < 0.4 mIU/l), and the prevalence of thyroid cancer was highest in those with subclinical hypothyroidism ($n=27$, TSH > 5.5 mIU/l). Further analysis indicated significantly increased odds ratios for the presence of malignancy, even for TSH concentrations within the normal range (Boelaert *et al.* 2006).

These findings were subsequently confirmed by others. Haymart *et al.* investigated 843 patients undergoing surgery and recorded the preoperative serum TSH concentration. The likelihood of malignancy was 16% when TSH was < 0.06 mIU/l, 25% for TSH between 0.40 and 1.39 mIU/l, 35% for TSH between 1.40 and 4.99 mIU/l and 52% in those with TSH of 5.0 mIU/l or greater (Haymart *et al.* 2008a). A further study by Polyzos *et al.* (2008) reported significantly increased adjusted odds ratios for the diagnosis of malignancy in those with TSH 1.5–4.0 mIU/l when compared with those with lower serum TSH concentrations at presentation. Finally, a report of a small series of 50 euthyroid patients undergoing thyroidectomy for a variety of reasons has confirmed increased risk of cancer diagnosis in subjects with serum TSH concentrations in the upper three quartiles of TSH values, compared with patients whose serum TSH was in the lower quartile. Furthermore, those who were subsequently diagnosed with thyroid cancer had lower serum concentrations of total tri-iodothyronine (T₃; Jonklaas *et al.* 2008). Taken together, these findings suggest that serum TSH concentrations can be used as a diagnostic adjunct in the identification of high-risk patients who require further investigation and/or surgical intervention.

Association between serum TSH and differentiated thyroid cancer stage

Haymart *et al.* demonstrated that higher preoperative serum TSH concentrations were not only associated with the incidence of differentiated thyroid cancer, but also with more advanced cancer stage at diagnosis. Mean serum TSH levels were significantly higher in those with stage III and IV disease when compared

with those with more localised (stage I and II) disease (Haymart *et al.* 2008a). In this month's issue, Fiore *et al.* confirm the finding of higher serum TSH in patients with T3–T4 tumour stage compared with those with stage T1–T2. Furthermore, median serum TSH concentrations were significantly higher in those with lymph node metastases compared with subjects without positive lymph nodes (Fiore *et al.* 2009). This escalating risk of advanced disease further suggests that TSH is involved in the pathogenesis or progression of thyroid cancer.

Unique among all malignancies, the majority of staging systems for well-differentiated thyroid cancers includes age as one of the key prognostic factors (Dean & Hay 2000, Haymart 2009). In iodine-replete healthy adult populations, such as the cohort investigated by Haymart *et al.* (2008a), there is an increase in serum TSH with advancing age (Surks & Hollowell 2007, Haymart *et al.* 2008b). Further analysis of this cohort confirmed an association between advanced stage disease and higher serum TSH concentrations, independent of age. In addition, there was a significant correlation between higher TSH levels and extra-thyroidal extension, but not with other factors associated with poor prognosis including age > 45 years, tumour size > 4 cm and presence of distant metastases. These findings raise the intriguing question whether higher serum TSH concentrations stimulate thyroid cancer invasion thereby facilitating extra-thyroidal extension of disease.

Serum TSH concentrations and development of thyroid autonomy

Thyroid nodules with autonomous function are less likely to harbour malignancy (Hegedus *et al.* 2003, Hegedus 2004). In accordance with this, we (Boelaert *et al.* 2006) and others (Haymart *et al.* 2008a, Polyzos *et al.* 2008) found the lowest rates of thyroid malignancy in those with TSH concentrations below the normal reference range, suggestive of the presence of thyroid autonomy (Ross 2006). The lower cancer incidence may be explained by the findings that the constitutive activating mutations of the TSH receptors, frequently found in these nodules, drive the cAMP pathways through G α s and very rarely the cancer-associated Ras-dependent MAPK pathway through G $\beta\gamma$ and phosphatidylinositol 3-kinase- γ (Du Villard *et al.* 2000).

Fiore *et al.* investigated the relationship between serum TSH and autonomous thyroid function in more detail. They found a significant age-dependent development of thyroid autonomy (TSH < 0.4 μ U/ml) in patients with benign thyroid disease, but this

reduction of TSH with age was less evident in those with PTC. Furthermore, in patients with multinodular goitre, the frequency of thyroid autonomy was higher and the risk of PTC was lower than in those with solitary nodules (Fiore *et al.* 2009). Clearly, the observed decrease in serum TSH with age is at odds with data from the NHANES III survey (Hollowell *et al.* 2002, Aoki *et al.* 2007, Surks & Hollowell 2007) and one explanation may be relative iodine deficiency in the cohort investigated by Fiore *et al.* Others have shown higher frequency of thyroid nodularity and autonomy in older people with long-standing iodine deficiency (Fenzi *et al.* 1985, Aoki *et al.* 2007). A further explanation for the finding of decreased serum TSH in older patients is that the NHANES cohort included patients with and without nodules, whereas the current study (Fiore *et al.* 2009) only includes patients with thyroid nodules. The authors propose that the finding of higher serum TSH in patients with malignant thyroid disease is mainly related to a reduction of serum TSH in those with nodular goitre rather than an increase in TSH in subjects with PTC. Although the development of thyroid autonomy may slow down cancer progression, the escalating cancer risk within patients with TSH in the euthyroid and hypothyroid reference range remains unexplained.

Autoimmune thyroid disease and thyroid cancer

Several studies have investigated the relationship between thyroid autoimmunity and differentiated thyroid cancer (Holm *et al.* 1985, Walker & Paloyan 1990, Baker 1995). Although not all studies are in agreement, a meta-analysis of ten studies showed a 2.77-fold increased incidence of thyroid cancer in patients with antibody evidence of Hashimoto's thyroiditis, compared with control populations (Singh *et al.* 1999). Similar to the controversy in Hashimoto's thyroiditis, there is an ongoing debate about the association between Graves' disease and thyroid cancer incidence, and aggressiveness (Filetti *et al.* 1988, Hales *et al.* 1992, Pellegriti *et al.* 1998, Yano *et al.* 2007). Because Hashimoto's is often associated with progression to hypothyroidism and thus elevated serum TSH concentration and because TSH receptor stimulation is crucial to the pathogenesis of Graves' disease, it is possible that humoral thyroid autoimmunity is linked to thyroid cancer through the TSH receptor.

We found significantly higher rates of cancer in patients with detectable thyroid peroxidase antibodies compared with those in whom antibodies were absent,

although antibody status was not an independent predictor of malignancy (Boelaert *et al.* 2006). In addition, Haymart *et al.* (2008b) found a significant association between pathological Hashimoto's thyroiditis and higher TSH levels, although thyroid antibody status was not determined in the patients investigated. In the current study by Fiore *et al.* (2009), the frequency of thyroid cancer was not significantly different between antibody-positive and antibody-negative patients, and higher serum TSH concentration was found in those with PTC when compared with subjects with benign disease regardless of antibody status. Taken together, the currently available data do not rule out an association between autoimmunity and thyroid cancer, but indicate that the mechanisms underlying the relationship between high serum TSH and thyroid cancer are different from those affecting the link between autoimmune thyroid disease and thyroid cancer. Clearly, further studies evaluating the role of autoimmune processes in the development and progression of thyroid cancer are required to support this.

Conclusions

There is increasing evidence that higher serum TSH concentrations are found in patients with thyroid nodules harbouring malignancy. In addition, baseline serum TSH levels are higher in patients with more aggressive thyroid cancer, regardless of age. Several studies have indicated that inclusion of serum TSH concentrations may be useful when evaluating the risk of thyroid malignancy in patients with nodular thyroid disease. The mechanisms underlying these observations have not been fully explained, although TSH is a known growth factor for thyroid cells and animal data have demonstrated that TSH suppression in rats exposed to radioiodine prevents the formation of thyroid cancer (Goldberg *et al.* 1964, Brewer *et al.* 2007). In addition, a few mouse models have suggested a carcinogenic role for TSH (Brewer *et al.* 2007, Yeager *et al.* 2007), although there is no evidence for a direct oncogenic role of TSH in human thyroid carcinogenesis.

In this issue, Fiore *et al.* present their findings in a large number of patients with thyroid nodules, confirming higher serum TSH concentrations in those with a diagnosis of PTC. In addition, their data indicate a lower incidence of thyroid cancer in patients with evidence of thyroid autonomy. The authors suggest that the development of thyroid autonomy, by reducing serum TSH concentrations, may represent a form of self-treatment similar to the use of suppressive doses

of L-T₄ in the long-term management of patients with thyroid cancer. Although plausible, this hypothesis does not explain the findings of higher rates of malignancy in patients with TSH levels in the upper half of the normal range as well as in those with subclinical and overt hypothyroidism. Further studies evaluating the role of TSH in the initiation as well as the progression of thyroid cancer are required.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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