COMMENTARY

The association between serum TSH concentration and thyroid cancer

Kristien Boelaert

School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Corresponding author: Dr K Boelaert, School of Clinical and Experimental Medicine, IBR Building 2nd floor, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. Tel: 44 121 414 7400, Fax: 44 121 415 8712, Email: k.boelaert@bham.ac.uk

Short title: TSH and thyroid cancer

Key words: TSH, thyroid cancer, autonomous thyroid function, autoimmune thyroid disease
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 and colleagues 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 μU/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.
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 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%) which 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 (<20y) or old age (>70y), 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 thyroid stimulating hormone (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 stage 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.

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 has long been known to positively affect outcomes in differentiated thyroid cancer (Mazzaferri & 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. investigated 10,178 patients presenting with nodular thyroid disease and submitted to fine needle aspiration biopsy (Fiore et al. 2009). They report higher TSH concentrations in those with a diagnosis of papillary thyroid cancer (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 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 which 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-thyroxine (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 thyroxine 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 the 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-thyroxine 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 IGF-1 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 for 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 thyroxine 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 greater than 0.9 mIU/litre 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 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 0.40-1.39 mIU/l, 35% for TSH between 1.40-4.99 mIU/l and 52% in those with TSH of 5.0 mIU/l or greater (Haymart et al. 2008a). A further study by Polyzos and co-authors 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 (Polyzos et al. 2008). 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 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 and co-authors demonstrated that higher pre-operative 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 and colleagues confirm the finding of higher serum TSH in patients with T3-T4 tumour stage compared with those with stage T1-2. 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 include 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 and co-authors (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 extrathyroidal extension but not with other factors associated with poor prognosis including age >45 years, tumour size >4cm and presence of distant metastases. These findings raise the intriguing question whether higher serum TSH concentrations stimulate thyroid cancer invasion thereby facilitating extrathyroidal 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 accord 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 Gαs and very rarely the cancer associated Ras-dependent MAPK pathway through Gβγ and phosphatidylinositol 3-kinase-γ (Du Villard et al. 2000).

Fiore and co-authors 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 μU/ml) in patients with benign thyroid disease but this reduction of TSH with age was less evident in those with papillary thyroid cancer (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 papillary thyroid cancer. 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 10 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 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. found a significant association between pathological Hashimoto’s thyroiditis and higher TSH levels, although thyroid antibody status was not determined in the patients investigated (Haymart et al. 2008b). In the current study by Fiore and colleagues (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 were found in those with papillary thyroid cancer 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 papillary thyroid cancer. 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, reducing serum TSH concentrations, may represent a form of self-treatment similar to the use of suppressive doses of levothyroxine 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 and funding

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Dr Boelaert is supported by a Clinician Scientist fellowship from the Medical Research Council (grant number: G0601811).
References


Brewer C, Yeager N & Di CA 2007 Thyroid-stimulating hormone initiated proliferative signals converge in vivo on the mTOR kinase without activating AKT. Cancer Res. 67, 8002-8006.


Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen
BR, Ladenson PW, Magner J, Robbins J, Ross DS, Skarulis M, Maxon HR &
Sherman SI 2006 Outcomes of patients with differentiated thyroid carcinoma
following initial therapy. *Thyroid* 16, 1229-1242.

Jonklaas J, Nsouli-Maktabi H & Soldin SJ 2008 Endogenous thyrotropin and
triiodothyronine concentrations in individuals with thyroid cancer. *Thyroid* 18, 943-952.

Regulation of thyroid cell proliferation by TSH and other factors: a critical

thyroidectomy for the treatment of Hashimoto's thyroiditis coexisting with papillary

Epidemiology of thyroid diseases in iodine sufficiency. *Thyroid* 8, 1179-1183.


Marqusee E, Benson CB, Frates MC, Doubilet PM, Larsen PR, Cibas ES & Mandel SJ
2000 Usefulness of ultrasonography in the management of nodular thyroid disease.

Matsuo K, Friedman E, Gejman PV & Fagin JA 1993 The thyrotropin receptor (TSH-R)
is not an oncogene for thyroid tumors: structural studies of the TSH-R and the
alpha-subunit of Gs in human thyroid neoplasms. *J. Clin. Endocrinol. Metab* 76,
1446-1451.

Mazzaferri EL & Jhiang SM 1994 Long-term impact of initial surgical and medical

Mazzaferri EL 1999 An overview of the management of papillary and follicular thyroid
carcinoma. *Thyroid* 9, 421-427.

Mazzaferri EL 2000 Thyroid cancer and Graves' disease: the controversy ten years later.
*Endocr. Pract.* 6, 221-225.

Nagataki S & Nystrom E 2002 Epidemiology and primary prevention of thyroid cancer.
*Thyroid* 12, 889-896.

Okayasu I, Fujiwara M, Hara Y, Tanaka Y & Rose NR 1995 Association of chronic
lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases


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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>No of patients studied</th>
<th>Country of study</th>
<th>Date of publication</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boelaert <em>et al.</em></td>
<td>Journal of Clinical Endocrinology and Metabolism</td>
<td>1,500</td>
<td>UK</td>
<td>November 2006</td>
<td>• Serum TSH is independent predictor of malignancy in thyroid nodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Risk of malignancy rises in parallel with serum TSH within normal range</td>
</tr>
<tr>
<td>Haymart <em>et al.</em></td>
<td>Journal of Clinical Endocrinology and Metabolism</td>
<td>843</td>
<td>US</td>
<td>March 2008</td>
<td>• Likelihood of thyroid cancer increases with higher TSH concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Higher serum TSH associated with advanced stage differentiated thyroid cancer</td>
</tr>
<tr>
<td>Jonklaas <em>et al.</em></td>
<td>Thyroid</td>
<td>50</td>
<td>US</td>
<td>September 2008</td>
<td>• Higher TSH concentrations are associated with diagnosis of thyroid cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Patients with thyroid cancer have lower serum total T3 concentrations</td>
</tr>
<tr>
<td>Polyzos <em>et al.</em></td>
<td>Journal of Cancer Research and Clinical Oncology</td>
<td>565</td>
<td>Greece</td>
<td>September 2008</td>
<td>• Higher rates of thyroid malignancy in patients with TSH in upper tertile of normal range</td>
</tr>
<tr>
<td>Haymart <em>et al.</em></td>
<td>Clinical Endocrinology</td>
<td>1,361</td>
<td>US</td>
<td>December 2008 (Epub)</td>
<td>• Thyroid cancer incidence correlates with serum TSH independent of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Higher TSH is associated with extra-thyroidal extension of disease</td>
</tr>
<tr>
<td>Fiore <em>et al.</em></td>
<td>Endocrine Related Cancer</td>
<td>10,178</td>
<td>Italy</td>
<td>September 2009</td>
<td>• Higher TSH in patients with T3-T4 disease and in those with lymph node metastases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Autonomously functioning thyroid nodules are less likely to be malignant</td>
</tr>
</tbody>
</table>