WOMEN IN CANCER THEMATIC REVIEW

Thyroid-stimulating hormone in thyroid cancer: does it matter?

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Abstract

Differentiated thyroid cancer is the most common endocrine malignancy and the incidence is increasing rapidly worldwide. Appropriate diagnosis and post-treatment monitoring of patients with thyroid tumours are critical. Fine needle aspiration cytology remains the gold standard for diagnosing thyroid cancer, and although there have been significant refinements to this technique, diagnostic surgery is often required for patients suspected to have malignancy. Serum thyroid-stimulating hormone (TSH) is higher in patients with malignant thyroid nodules than in those with benign disease, and TSH is proportionally increased in more aggressive tumours. Importantly, we have shown that the pre-operative serum TSH concentration independently predicts the presence of malignancy in subjects presenting with thyroid nodules. Establishing the use of TSH measurements in algorithms identifying high-risk thyroid nodules in routine clinical practice represents an exciting, cost-efficient and non-invasive approach to optimise thyroid cancer diagnosis. Binding of TSH to receptors on thyrocytes stimulates a number of growth promoting pathways both in normal and malignant thyroid cells, and TSH suppression with high doses of levothyroxine is routinely used after thyroidectomy to prevent cancer recurrence, especially in high-risk tumours. This review examines the relationship between serum TSH and thyroid cancer and reflects on the clinical potential of TSH measurements in diagnosis and disease monitoring.

Key Words
- TSH
- thyroid cancer
- nodules
- suppression
- prediction

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Introduction

Differentiated thyroid malignancy is the most common endocrine malignancy and over the last few decades, its incidence has increased dramatically worldwide (Sipos & Mazzaferri 2010, Kitahara & Sosa 2016). It is currently the fifth most common malignancy in women in the US and an estimated 62,000 new cases were found in North American men and women in 2015 (American Cancer Society 2015). Thyroid cancer causes more deaths than any other endocrine cancer (Monson 2000), and there will be an estimated 1980 deaths from thyroid cancer in the US in 2016 (American Cancer Society 2016). The reasons for the observed increase in incidence have been widely debated (Wartofsky 2010) and include enhanced detection of subclinical thyroid cancer due to the growing use of diagnostic imaging and exposure to a number of environmental factors (Kitahara & Sosa 2016). Although better access to health care in countries with high socioeconomic status may in part explain the rising incidence, observations of increased thyroid cancer rates in lower socioeconomic countries, an increasing number of larger tumours and the changing thyroid cancer molecular profiles indicate that other

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factors are likely to be involved (Vigneri *et al*. 2015). A number of disease-modifiable factors including obesity have been identified as potential aetiological factors (Schmid *et al*. 2015). Moreover, a variety of thyroid-specific environmental carcinogens have been implicated including ionising radiation, increased dietary iodine intake and environmental pollutants (Vigneri *et al*. 2015). Overall, the observed changes in thyroid cancer incidence are likely due to a combination of detection bias and true increases in incidence.

Thyroid cancer often presents as a solitary nodule or as a part of a multinodular goitre. This creates an important clinical dilemma as thyroid nodules are very common in 50–67% of the population, and more than 90% are benign (Mazzaferri 1992, Hegedus 2004, Popoveniuc & Jonklaas 2012, Durante *et al*. 2015). Detection rates of thyroid nodules are increasing due to widespread use of imaging modalities in advanced health care systems (Cramer *et al*. 2010, Popoveniuc & Jonklaas 2012). Although incidental thyroid neoplasms have long been recognised due to their presence during post-mortem examinations (Dean & Gharib 2008), there is a significant and increasing clinical burden associated with detecting this disease in patients (Brito *et al*. 2014), for whom the differentiation between aggressive and indolent diagnoses is crucial (Cabanillas *et al*. 2016*a*).

There are a number of well-established and evolving clinical tools to discern malignant from benign thyroid nodules (He *et al*. 2016). Most international guidelines recommend the use of a combination of diagnostic tools, including measurement of thyroid-stimulating hormone (TSH) to assess functional thyroid status, high resolution ultrasonography (US) scanning to assess the morphological characteristics of the thyroid and nodule(s) and fine needle aspiration for cytological evaluation of the presence of malignancy (Hegedus *et al*. 2003, Perros *et al*. 2014, Pitoia & Miyauchi 2015). In recent years, the use of panels of molecular markers to refine the cytological diagnosis of malignancy has received significant attention, although these tests are very expensive and not used routinely in all centres (Xing *et al*. 2013). As most benign nodules do not require further intervention, it is pertinent that thyroid malignancy is diagnosed accurately and further refinement of current diagnostic approaches is required.

If malignancy is diagnosed, surgery is the primary treatment modality for differentiated thyroid cancer, followed by adjuvant radioiodine ablative therapy in a significant number of patients (Burns & Zeiger 2010, Perros *et al*. 2014, Pitoia & Miyauchi 2015). As TSH is a growth factor for thyroid cells, therapy with suppressive doses of levothyroxine is often used postoperatively, and this has long been known to positively affect outcomes in differentiated thyroid cancer (Mazzaferri & Jhiang 1994, Pujol *et al*. 1996, McLeod *et al*. 2012). Current guidelines recommend the medium-to-long-term use of TSH suppression in high-risk thyroid cancer but not in lower-risk tumours because of the health risks associated with the induction of subclinical and overt thyrotoxicosis (Perros *et al*. 2014, Pitoia & Miyauchi 2015).

The diagnosis and post-therapy monitoring of patients with thyroid nodules and cancer is important. We were the first to publish that serum TSH is raised in patients with malignant thyroid nodules compared with those with benign disease (Boelaert *et al*. 2006), and subsequent studies have shown that pre-operative serum TSH is proportionally higher in those with more aggressive disease (Boelaert *et al*. 2006, Jonklaas *et al*. 2008, Haymart *et al*. 2009, McLeod *et al*. 2014, Fighera *et al*. 2015). This review aims to explore the relationship between TSH and thyroid cancer, both before and after a diagnosis of malignancy is made.

Thyroid-stimulating hormone

Hormone structure and biochemical details

Thyroid-stimulating hormone (TSH) is a two-subunit glycoprotein, released from the pituitary gland in response to hypothalamic release of thyrotropin-releasing hormone (TRH). The alpha subunit of the glycoprotein is similar to that of luteinising hormone (LH) and follicle-stimulating hormone (FSH), with specificity only related to the beta subunit. TSH, or thyrotropin, stimulates the thyroid to produce and secrete thyroxine (T4) and triiodothyronine (T3). The released T4 becomes effective once converted peripherally to triiodothyronine (T3) by deiodinase enzymes. The functionally active circulating hormones provide a feedback loop directly to both the hypothalamus and the pituitary suppressing further release of TSH and TRH, thereby maintaining homeostatic control of the hypothalamic–pituitary–thyroid axis (Magner 1989, Szkudlinski *et al*. 2002, Sarapura *et al*. 2011).

TSH function in the normal thyroid

TSH acts on thyroid cell signalling through the TSH receptor, which is found predominantly on follicular thyroid cells. TSH is a growth factor for thyrocytes, with prolonged exposure causing hyperplasia and hypertrophy

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(Sarapura *et al*. 2011). Stimulation of the TSH receptor causes activation of the adenylate cyclase pathway, resulting in alterations in cell-cycle proteins causing changes in thyroid gland growth and cell morphology, as well as the production of thyroid hormones. The effects of TSH can be broadly summarised as follows: synthesis of thyroid hormones, thyroid gland growth, changes in thyrocyte morphology, regulation of post-transcriptional activation of the sodium iodide symporter (NIS) and modulating extra-thyroidal effects (Sarapura *et al*. 2011).

Diagnosing thyroid malignancy

Types of thyroid cancer

Thyroid cancers arise from thyroid follicular cells or parafollicular cells. Differentiated thyroid cancer (DTC) includes two subtypes, papillary and follicular cancers, both of which arise from follicular cells and together make up 90% of thyroid cancers. Papillary thyroid cancers are the most common and represent 85% of all thyroid malignancies. Medullary thyroid cancers account for 3–4% of all thyroid cancers and 80% arise from sporadic mutations, whereas the remainder are hereditary, usually as part of multiple endocrine neoplasia syndromes. Finally, thyroid cancers can be undifferentiated, referred to as anaplastic thyroid cancers, and these tumours have the most aggressive phenotype and the worst prognosis with median survival rates of 3–7 months (Cabanillas *et al*. 2016*b*).

Current diagnostic approaches and limitations

Guidelines recommend that patients suspected to have thyroid malignancy are assessed by a physician with a specialist interest in thyroid cancer care, and who is a regular member of the multi-disciplinary team (Perros *et al*. 2014). It is paramount to perform a full clinical assessment, which includes taking a personal and family history as well as careful clinical examination (Hegedus *et al*. 2003, Hegedus 2004, Perros *et al*. 2014, Pitoia & Miyauchi 2015). In many cases, however, thyroid glands harbouring malignancy are clinically indistinguishable from those that do not, and there is substantial variation among practitioners in evaluating nodules. Features suggestive of malignancy include the presence of firm, fixed thyroid lumps, vocal cord palsy, a positive family history, rapid nodule growth and being at the extremities of age (>60 years or <20 years) (Hegedus *et al*. 2003). Table 1 displays clinical characteristics associated with an increased risk of malignancy.

Table 1 Clinical features suggestive of thyroid malignancy (Hegedus 2004, Popoveniuc & Jonklaas 2012).

History	Physical examination
Family Hx of MEN, MTC, PTC	Firm nodule
History of head and neck irradiation as child or adolescent	Nodule fixed to adjacent structures
History of Hodgkin and non-Hodgkin lymphoma and irradiation	Growth of nodules, especially during therapy to suppress TSH
Age <20	Abnormal cervical lymph nodes
Age >70	Vocal cord paralysis
Male gender	
Symptoms of compression: hoarseness, dysphagia, dyspnoea, cough, dysphonia	

The serum TSH concentration is routinely measured to exclude the presence of a toxic nodular disease causing subclinical or overt hyperthyroidism in all patients (Hegedus *et al*. 2003, Perros *et al*. 2014, Pitoia & Miyauchi 2015). If the TSH is below the laboratory reference range, assays for free triiodothyronine (fT3) and free thyroxine (fT4) are required to exclude overt hyperthyroidism (raised free T4 and free T3) or 'T3-toxicosis' (raised serum-free T3 alone). Similarly, if TSH is raised, then overt hypothyroidism must be excluded (this being indicated by low fT4 with a raised TSH concentration). Although virtually all patients with thyroid carcinoma are euthyroid, the presence of a suppressed serum thyrotropin (TSH) level (generally indicative of subclinical or overt thyrotoxicosis) does not rule out the presence of malignancy (Hegedus *et al*. 2003, Hegedus 2004, Perros *et al*. 2014, Pitoia & Miyauchi 2015). Measurement of serum thyroglobulin is of little value in the initial diagnosis of thyroid cancer, whereas this remains an important tumour marker in the follow-up of patients with thyroid cancer (Perros *et al*. 2014, Pitoia & Miyauchi 2015). Measurements of basal plasma calcitonin and carcino-embryonic antigen (CEA) are useful if medullary carcinoma is suspected but do not form part of the routine evaluation of thyroid nodules (Perros *et al*. 2014).

Thyroid ultrasonography is an extremely sensitive tool for the diagnosis of thyroid nodules and may be specific in diagnosing papillary thyroid cancer (Cesur *et al*. 2006, Hambly *et al*. 2011). Moreover, this imaging modality aids the decision-making processes of which nodules to target for fine needle aspiration biopsy (FNAB) and increases the diagnostic yield of thyroid cell sampling (Perros *et al*. 2014, American Cancer Society 2015, Pitoia & Miyauchi 2015). Multiple studies have confirmed typical sonographic features associated with increased risks of

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malignancy (Table 2) (Frates *et al*. 2005, Hambly *et al*. 2011, Lee *et al*. 2011), and current guidelines now recommend the use of a combination of these features in algorithms predicting the likelihood of thyroid malignancy as well as the selection of nodules requiring FNAB (Perros *et al*. 2014, Haugen *et al*. 2015, Pitoia & Miyauchi 2015). High-resolution ultrasonography by an experienced operator is highly recommended in the initial evaluation of patients with thyroid nodules.

Fine needle aspiration cytology remains the gold standard to confirm the absence or presence of thyroid malignancy. The results can confirm that a nodule is benign, triage patients requiring diagnostic surgery or confirm a diagnosis of malignancy enabling one-step therapeutic surgery (Perros *et al*. 2014, Pitoia & Miyauchi 2015). In the UK, cytology results are reported using the THY classification (The Royal College of Pathologists 2009), whereas in the US, the Bethesda scoring system (Bongiovanni *et al*. 2012) is used. Despite accuracy of diagnosis in the majority of thyroid nodules, FNAC has drawbacks including the sometimes high rate of insufficient/inadequate samples, the inability to distinguish between benign and malignant follicular lesions and difficulties in detecting follicular variant papillary carcinomas (Sangalli *et al*. 2006, Rago *et al*. 2007).

Indeterminate or suspicious thyroid lesions represent 10–26% of nodules evaluated cytologically. These nodules usually require diagnostic surgery, and a median 34% of patients with indeterminate nodules have thyroid malignancy (Xing *et al*. 2013). To avoid unnecessary thyroidectomy, a number of centres use gene expression classifiers or mutation analysis panels to further refine the cytological diagnosis. These diagnostic tools, however, are very expensive and only routinely available in a limited number of centres worldwide (Bernet *et al*. 2014, Pitoia & Miyauchi 2015). Although there have been significant advances in our current diagnostic approaches for thyroid cancer, further cost-efficient and easily applicable approaches are needed to allow informed decision making for both physicians and patients when evaluating the likelihood of malignancy in thyroid nodules.

Serum TSH in the diagnosis of thyroid cancer

TSH and promotion of thyroid cancer growth

Several studies including two large meta-analyses (McLeod *et al*. 2012, Zheng *et al*. 2016) have confirmed that higher serum TSH is associated with an increased risk of differentiated thyroid cancer. Table 3 demonstrates a range of original research studies investigating the link between serum TSH concentrations and differentiated thyroid cancer. Importantly, several studies have shown higher TSH to predict thyroid malignancy, independent of other risk factors including patients' age and gender and a positive family history (McLeod *et al*. 2012, Kim *et al*. 2013). The first study was performed by our group, and demonstrated an increase in risk of diagnosis of malignancy in parallel with an increase in serum TSH (Boelaert *et al*. 2006). The lowest risk of thyroid cancer diagnosis was in those with a TSH below the lower limit of the reference range (<0.4 IU/L). There was a significant cut-off at serum TSH of 0.9 IU/L, with an increased risk of cancer diagnosis in those with serum TSH concentrations above this. The highest risk of cancer diagnosis was in the group with subclinical hypothyroidism who had serum TSH >5.5 IU/L. Importantly we found that, even within the normal range, higher TSH concentrations correlate with a higher risk of DTC, and this was subsequently confirmed by others (Haymart *et al*. 2008).

Higher pre-operative serum TSH concentrations have also been associated with more advanced cancer stage at diagnosis. Mean serum TSH levels were higher in those with stage III and IV disease and in those with larger tumours or in cancers associated with lymph node metastases (Haymart *et al*. 2008, Fiore *et al*. 2009, Shi *et al*. 2016). A meta-analysis of 28 studies, analysing 42,032 control subjects and 5786 patients with thyroid cancers has confirmed that higher pre-operative TSH levels are associated with increased risk of thyroid malignancy as well as a correlation with higher disease grade (McLeod *et al*. 2012). A more recent meta-analysis of 56 studies encompassing 20,227 thyroid cancer cases and 50,003 controls with benign thyroid

Table 2 US features associated with thyroid malignancy (Perros *et al*. 2014).

Benign nodule	Malignant nodule: papillary/medullary	Follicular lesion
Spongiform/honeycomb	Solid and hypoechoic	Hyperechoic/homogeneous/halo benign
Purely cystic	Irregular margin	Hypoechogenicity/loss of halo suspicious
Egg shell calcification	Intranodular vascularity	
Isoechoic/hyperechoic (hypoechoic halo)	Absence of halo	
Peripheral vascularity	Taller than wide	
	Microcalcifications	

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Table 3 Summary of studies investigating serum TSH and thyroid cancer diagnosis.

Reference	Journal	Number of patients	Country of study	Significant findings	Serum TSH 'cut-off' value*
Boelaert *et al*. (2006)	Journal of Clinical Endocrinology and Metabolism	1500	UK	Serum TSH is an independent predictor of malignancy in thyroid nodules. Risk of thyroid cancer rises in parallel with serum TSH in the normal range.	0.9 mIU/L
Polyzos *et al*. (2008)	Journal of Cancer Research and Clinical Oncology	565	Greece	Higher rates of thyroid malignancy in patients with TSH in upper tertile of normal range.	1.5 mIU/L
Haymart *et al*. (2008)	Journal of Clinical Endocrinology and Metabolism	843	USA	Higher serum TSH is associated with advanced stage-differentiated thyroid cancer.	1.4 mIU/L
Jonklaas *et al*. (2008)	Thyroid	50	USA	Higher TSH is associated with increased likelihood of diagnosis of thyroid cancer. Patients with thyroid cancer have lower serum total T3 concentrations.	1.8 mIU/L
Haymart *et al*. (2009)	Clinical Endocrinology	1361	USA	Risk of thyroid cancer increases with increased TSH independent of age.	No cut-off value
Fiore *et al*. (2009)	Endocrine Related Cancer	10,178	Italy	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.	1.6 mIU/L
Gerschpacher *et al*. (2010)	Thyroid	87	Austria	TSH may play a role in thyroid cancer progression rather than oncogenesis.	No cut-off value
Zafon *et al*. (2012)	Journal of Thyroid Research	386	Spain	TSH levels are higher in patients with DTC.Increment in tumour size rises in parallel with incremental rise in TSH.	No cut-off value
Kim *et al*. (2013)	Clinical Endocrinology	1759	South Korea	High TSH level within the normal range is an independent risk factor for DTC and can be used as a diagnostic adjunct.	2.31 mIU/L
Sohn *et al*. (2014)	Head and Neck	3791	South Korea	Serum TSH may not be useful for clinical risk assessment of small thyroid nodules.	2.13 mIU/L
Fighera *et al*. (2015)	Endokrynologia Polska	622	Brazil	Risk of carcinoma in nodular disease rises in parallel with serum TSH.	1.64 mIU/L
Khan *et al*. (2016)	Asian Pacific Journal of Cancer Prevention	73	Pakistan	Higher pre-surgical TSH correlates with thyroid cancer.	No cut-off value
Shi *et al*. (2016)	Endocrine Journal	1870	China	Raised TSH is related to cancer stage but not likely to be related to initiation.	Meta-analysis

*'Cut-off' values from studies that stated a cut-off or divided groups into tertiles and quartiles, in this latter case, the lower value of the highest tertile/quartile is used.

nodules has confirmed that higher serum TSH levels were significantly associated with thyroid cancer size and with the presence of lymph node metastasis (Zheng *et al*. 2016). These findings are consistent with serum TSH having a role in the promotion of thyroid tumour growth and aggressiveness.

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Indeed TSH is a known growth factor for thyroid nodules and suppression of serum TSH concentrations by administering exogenous thyroid hormone may inhibit the growth of established nodules and the development of new nodules (Papini *et al*. 1998). Benign and malignant thyroid tumours express functional TSH receptors on the plasma membrane (Ichikawa *et al*. 1976) and TSH increases adenylate cyclase activity leading to cAMP production and cell growth through stimulation of these receptors *in vitro* (Carayon *et al*. 1980). Importantly, the expression of TSH receptors in DTC has been associated with an improved prognosis (Shi *et al*. 1993). Differentiated thyroid cancers usually retain responsiveness to TSH, and suppressive doses of levothyroxine can be used to inhibit the progression of metastatic thyroid cancer (Simpson *et al*. 1988) as well as decrease the rates of recurrence in patients treated with surgery or radioactive iodine (McGriff *et al*. 2002, Biondi *et al*. 2005), in keeping with TSH's tropic effect on thyroid tissue promoting neoplasia and carcinogenesis.

TSH and the initiation of thyroid cancer

It has been demonstrated that even in patients who do not present with thyroid nodules, higher serum TSH concentrations are associated with increased risks of thyroid malignancy. In a large sample drawn from the general population TSH levels were significantly higher in patients with DTC compared with the control group. Among 1548 controls, 606 subjects had thyroid nodules detected on ultrasound. Further subgroup analysis demonstrated that control subjects without detectable thyroid nodules had proportionally higher risks of DTC as TSH concentration rose, suggesting a role for TSH in the generation of thyroid cancer. This study (Kim *et al*. 2013) did not indicate a relationship between higher serum TSH concentrations and more advanced thyroid cancer in contrast with others (Haymart *et al*. 2008, Fiore *et al*. 2009, McLeod *et al*. 2012, Zheng *et al*. 2016).

Evidence for a role of TSH in the development of thyroid tumours comes from studies of the *Thrb*$^{PV/PV}$ mouse, which has a dominant negative mutant thyroid hormone nuclear receptor gene inserted in the TRβ locus. This mouse model has disrupted pituitary–thyroid axis signalling resulting in raised serum TSH concentrations and the rapid development of metastatic thyroid cancer (Suzuki *et al*. 2002). Crossing of this model with TSH receptor gene-knockout mice (*Tshr*$^{-/-}$) resulted in impaired thyroid growth and no occurrences of thyroid cancer, consistent with a role for TSH in thyroid tumourigenesis (Lu *et al*. 2010).

Serum TSH and thyroid autoimmunity

Several studies have indicated an association between thyroid autoimmunity and thyroid malignancy (Haymart *et al*. 2008, Boelaert 2009, McLeod *et al*. 2012). There is an increased incidence of thyroid cancer in patients with Hashimoto's disease. Our previous study (Boelaert *et al*. 2006) demonstrated that although raised thyroid peroxidase (TPO) levels did not independently predict malignancy, patients with cancer had significantly higher levels of TPO antibody than patients with benign disease. Fiore *et al*. (2009) demonstrated that TSH was higher in patients independent of whether they had raised TPO antibodies or not, and that there was no difference in rates of thyroid carcinoma between the autoimmune thyroid disease population and antibody-negative patients. Haymart *et al*. (2008) observed the debate about association of thyroid cancer with both Hashimoto's disease and Graves' disease. They suggest that as Hashimoto's disease often progresses to hypothyroidism resulting in elevated TSH concentrations and because Graves' disease is associated with TSH receptor stimulation, which is associated with thyroid cancer (Mazzaferri 2000), it follows that TSH receptor activation is the link between thyroid cancer and thyroid autoimmune disease. More recently, a study directed at assessment of anti-thyroglobulin antibody (TgAb) measured pre-operative levels in differentiated thyroid cancer patients and concluded that TgAb was not an independent predictor of DTC prognosis, once adjusted for age and gender (McLeod *et al*. 2014). They noted that TgAb may be raised in autoimmunity and in patients exhibiting an immune response to the tumour, and may not be a true representation of thyroid autoimmune disease. Figure 1 summarises the potential effects of TSH as a tumour initiator, cancer promoter or in relation to thyroid autoimmunity.

Aetiology of raised serum TSH concentrations in thyroid cancer

There is no consensus on why serum TSH is raised in differentiated thyroid cancer nor do we fully understand the cause and effect relationship (Boelaert 2009). Iodine deficiency causes 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 cancer (Lind *et al*. 1998, Feldt-Rasmussen 2001, Nagataki & Nystrom 2002). However, a causal role for TSH in the initiation of thyroid cancer has

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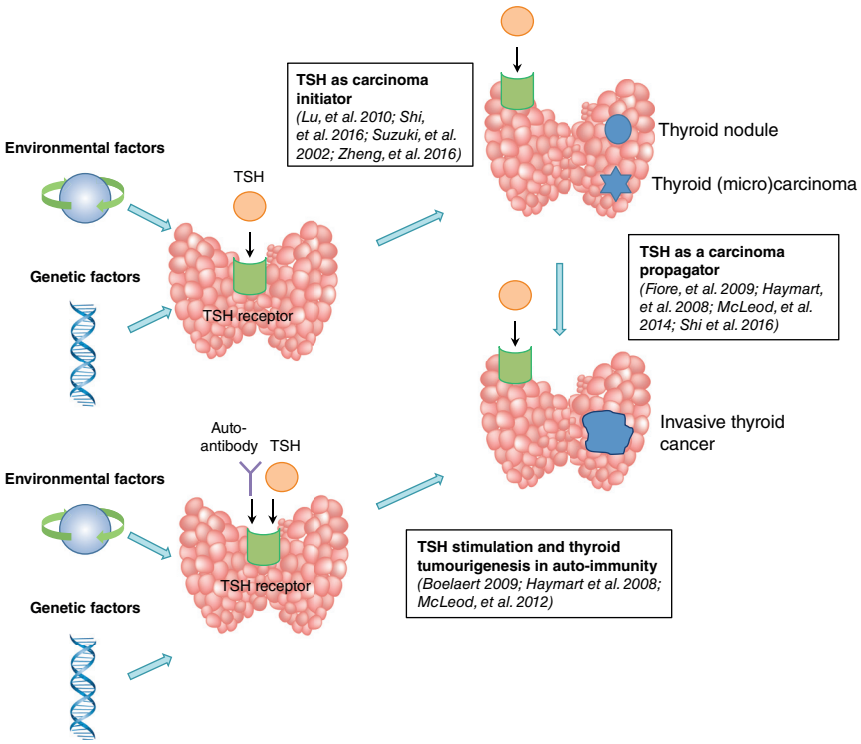

Figure 1
Illustrating binding of TSH to its receptor in normal thyroid physiology. Potential roles of high serum TSH concentrations in the initiation and progression of thyroid carcinogenesis as well as putative links with thyroid autoimmunity in the context of contributing environmental and genetic factors are indicated.

not been exclusively demonstrated, and it remains unclear if serum TSH concentrations are higher as a consequence of the presence of thyroid malignancy.

A further potential explanation is that patients with lower serum TSH concentrations already have or are progressing towards development of autonomously functioning thyroid nodules, which are less likely to be malignant (Mann *et al*. 1988, Hegedus *et al*. 2003, Hegedus 2004). Fiore and coworkers demonstrated significant age-dependent development of thyroid autonomy (serum TSH <0.4 IU/L) in patients with benign thyroid disease, but this was less evident in those with papillary thyroid cancer and in patients with multi-nodular goitre. The frequency of thyroid autonomy was higher and the risk of papillary thyroid cancer was lower than in those with solitary nodules, consistent with a protective effect of lower serum TSH concentrations on thyroid cancer development or progression (Boelaert 2009, Fiore *et al*. 2009).

Serum TSH in different thyroid cancer subtypes

Serum TSH and papillary microcarcinoma Papillary microcarcinomas, defined as thyroid cancer <10 mm in diameter, are increasing dramatically in frequency, and distinguishing those that proliferate and progress aggressively from small indolent tumours is difficult. The increased incidence is partly due to the finding of incidentalomas on routine imaging and on histopathological examination of thyroid specimens removed for reasons not associated with the suspicion of malignancy (Roti *et al*. 2008). Current guidelines neither recommend completion thyroidectomy nor the administration of radioiodine routinely for these tumours. A more conservative approach for their management has been recommended, and for low-risk patients, who have isolated and intrathryoidal tumours, without nodal metastases, lobectomy is sufficient (Pacini *et al*. 2012, Perros *et al*. 2014, Haugen *et al*. 2015). In those with evidence of metastases, a positive family history, previous radiation to the head and neck or in subjects older than 45 years, total thyroidectomy and radioiodine ablation may be indicated (Mazzaferri 2007, Perros *et al*. 2014, Pitoia & Miyauchi 2015).

Two main difficulties arise from these modern guidelines: (i) a subset of these tumours progresses and metastasises (Roti *et al*. 2006, Page *et al*. 2009); (ii) patients, when presented with a cancer diagnosis, often prefer comprehensive therapy, which leaves them with the best prognosis and the lowest risk of recurrence, often despite the potential cost of any associated treatment morbidity. Although current tumour staging systems are unable to guide therapy in papillary microcarcinomas, the potential for use of TSH to assist in assessing prognosis is appealing.

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The association between raised serum TSH measurements and papillary thyroid microcarcinoma has been studied (Table 4), and some have suggested this as a means to estimate thyroid cancer risk in those with thyroid nodule of less than 1 cm in size (Moon *et al*. 2012). However, not all studies are consistent. Sohn *et al*. (2014) demonstrated the association between higher TSH and risk of malignancy in tumours over 1 cm, but not in papillary microcarcinomas. Similarly, an Italian study showed that TSH was not significantly different in thyroid papillary microcarinoma patients compared with their controls consisting of patients with negative histology (Negro *et al*. 2013, Sohn *et al*. 2014). A meta-analysis of nine studies encompassing 6523 subjects demonstrated that some smaller studies were biased due to heterogeneous controls, and overall confirmed a significant association between higher serum TSH and papillary microcarcinoma, supporting the hypothesis that TSH is involved in differentiated thyroid tumourigenesis. The authors stated that there is insufficient evidence to show that TSH is directly involved in thyroid carcinoma initiation, but the data support the hypothesis that raised TSH is associated with risk of cancer and progression (Shi *et al*. 2016). At present, it is unclear how the increased detection of small indolent microcarcinomas influences the utility of using serum TSH in clinical decision algorithms.

Whether TSH is an important factor in disease initiation or progression remains unclear. An argument against its involvement in tumour initiation is the lack of TSH receptor mutations interfering with signal transduction in thyroid carcinomas (Matsuo *et al*. 1993). Furthermore, thyroid carcinomas can occur in patients with a range of serum TSH, including in those who take exogenous thyroid hormones and have suppressed serum TSH concentrations for treatment of other thyroid diseases (Satta *et al*. 1993).

On the contrary, a mouse model with a knock-in of oncogenic BRAF generated by Franco and coworkers developed invasive thyroid carcinomas and concomitantly became profoundly hypothyroid as demonstrated by significantly raised TSH levels. After knockout of the TSH receptor (to genetically replicate ablation of the TSH signalling pathway), there was a significant lag in the period before tumour formation, and the tumours that developed were much less aggressive (Franco *et al*. 2011). These findings contribute to the idea that TSH *per se* may not be oncogenic independently, but raised concentrations are likely to contribute significantly to tumour development and progression.

Serum TSH and follicular thyroid cancer Follicular thyroid carcinomas provide a unique diagnostic challenge, in that they cannot be diagnosed by cytological evaluation alone. Although there may be factors indicating neoplastic

Table 4 Table summarising studies investigating TSH and papillary microcarcinoma.

Reference	Journal	Number of patients	Country of study	Significant findings
Haymart *et al*. (2008)	Journal of Clinical Endocrinology and Metabolism	843	US	Escalating cancer risk with higher TSH level in microcarcinomas. More research warranted
Moon *et al*. (2012)	Head and Neck	483	South Korea	TSH measurement in the context of thyroid micronodule can exclude cancer
Shi *et al*. (2012)	Endocrine Journal	1870	China	TSH does not correlate with microcarcinoma presence and therefore TSH can only be linked with progression of carcinoma
Negro *et al*. (2013)	Endocrine Practice	205	Italy	No difference in serum TSH between papillary microcarcinoma group compared with controls
Sohn *et al*. (2014)	Head and Neck	3791	South Korea	Serum TSH may not be useful for clinical risk assessment of small thyroid nodules
Jiao and Zhou (2015)	Zhonghua Yi Xue Za Zhi	365	China	TSH is probably associated with oncogenesis in papillary microcarcinoma (PTMC) although it may only be involved in growth of pre-existing PTMC

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change in fine needle aspirates, follicular carcinoma is defined as a tumour that invades the capsule, a feature that cannot be identified on cytological evaluation rendering these cancers indistinguishable from thyroid adenomas using cytopathology. The standard treatment of choice is therefore diagnostic hemithyroidectomy, which requires no further surgery in adenomatous lesions, but is usually followed by completion hemithyroidectomy, radioiodine ablation and suppression of TSH in the majority of invasive follicular carcinomas (McHenry & Phitayakorn 2011, Perros *et al*. 2014, Pitoia & Miyauchi 2015).

Raised serum TSH levels have been demonstrated in patients with follicular carcinoma compared with those with benign follicular disease (Kunt *et al*. 2015). Although the TSH level is unlikely to be the single factor in follicular thyroid cancer development, some have advocated using its measurement in combination with other determinators of risk stratification, even to the point of defining treatment, that is, whether to proceed with hemithyroidectomy or not (Kuru *et al*. 2009). Despite the potential for the application of TSH measurements in the management of follicular thyroid carcinomas, there is a paucity of studies addressing this specifically (Zheng *et al*. 2016).

TSH and non-differentiated thyroid cancer Due to the different pathophysiology of medullary thyroid cancer, TSH concentrations are implicated neither in the likelihood of diagnosis nor in the follow-up monitoring of these tumours. Responsiveness of thyroid cancer to TSH depends on TSH receptor expression, and dedifferentiated cancers demonstrate significant reductions in expression of thyroid-specific proteins including TSH receptors, thyroid peroxidase and thyroglobulin (Brabant *et al*. 1991, Sheils & Sweeney 1999). Anaplastic thyroid cancers represent extreme forms of dedifferentiated tumours, and these tumours are characteristically very difficult to treat due to the lack of expression of proteins involved in the thyroid machinery. Expression of the sodium iodide symporter is often absent, thereby significantly reducing the functional effectiveness of radioiodine ablation and treatment. Current therapeutic approaches include the redifferentiation of these tumours with various agents to improve treatability (Schmutzler & Kohrle 2000, Kang *et al*. 2011, Dong *et al*. 2013). In view of the inherent lack of expression of normal TSH receptors in anaplastic thyroid cancers, serum TSH concentrations have not been studied in relation to the diagnosis or progression of these tumours. It seems that finding of altered TSH levels in this context would neither aid the choice of available treatment options nor would it affect the very poor prognosis associated with these rare thyroid cancers.

TSH in follow-up of patients with thyroid malignancy

Until recently, the long-term management of differentiated thyroid cancers included the suppression of serum TSH concentrations with supraphysiological concentrations of levothyroxine for extended periods of time, regardless of the tumour-specific risk stratification. Current guidelines recommend against TSH suppression in low-risk tumours, which have not been treated with radioiodine or those who are stratified in the excellent response categories after dynamic risk stratification (Perros *et al*. 2014, Haugen *et al*. 2015, Pitoia & Miyauchi 2015). For those tumours that have not undergone further risk stratification at 1 year after treatment, current practice is to suppress TSH levels with exogenous thyroid hormone to less than 0.1 U/L for 5–10 years after treatment. At this point, depending on the clinical response, the TSH suppression can be relaxed (Perros *et al*. 2014). Some studies have indicated that TSH suppression may inhibit the generation of new thyroid nodules, as well as the growth and tumourigenic potential in existing nodules (Papini *et al*. 1998), although current guidelines do not recommend of thyroid hormone suppressive therapy in patients with thyroid nodules (Perros *et al*. 2014, Haugen *et al*. 2015, Pitoia & Miyauchi 2015).

TSH suppression in differentiated thyroid cancer follow-up

Suppressive serum TSH to very low levels reduces the rates of thyroid cancer recurrence and has been shown to improve differentiated thyroid cancer patient outcomes. TSH is a growth factor for thyroid nodules, and it is considered that suppression of TSH can prevent new nodule formation as well as inhibition of current nodules (Papini *et al*. 1998). In the context of differentiated thyroid carcinoma treatment, after resection of thyroid carcinoma and radioiodine treatment, TSH suppression therapy positively affects cancer outcomes including disease-specific survival (Mazzaferri & Jhiang 1994), and reduces recurrence (Pujol *et al*. 1996). Therefore, it is widely recommended that patients have TSH suppression after successful treatment in the early post-operative period (Haugen *et al*. 2015).

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Risks associated with TSH suppression

Despite the widespread use of TSH suppression in patients who have been treated for differentiated thyroid cancer, this treatment approach is not completely without risk. Subclinical hyperthyroidism has been demonstrated to have significant deleterious health consequences. This includes a spectrum of cardiovascular risks, including atrial fibrillation and coronary heart disease morbidity and mortality (Collet *et al*. 2012). There is also a documented association with dementia, decreased cognitive function (Annerbo & Lokk 2013) and osteoporosis (Biondi *et al*. 2015, Polovina *et al*. 2015).

Outcomes for high-grade thyroid cancers have been improved with TSH suppression, and some advocate the need for more aggressive suppression in higher-stage disease (Jonklaas *et al*. 2006). In view of the aforementioned risk factors associated with this approach, current guidelines (Perros *et al*. 2014) now recommend the use of tools including the FRAX score to determine bone health and fracture risk (Kanis *et al*. 2008) in patients who are on suppressive therapy with levothyroxine for 5 years or longer during thyroid cancer follow-up. Overall, an individualised approach combining assessment of the patient's response to treatment and risk of disease progression with an evaluation of the potential health risks associated with long-term TSH suppression is advised in establishing the required dose and length of course of levothyroxine therapy.

Conclusion

Patients presenting with a thyroid nodule or thyroid enlargement should have their serum TSH measured as part of the initial assessment. After our paper in 2006 (Boelaert *et al*. 2006), a significant body of evidence has accumulated confirming the association between higher serum TSH concentrations and likelihood of thyroid cancer diagnosis. A recent meta-analysis demonstrated this relationship in thyroid tumours of all sizes, including papillary microcarcinomas in adult as well as in paediatric thyroid cancers (Zheng *et al*. 2016). Several studies and meta-analyses have also established a relationship between raised TSH levels and cancer progression, and increased concentrations were associated with advanced disease and lymph node metastasis (Fiore *et al*. 2009, McLeod *et al*. 2012, Zheng *et al*. 2016).

The diagnostic accuracy of serum TSH as a biochemical predictor of malignancy, however, has not yet been established and meta-analyses have failed to provide conclusive data to provide a single useful cut-off value to pass TSH as an independent and validated test (McLeod *et al*. 2012, Zheng *et al*. 2016), and measurement of this biochemical marker has not yet been incorporated into clinical decision algorithms. There have been suggestions that its measurement may be useful in combination with other tests including ultrasonography and fine needle aspiration cytology. At a time when thyroid nodules are increasingly being diagnosed, and although the differentiation between benign and malignant lesions remains difficult in a significant proportion of subjects, it is important to consider incorporating TSH levels into the stratification of patients' thyroid cancer risk.

Furthermore, treatment with TSH suppression in the follow-up of patients with thyroid cancer has been re-evaluated. There are significant long-term health risks associated with TSH suppression, and further refinement of the stratification approaches regarding the risk of disease progression or recurrence will help identify those patients in whom the risks of long-term suppressive therapy outweigh the risks. Large prospective studies to evaluate this further will be of utmost importance. Although there is little doubt that serum TSH is raised in differentiated thyroid cancer, the full integration of this finding into clinical pathways relating to the diagnosis and management of patients is yet to be undertaken.

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