Levothyroxine and Cancer

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Treatment with LT4 is used to suppress thyrotropin levels after the management of differentiated thyroid cancers after surgery, with doses and targets for thyrotropin (thyroid-stimulating hormone, TSH) determined by the risk of cancer recurrence determined in the individual patient. Moreover, the role of thyroid hormones and their receptors in the initiation—and, potentially, cure—of a range of cancer types is an active area of research.

1 Introduction

1.1 Overview of the Management of Differentiated Thyroid Cancer

In general, the treatment of differentiated thyroid cancers (DTC) consists of surgery, post-operative/adjuvant radioactive iodine (RAI, ^{131}I) treatment and hormonal therapy with levothyroxine (LT4) [1, 2]. Surgery is the standard intervention for the management of DTC (although the management of microcancers of the thyroid remains a matter of debate) [1, 2]. Where the patient receives a total thyroidectomy, the resulting athyroid state induces a severe hypothyroidism that causes thyrotropin (TSH) to rise to high levels, typically at least 30 IU/mL after several weeks (compared with the usual upper limit of the normal reference range of about 4 mIU/L) [3].

For papillary or follicular thyroid tumours, the high TSH level stimulates any remaining unresectable thyroid tissue or metastatic tumour cells that retain some

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G. J. Kahaly (ed.), *70 Years of Levothyroxine*,
https://doi.org/10.1007/978-3-030-63277-9_9

endocrine activity to take up iodine from the circulation [3]. Treatment with RAI is then administered periodically over a period of years and the RAI is taken up avidly by these cells resulting in their irradiation and ablation: in this way, the majority of these cancers can be eradicated successfully [1, 3]. Injections of recombinant human TSH may also be used to increase RAI uptake of residual thyroid cancer cells [3, 4].

Patients may require lifelong substitution of LT4 after thyroid surgery for DTC, depending on the amount of thyroid tissue removed [3, 5]. Moreover, high-risk patients may receive TSH-suppressive therapy with LT4. The decision on whether to aim for full suppression of TSH (TSH < 0.1 mIU/L), or partial TSH suppression (TSH 0.1–0.4 mIU/L) should be personalised [2, 3].

1.2 Scope of This Chapter

This chapter reviews the benefits and risks associated with LT4-suppressive therapy in patients who have undergone surgery and RAI for DTC. The diagnosis of thyroid cancer, tumour staging, allocation of patients to different modalities of surgery and their outcomes, and the application, effectiveness of and development of refractoriness to RAI *per se* are beyond its scope and will not be discussed further here (we refer the reader to current guidelines in these areas [1, 3, 5, 6]). In addition, the consequences of long-term suppressive LT4 administration for bone homeostasis and health in these patients are considered in chapter "Levothyroxine and Bone" of this book, and are also not discussed in detail here. Chapter "Levothyroxine and the Heart" of this book reviews the effects of TSH-suppressive doses of LT4 on the heart. Finally, medullary thyroid tumours arise from calcitonin-secreting parafollicular cells (C-cells) that do not secrete thyroxine: these patients are not treated with RAI and LT4 and their management is also not addressed here [7].

2 Application of Thyrotropin-Suppressive Doses of Levothyroxine After Surgery and Radioactive Iodine for Well-Differentiated Thyroid Tumours

2.1 Need for Suppression of Thyrotropin in Thyroid Cancer Survivors

TSH promotes the growth of thyroid tumours, and levels of this hormone are suppressed in the initial period following surgery for many DTC. A meta-analysis supports the effectiveness of this approach in improving long-term clinical outcomes post-thyroidectomy, compared with patients who did not receive TSH-suppressive therapy [8]. However, it has become clear in recent years that stringent suppression of TSH does not improve long-term clinical outcomes in patients with other than high-risk presentations of well-differentiated thyroid cancer [9–13]. Accordingly,

patients with thyroid cancer assessed as being at lower risk of disease recurrence do not require complete suppression of TSH. This approach is designed to optimise the balance between suppression of disease recurrence (benefit) and the potential for adverse effects on bone [9].

For adults, the level of thyroglobulin has been found to be strongly predictive of the risk of recurrent disease (see Fig. 1a) [14], and thus different targets for TSH suppression are provided in guidelines for low-risk patients according to their post-surgery thyroglobulin levels [1, 3]. A recent meta-analysis has confirmed the diagnostic and prognostic power of thyroglobulin measurement during post-thyroidectomy TSH suppression using LT4, with negative predictive value for ruling out evidence of structural thyroid carcinoma in excess of 99% [15]. The relationship between thyroglobulin and post-surgical outcome is less well understood in children, for whom targets for TSH suppression are accordingly not stratified formally according to the thyroglobulin level [3].

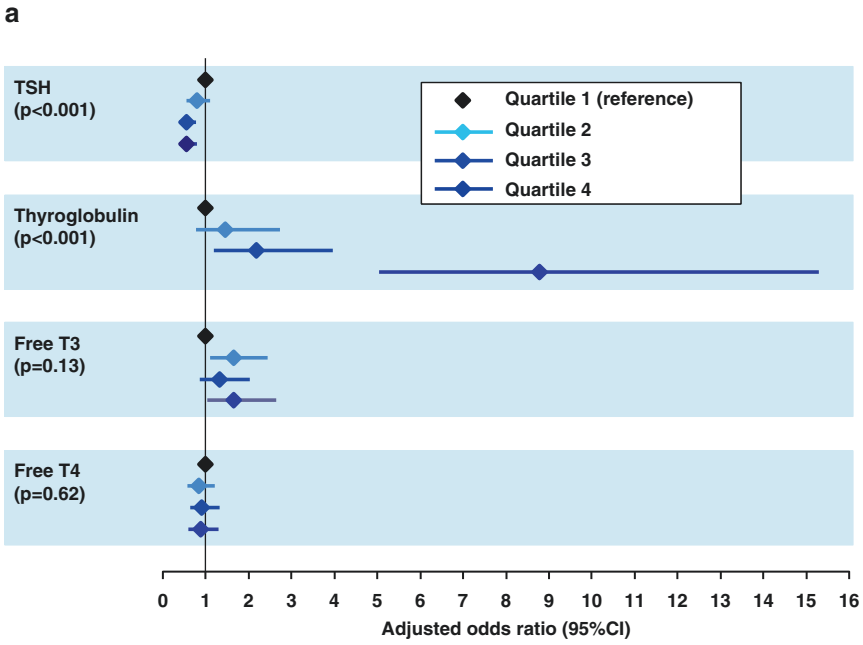

Fig. 1 Thyroid hormones homeostasis and the risk of thyroid cancer. (**a**) Case-control study from the EPIC cohort. A population of 357 individuals with differentiated thyroid cancer were matched with 2 (women) or 3 (men) cancer-free control subjects. Significance values shown are p for trend. Total thyroxine (T3) and total triiodothyronine (T3) did not significantly influence cancer risk and have been omitted for clarity. Adjusted for study site, age, gender, time/data of blood draw. (Drawn from data presented in Ref. [14]). (**b**) Risk factors for malignancy within the thyroid nodules in a multivariable logistic regression analysis that included variation of thyrotropin (TSH) levels within the normal range. Adjusted for gender, age, nodule size, preoperative TSH in patients not on levothyroxine. (Drawn from data presented in Ref. [26])

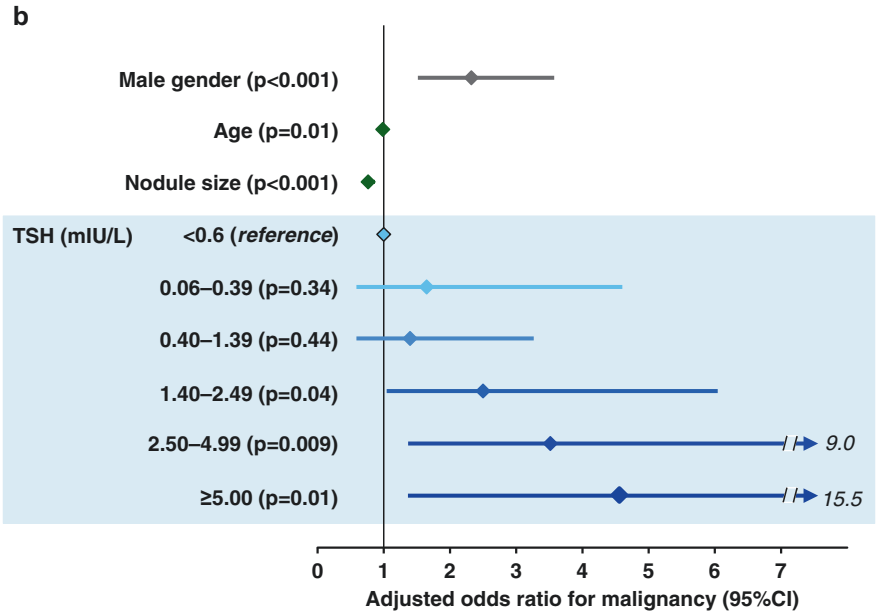

Fig. 1 (continued)

2.2 *Long-Term Consequences of Thyroidectomy and Thyrotropin Suppression*

TSH-suppressive LT4 therapy induces a thyroid hormone status that is broadly equivalent to subclinical hyperthyroidism [13]. Overt hyperthyroidism during LT4-suppressive therapy should be avoided. Accordingly, care must be taken to achieve a balance between the achievement of adequate suppression of TSH levels to optimise cancer-free survival, with the potential adverse effects associated with subclinical hyperthyroidism [16]. Clinical studies in patients who have received LT4-based TSH-suppressive therapy have revealed several areas of concern or benefit, which are described briefly below.

2.2.1 Bone

Untreated longstanding hyperthyroidism is associated with loss of bone mineralisation, osteoporosis and increased risk of fractures. Studies in TSH-suppressed populations have been conflicting, but some studies have demonstrated increased osteoporosis and fracture risk associated with LT4 treatment (reviewed in chapter "Levothyroxine and Bone" of this book).

2.2.2 The Cardiovascular System

A retrospective study from the Korean National Health Insurance database, which covers 97% of people in that country, evaluated the risk of coronary heart disease (CHD) and ischemic stroke over a follow-up period of 4.3 years in 182,419 patients following thyroidectomy for differentiated thyroid cancer [17]. Higher hazard ratios for CHD and stroke were found for the thyroidectomised population, relative to propensity score-matched controls. The signal for adverse cardiovascular outcomes became stronger at doses of LT4 that were higher than 115–144 μg/day. Although atrial fibrillation was more common in patients receiving higher doses of LT4, this was associated with only 4% of strokes. As expected, cardiovascular risk factors increased the risk of CHD or stroke. Another chart review in thyroid cancer survivors found no association between up to 9 years of over-suppression of TSH with LT4 (according to guideline recommendations based on risk of thyroid cancer recurrence) and adverse cardiovascular outcomes, but this study only contained 14 subjects [18]. Chapter "Levothyroxine and the Heart" of this book reviews the effects of LT4 on the heart.

2.2.3 Patient-Reported Outcomes

Fatigue is often reported as a long-term complication of thyroidectomy and subsequent TSH suppression [19]. One study showed that the persistence of residual symptoms reminiscent of hypothyroidism on TSH-suppressive therapy were correlated with a low level of FT3 [20]. Altering the dose of TSH, or switching to a combination of LT4 and T3 administration did not induce a clear improvement of fatigue, however [21, 22]. Current guidelines for the management of hypothyroidism recommend that LT4 remains the first-line treatment. Exercise appears to be an effective way of combating fatigue and improving the quality of life in this setting [21, 23]. A similar benefit was observed in LT4-treated breast cancer patients undergoing chemotherapy [24]. More clinical studies of this relatively common, and potentially disabling, complication of thyroid cancer management are needed [21].

3 Thyroid Hormones and Cancer Risk

Variations in thyroid hormones have been associated with changes in the risk of a wide range of cancer types [25]. Examples of effects of thyroid hormones on the risk of various tumour types in epidemiological studies are shown below. However, the results are often conflicting and have to be judged cautiously since association does not prove causation.

Thyroid: Observational data have associated an increased circulating level of TSH with an increased risk of developing differentiated thyroid cancer [26, 27] and/or a more advanced stage of this tumour at presentation [26]. Other studies found that low TSH increased the risk of thyroid cancer [14], that high TSH in men, but low TSH in women, was associated with thyroid cancer [28], or that the influence of

abnormal TSH on cancer risk was amplified in non-diabetic subjects with higher levels of fasting serum glucose [29]. Fig. 1 shows the risk of cancer associated with thyroid nodules at different levels of TSH and other markers of thyroid homeostasis from two of these observational studies. Higher TSH levels were associated with a lower risk of incident differentiated thyroid cancer in one study (Fig. 1a) [14], while increases in TSH levels within the normal reference range increased thyroid cancer risk in the other study, in patients with thyroid nodules (Fig. 1b) [26].

Breast: Hyperthyroidism (high TT4 or FT4 and/or low TSH) has been associated with increased risk of breast cancer in some observational studies [30–32]. This association was shown to extend into the euthyroid range [33], and to be present pre- and post-menopause [34]. There was no effect of variation of TSH in other studies [31, 35], and the impact of anti-thyroid antibodies on breast cancer risk was variable [30–32]. A meta-analysis of 8 cross-sectional studies found a positive association between elevated T4, T3, anti-thyroid peroxidise antibodies and anti-thyroglobulin antibodies and the prevalence of breast cancer [36]. Likewise, autoimmune thyroiditis has been found to be more common in women with vs. without breast cancer [37].

A population-based case-control study from Taiwan (65,491 breast cancers, 261,964 controls) found that LT4 administration vs. no LT4 use was associated with a modestly higher risk of breast cancer, with a greater effect in older (≥65 years) patients (odds ratio [OR] 1.45 [95%CI 1.23–1.71], $p < 0.01$) compared with younger patients (OR 1.19 [95%CI 1.09–1.29], $p < 0.01$) [38]. However, the ORs were similar for patients who received LT4 for ≤1 year (1.22) and >1 year (1.26), and further study is required to confirm this association.

Prostate: Low TSH/high T4 increased the risk of prostate cancer in a population-based observational study [30]. Conversely, and consistent with this study, high TSH was protective against prostate cancer in the population of a clinical trial conducted to answer a clinical question that was unrelated to thyroid function [39].

Gastrointestinal: A population-based study found no effect of TSH or FT4 levels on colorectal cancer risk [30]. However, high FT4, but not a diagnosis of hypothyroidism or hyperthyroidism, predicted shorter survival in a cohort of 258 patients with advanced gastro-oesophageal cancer [40]. Low FT3 was associated with prolonged survival in this study, which is difficult to reconcile with the adverse effect of high FT4 [40].

A large population-based case-control study from a UK general practice database (The Health Improvement Network, 20,990 colorectal cancer cases and 82,054 controls) found that both hyperthyroidism and untreated hypothyroidism predicted an increased risk of having colorectal cancer [41]. Long-term treatment with LT4 was associated with a reduced risk of colorectal cancer, with a lower risk for a longer treatment duration [41].

Liver: Higher TSH was associated with larger tumours in a cohort of 838 patients with advanced hepatocellular carcinoma, and higher FT4 (≥16.6 ng/L) predicted poorer survival vs. lower levels of FT4 [42].

Pancreas: A retrospective study found that survival with pancreatic cancer did not vary according to hypothyroid or euthyroid status overall, but that hypothyroid patients taking LT4 demonstrated higher tumour stage, and more localised and distant tumour spread than euthyroid patients [43]. However, this study is difficult to interpret, as there were only 71 hypothyroid patients included, and there was no information presented on how many were taking LT4 [43].

Table 1 summarises briefly some potential mechanisms that have been demonstrated in clinical or experimental studies to explain an association between thyroid hormone status and tumorigenesis [44–67]. Thyroid hormones mediate their effects

Table 1 Potential mechanisms linking thyroid hormone actions to tumourigenesis or tumour suppression

Ref.	Potential mechanisms
	Promotion of invasion and metastasis
[44–47]	Promotion of proliferation of tumour cells or metastasis by altered intracellular downstream signalling pathways following interaction of T3 or T4 with a binding site on integrin αvβ3 in the extracellular matrix (breast, ovary)
[48, 49]	Promotion of metastasis and/or angiogenesis by enhanced epithelial-mesenchymal transition in tumour cells, also involving the integrin αvβ3–thyroid hormone axis
[50, 51]	Inhibition of apoptosis mediated via downstream signalling from thyroid hormone and other ligand binding sites on integrin αvβ3 (ovary)
[43]	Increased proliferation, migration, and invasion of pancreatic cancer cell lines in vitro after exposure to T3
[52]	Crosstalk between thyroid oestrogen receptors increased the growth of cancer cells, and this relationship was modulated by integrin αvβ3 (lung)
	Modulation of tumour cells
[53–55, 64]	Enhanced differentiation or renewal of cancer stem cells (colorectal, hepatocellular)
[65]	Release of inhibition of epigenetic regulation of gene expression reduced cancer cell growth (liver)
[56]	T3 may induce senescence in prostate cancer cells, which would oppose tumour growth
	Altered expression of thyroid hormone receptors α and β (TRα and TRβ)
[57, 58]	Expression of TRα drove tumour growth and worsened prognosis (breast)
[57, 59]	Higher expression of THRα2 receptor improved prognosis (breast)
[57, 59, 60, 63]	Expression of TRβ opposed tumour growth (breast)
[61, 62]	Suppression of the oncogenic RUNX2 transcription factor by increased expression of TRβ (breast, thyroid)
[63]	Cytoplasmic TRβ1 predicted improved survival, but nuclear TRβ1 predicted reduced survival (breast)
[64]	Activation of the T3/TRβ axis shifted hepatocellular tumour cells to a more benign, normal tissue-like phenotype
[60, 65, 66]	Reversal of epigenetic silencing of tumour suppressor genes via activation of thyroid receptors by T3 (thyroid, hepatocellular, kidney)
[67]	Reduced tumour growth by activation of the RhoB signalling pathway (thyroid)

on the cancer cell through several non-genomic pathways including activation of integrin avβ3 promoting metastasis and angiogenesis within tumours. Furthermore, cancer development and progression are affected by dysregulation of local bioavailability of thyroid hormones and thyroid hormone receptor changes [25, 45, 49, 68–70].

Tetraiodothyroacetic acid may oppose these actions [69]. The thyroid receptor, TRβ is downregulated in many tumours, and activation of this receptor has been proposed as a strategy for increasing the sensitivity of triple-negative breast cancer cells to chemotherapy [71].

Ovarian cancer is a highly metastatic tumour, and several thyroid hormone analogues exerted cytotoxic effects in ovarian cancer cell lines, probably by antagonising the effects of thyroid hormones on the integrin αvβ3 axis [72] A similar phenomenon has been observed in thyroid and lung cancer cells, among others [49, 51, 52, 69]. Tetraiodothyroacetic acid, a metabolite of T4, may reduce the resistance of cancer cells to radiotherapy [73]. Deiodinases modulate the local bioavailability of thyroid hormones, by controlling T4 conversion to T3 and other thyroid hormone derivatives and this expression of these enzymes differs in a range of tumour types, compared with non-neoplastic tissues [74, 75]. These observations provide promising avenues for future research on the development of novel anticancer agents.

4 Conclusions

Observational data have implicated variations in the levels of thyroid hormones with variations in the risk of a range of cancer types, including of the thyroid itself. This association extends to within the currently accepted “normal” range for thyroid hormones. In addition, the discovery of novel interactions between thyroid hormones and receptors both inside cells and in the extracellular space have opened up new avenues for anticancer research. Treatment with suppressive doses of LT4 is one of the key components of the management of differentiated thyroid cancers after surgery, where careful evaluation of the risk of cancer recurrence in the individual patient aids a balancing of the need to suppress TSH sufficiently with the need to avoid over treatment.

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