Thyroid hormones and cancer: clinical studies of hypothyroidism in oncology

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Purpose of review

To collect and assess clinical reports of a putative relationship between thyroid state and the biology of cancers of various types.

Recent findings

A number of prospective case–control studies reviewed here have suggested that subclinical hyperthyroidism increases risk of certain solid tumors and that spontaneous hypothyroidism may delay onset or reduce aggressiveness of cancers. Small case studies have reached similar conclusions. A controlled prospective trial of induced hypothyroidism beneficially affected the course of glioblastoma. A context in which to interpret such findings is the recent description of a plasma membrane receptor for thyroid hormone on cancer cells and dividing tumor-associated endothelial cells.

Summary

Accumulating clinical evidence may justify new, broadly-based controlled studies in cancer patients of the possible contribution of thyroid hormone to tumor behavior.

Keywords

cancer, hypothyroxinemia, integrin αvβ3, L-thyroxine, triiodothyronine

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Introduction

A relationship between the thyroid gland and cancer was first alluded to by Beatson in 1896 [1]. Much experimental, clinical and epidemiological effort has subsequently been directed at defining and clarifying this putative and controversial relationship. The possibility that a severe deficiency in ambient thyroid hormone levels might have a therapeutic impact on metastatic cancer was originally suggested by Hercbergs and Leith [2]. In that report, a complete, sustained regression of metastatic nonsmall cell lung cancer (NSCLC) occurred in a man who had lapsed into and was then successfully resuscitated from myxedema coma. He lived 5 years without recurrence before dying of unrelated causes. This unique event found support in preclinical studies that revealed that thyroid hormone deprivation slowed solid tumor growth rates, whereas thyroid hormone supplementation increased tumor growth rates [3–6]. If endogenous thyroid hormone in euthyroid patients may in fact influence cancer development [7], then the spontaneous or induced hypothyroid state might be associated with a more favorable prognosis in cancer patients.

The possible association between thyroid hormone and cancer may now be better understood following the discovery of a membrane receptor for L-thyroxine (T_4) and 3,5,3′-triiodo-L-thyronine (T_3) on a structural protein of the plasma membrane, integrin αvβ3 [8,9]. This integrin and the cell surface thyroid hormone receptor appear to mediate the proliferative action of the hormone on blood vessel cells and on tumor cells [9]. Integrin αvβ3 is primarily expressed on rapidly dividing cells. This recently understood molecular mechanism of thyroid hormone action may shed light on the numerous and controversial clinical studies of thyroid hormone and cancer that have sporadically appeared in the literature.

After a brief review of experimental thyroid hormone actions relevant to cancer, we review clinical studies and reports of outcomes in cancer patients with primary hypothyroidism, spontaneous and iatrogenic.

Cell biology of thyroid hormones and tumorigenesis and tumor cell proliferation

More than 20 years ago, Guernsey *et al.* [10] found that removal of T_3 and T_4 from serum eliminated X-ray-induced neoplastic transformation without modifying cell survival. Moreover, addition of T_3 to thyroid hormone-depleted medium re-established the expected frequency of transformation. Borek *et al.* [11] also found that T_3 facilitated chemical carcinogenesis. Using propylthiouracil (PTU) to induce hypothyroidism in intact rats, Goodman *et al.* [12] showed that hypothyroidism reduced the risk of breast cancer after 7,12-dimethylbenz(a)anthracene (DMBA) exposure to 7% from 63% in

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controls. PTU and thyroid hormone replacement resulted in a 78% incidence of mammary cancer in DMBA-treated animals. Such studies were not widely cited, at least in part because the traditional concept of genomic thyroid hormone action – through nuclear receptor proteins (thyroid hormone receptors) (see review [9]) – resulted in transcription of genes that supported homeostasis of the activities of normal cells [13,14]. Further, there were at the time of publication of these reports no substantial clinical studies of thyroid hypofunction or hyperfunction and cancer risk.

A plasma membrane receptor for thyroid hormone is the basis for a nongenomic mechanism of hormone action that appears to contribute to proliferation of integrin αvβ3-bearing cells [9,15•,16]. As noted above, such cells are usually tumor cells or dividing endothelial or vascular smooth muscle cells. In this context, earlier animal studies of thyroid hormone and cancer [3–6] may be more understandable. Similarly, there are recent studies on animals of tetraiodothyroacetic acid (tetrac), a thyroid hormone analogue that disrupts the function of the integrin αvβ3 receptor on human cancer xenografts and induces tumor regression and slower growth [15•,16,17]. This receptor also is apparently required for induction by thyroid hormone of angiogenesis, including that relevant to tumor support [8,9].

Cancer and thyroid function

Epidemiological studies of cancer and thyroid function.

Does hyperthyroidism increase and hypothyroidism reduce cancer risk?

In a prospective study of almost 30 000 individuals followed for 9 years, a low thyrotropin (TSH) level, suggestive of subclinical hyperthyroidism (TSH <0.5 mU/l), was associated with increased cancer risk specifically with lung (hazard ratio 2.60) and prostate cancers (hazard ratio 1.96). Hypothyroid function was not associated with cancer risk [18•].

In a population-based case–control study, hyperthyroidism was identified as a significant ovarian cancer risk factor, with an odds ratio (OR) of 1.8 [19].

Of 1362 breast cancer patients and 1250 controls, women with untreated hypothyroidism or goiter had a significantly reduced risk of breast cancer [relative risk (RR) = 0.3]. If they had received thyroid hormone for fertility issues, the RR rose to 4.2. If there was a family history of breast cancer, RR was 2.6, or if late age at first childbirth, 2.4 [20]. Postmenopausal women with breast cancer who had the elevated thyroid hormone and reduced TSH levels consistent with subclinical hyperthyroidism, as well as an increased thyroid hormone/estradiol ratio, had more breast cancers than matched controls [21].

A large population-based case–control study involving 532 pancreatic cancer patients found that a history of hyperthyroidism gave an OR of 2.1 for its development [22].

In women with renal cell carcinoma (RCC), a statistically significantly higher use of thyroid hormone was observed ($P = 0.041$) [23].

Is the onset of cancer delayed in hypothyroid patients?

Hypothyroidism was associated with older age at cancer (breast, lung cancers) diagnosis in several studies. In the breast cancer group, hypothyroid patients were 7 ($P < 0.001$) [24], 7 [25] and 6 years older ($P < 0.035$) [26] at diagnosis in three studies. Breast cancer incidence was significantly lower in the hypothyroid group ($P < 0.003$). Tumors were also smaller in the hypothyroid group ($P < 0.047$) and were more likely to be localized. Euthyroid patients were also more likely to have metastatic disease [24].

In a case–control study of lung cancer, patients with lung cancer and a history of thyroid hormone requirement (= thyroid hormone replacement) had a mean age at diagnosis of 73 years vs. 64 years for euthyroid patients ($P = 0.0006$). The thyroid hormone group median survival was 14.5 vs. 11.1 months ($P = 0.014$) [27].

A possible explanation is that hypothyroidism takes a number of years to evolve to a clinical requirement for thyroid hormone supplementation, which might then elicit progression of a pre-existing, indolent, subclinical cancer [28]. This sequence is wholly speculative.

Does cancer chemotherapy-induced hypothyroidism contribute to outcome?

The tyrosine kinase inhibitor, sunitinib, as used in RCC, induces unintended hypothyroidism in up to 71% of patients [29]. Of interest is that, in a recent study, progression-free survival (PFS) in such patients seemed better than that in euthyroid cohorts, even with and in spite of T_4 supplementation ($P = 0.07$) [30]. However, there are as yet no studies comparing replacement with nonreplacement thyroid hormone so that any relationship between sunitinib-induced hypothyroidism and tumor behavior is speculative.

Hypothyroidism, chemoradiation therapy, disease response and survival

Hypothyroidism may increase response rates to chemotherapy and radiation therapy of a variety of solid tumors [31–36]. Certain of these observations have appeared only in preliminary form [32,34].

Table 1 Cancer outcomes across a spectrum of thyroid functions

Thyroid function	Type of research	No. of cases	Cancer type/disease	Clinical outcome	References
Spontaneous hyperthyroid	Prospective population study	29 691	Several malignancies	Significantly higher hazard ratios for lung and prostate cancer vs. significantly lower for HT	Hellevik *et al.* [18•]
	Case–control	532	Pancreas	Increased risk with prior hyperthyroidism	Ko *et al.* [22]
	Case–control	26 pts, 22 matched controls	Breast	Subclinical hyperthyroidism associated with more frequent cancers	Saraiva *et al.* [21]
Spontaneous hypothyroid	Case report	1	NSCLC, metastatic	'Spontaneous' CR following myxedema coma	Hercbergs and Leith [2]
	Series	28	Various solid tumors	100% response (CR and PR) rate to radiation therapy in chemically HT pts	Hercbergs [32]
Primary hypothyroidism-Thyroid hormone supplemented	Population-based	1136 pts, 1088 controls	Breast, primary	Less aggressive disease in HT group, fewer metastases, 7 years older age at onset, smaller tumors	Cristofanilli *et al.* [24]
	Comparative study	280	Breast, all stages	5 years older for HT	Backwinkel and Jackson [25]
	Comparative study	68, 91 matched controls	Breast, all stages	6 years older, smaller tumors, lower stage, lower S phase for HT	Hercbergs *et al.* [26]
	Comparative study	85, 85 matched controls	Lung, all stages	4.3 years older, longer survival for HT	Hercbergs *et al.* [27]
	Comparative study	247, 234 matched controls	RCC, all stages	Greater use of TH in RCC pts	Rosenberg *et al.* [23]
	Case report	1	Breast	Apparent tumor stimulation with TH	Hercbergs [7]
	Case report/ review	1	NSCLC	Apparent tumor stimulation with TH	Hercbergs [33]
	Case report	1	Anaplastic thyroid	Apparent tumor stimulation with TH, CR while clinically HT, 10-year survival	Hercbergs *et al.* [44]
	Series	5	Pancreas, CRC	Long-term survival while on lower dose; TH/TH discontinued	Hercbergs *et al.* [34]
	Series	176	Breast	Pts taking TH before diagnosis had greater relapse rate, larger tumors	Burt and Schapira [37]
Hypothyroid -[iatrogenic] 2^0 to XRT/CHEMORX/ SURG/Biologics	Retrospective	54	RCC treated with sunitinib	Pts becoming HT with sunitinib and treated with TH seemed to have worse outcome	Sabatier 2009 *et al.* [30]
	Retrospective	155, with 59 developing HT	HNSCC	Pts developing HT seemed to have better survival	Nelson *et al.* [35]
	Population-based	5916 (age >65)	HN (excluding thyroid, larynx, prior HT)	Longer survival in those developing HT	Smith *et al.* [36]
	Phase II, subset analysis	34	RCC, melanoma treated with IL-2/LAK cells	Higher responses with development of HT	Atkins *et al.* [39]
	Phase II, subset analysis	16	RCC, metastatic, treated with IL-2/LAK cells	Development of HT correlated with better response rate	Weijl *et al.* [40]
Interventional hypothyroxinemia	Phase I–II	36	Recurrent, high-grade gliomas made HT with PTU	Early-onset HT associated with improved survival	Hercbergs *et al.* [41] Hercbergs *et al.* [42]
	Phase II	20	Recurrent, high-grade gliomas made HT with PTU	HT associated with improved survival	Linetsky *et al.* [43]
Recurrent disease following [re-] initiation of L-thyroxine in HT pts	Case reports	4	Breast	7/9 women given TH after mastectomy developed recurrence, 4 of which were late	Burt and Schapira [37]
	Case report	1	Breast	Rapid progression, death after re-starting TH, 3+ years after being in CR	Hercbergs [7]

CR, complete response; CRC, colorectal cancer; HN, head and neck; HNSCC, head and neck squamous cell carcinoma; HT, hypothyroidism; IL-2, interleukin 2; LAK, lymphokine-activated killer; NSCLC, nonsmall cell lung cancer; PR, partial response; pts, patients; PTU, propylthiouracil; RCC, renal cell carcinoma; TH, thyroid hormone; XRT, radiation therapy.

Progression or relapse of disease following L-thyroxine [T_4] supplementation

The records of 1465 patients with breast cancer, of whom 176 had taken thyroid hormone, were reviewed. Patients who had taken thyroid hormone for more than 2 years within 10 years of developing breast cancer showed a greater relapse rate compared with controls at 3 years (43.9 vs. 18.8%, $P = 0.002$). Their tumors were also larger ($P = 0.01$) [37].

The incidence of breast cancer was significantly higher among patients receiving thyroid hormone in comparison to control patients. The risk increased with duration of use, being almost 20% in those receiving it for more than 15 years. The risk was more than three-fold higher in nulliparous women receiving thyroid hormone, reaching 33%, whereas it was only 9.25% in those not receiving thyroid hormone [38].

Induced hypothyroidism in cancer patients

A significantly increased rate of tumor regression (5/7 = 71%) was seen in patients with advanced RCC and melanoma who became hypothyroid, even transiently, from interleukin-2 (IL-2) and lymphokine-activated killer (LAK) cell therapy, compared with euthyroid patients (5/27 = 19%) who did not ($P < 0.02$) [39]. A meta-analysis similarly found a significant correlation of response with hypothyroidism ($P = 0.001$) [40].

A prospective study of PTU-induced mild hypothyroidism revealed that hypothyroidism was associated with tumor regression and a statistically significant prolongation of survival and time-to-progression in patients with recurrent/progressive primary brain tumors [41]. PTU induced hypothyroidism in 36 such patients and early onset chemical hypothyroidism (within 2 months) was seen in 18 patients. The 6-month PFS of patients with at least two consecutive monthly readings of serum-free [F]T4 levels below the reference range (hypothyroxinemia) was 58 vs. 0% for nonhypothyroid patients ($P < 0.002$). Initial FT4 decline was an independent prognostic variable and the nadir of FT4 decline also correlated positively with overall survival ($P < 0.003$) [42].

A preliminary report of recurrent glioma patients rendered hypothyroid similarly found that survival was significantly prolonged with an associated clinical improvement (8/12). This led to withdrawal of steroid therapy in two patients and dose reduction in the other six. Responding patients also had marked decrease in seizure activity. Median time to tumor progression (TTP) was significantly longer in the hypothyroid group (5 vs. 2.7 months; $P = 0.002$) with 6-month PFS of 33 vs. 0% in the euthyroid group [43] (see Table 1) [44].

Conclusion

Review of published clinical studies and accumulating preliminary data in cancer patients with spontaneous, chemically, or iatrogenically induced hypothyroidism heightens suspicion that thyroid hormone is a permissive factor in some patients with solid tumors. Validation or refutation of this concept requires additional prospective, controlled studies of induced, clinically mild hypothyroidism in cancer patients. A consensus statement of the American Thyroid Association (ATA) [45] recommends withholding thyroid hormone replacement in asymptomatic patients – without cancer – who have modest elevation of serum TSH concentration above the reference range. This recommendation provoked controversy [46]. Until additional information is available from prospective studies of hypothyroidism and cancer, however, we suggest it is prudent to consider the ATA consensus recommendation on thyroid hormone replacement when managing chemically hypothyroid patients with cancer.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 486).

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