

Associations of Serum Thyrotropin Concentrations with Recurrence and Death in Differentiated Thyroid Cancer

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Objective: The relation between serum TSH levels and risk for recurrence or thyroid carcinoma-related death in patients with differentiated thyroid carcinoma has only been studied to a limited extent.

Design: We conducted a single-center observational study in 366 consecutive patients with differentiated thyroid carcinoma, who had all been treated according to the same protocol for initial therapy and follow-up. Median duration of follow-up was 8.85 yr.

Methods: The relation between summarizing variables of unstimulated serum TSH concentrations (25th, 50th, and 75th percentiles, the percentage of suppressed and unsuppressed TSH values) and risk for recurrence or thyroid carcinoma-related death was analyzed by Cox survival analyses in patients with at least four TSH measurements.

Results: In Cox regression analysis, we found a positive association between serum TSH concentrations and risk for thyroid carcinoma-related death and relapse, even in initially cured patients. The median of the individual TSH concentrations was the best indicator for thyroid carcinoma-related death (hazard ratio 2.03; confidence interval 1.22–3.37) and relapse (hazard ratio 1.41; confidence interval 1.03–1.95). A threshold of 2 mU/liter differentiated best between relapse-free survival and thyroid carcinoma-related death or relapse.

Conclusion: Our study supports current guidelines, which advise to aim at TSH levels in the low normal range in cured low-risk patients, whereas TSH levels should be suppressed in noncured or high-risk patients. (*J Clin Endocrinol Metab* 92: 2610–2615, 2007)

PATIENTS TREATED FOR differentiated thyroid carcinoma (DTC) receive thyroxin replacement therapy. The purpose of this therapy is not only to replace endogenous thyroid hormone, but also to suppress serum TSH levels to prevent relapse or progression of thyroid cancer. The rationale for TSH suppressive thyroxin replacement therapy is based on multiple clinical and experimental observations (1). It has been observed in case reports that high TSH levels may promote tumor growth, which is reversed by thyroxin therapy (2–4). Experimental studies have confirmed the expression and functional activity of TSH receptors in DTC (5–7) and the proliferative effects of TSH on thyroid carcinoma cells *in vitro* (8, 9). TSH also stimulates protein synthesis and metabolism in DTC, which is the rationale for clinical diagnostic procedures, like TSH-stimulated serum thyroglobulin (Tg) measurements (10, 11) and TSH-stimulated 2-fluoro-2-deoxy-D-glucose positron emission tomography scintigraphy (12). Despite this notion, only four observational clinical studies have been published on the effects of thyroxin-induced TSH suppression on the prevention of DTC recurrence or thyroid carcinoma-related death (13–16). In the first study, Mazzaferri and Jhiang (13) found fewer recurrences and thyroid carcinoma-related deaths in patients treated with TSH suppressive thyroxin dosages. In the second study, Cooper *et al.* (15) showed that

TSH suppression was an independent predictor in nonradioiodine treated high-risk papillary cancer patients. However, in these two studies, initial therapy was not uniform with respect to the extent of surgery and radioiodine ablation therapy (13, 15). In a recent publication, Jonklaas *et al.* (16) demonstrated in a multicenter study that the degree of TSH suppression is a predictor of thyroid carcinoma-specific survival in high-risk patients, independent of radioiodine ablation therapy and the extent of thyroid surgery. Because initial therapy in their cohort was not distributed uniformly, it was not studied whether TSH suppression after uniform initial therapy consisting of both near total thyroidectomy and radioiodine ablation has additional value. In addition, they did not study the value of TSH suppression in patients who were cured after initial therapy. In the fourth study, Pujol *et al.* (14) studied 121 DTC patients who were all treated with total thyroidectomy and thyroid remnant ablation. They showed that a percentage of undetectable TSH values of less than 10% significantly predicted a lower relapse-free survival. In this study only the comparison of extreme TSH values showed a significant difference in relapse-free survival. The low number of thyroid carcinoma-related deaths did not allow to assess the prognostic value of TSH with respect to mortality. This lack of compelling evidence that prolonged suppression of serum TSH levels is associated with a better prognosis in low-risk DTC together with the adverse effects of hyperthyroidism on bone mineral density (17) and cardiac function (18) was also reflected in recent guidelines to aim at normal TSH levels in low-risk DTC patients (19).

To assess the relation between the degree of TSH suppression and prognosis in more detail, we studied the asso-

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Abbreviations: CI, Confidence interval; DTC, differentiated thyroid carcinoma; HR, hazard ratio; Tg, thyroglobulin; TNM, Tumor Node Metastasis.

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ciation between the degree of TSH suppression and long-term prognosis in a group of 366 consecutive DTC patients who were all treated with total thyroidectomy and radioiodine ablation therapy. Because the median duration of follow-up was 8.85 yr, the number of thyroid carcinoma-related deaths allowed us to study both relapse-free survival and mortality, both in the total group and in a subgroup of patients who were cured 1 yr after initial therapy.

Patients and Methods

A total of 366 consecutive patients were included in the study. These patients had received initial therapy for DTC between January 1986 and January 2000. January 1986 was chosen as a starting date because from that date forward, all relevant patient data were registered in a computerized database. Initial surgery and radioiodine ablation therapy were performed at the Leiden University Medical Centre or at one of the connected general hospitals. All hospitals are affiliated with the Regional Comprehensive Cancer Centre, using the same standardized protocol for the treatment and follow-up of DTC.

All patients were treated with near-total thyroidectomy, followed by routine radioiodine ablative therapy with 2800 MBq I-131. In case of incomplete tumor resection or when metastases were present, 6000 MBq was administered after thyroidectomy. Lymph node surgery was performed as follows: when lymph node metastases were the presenting symptom, a modified radical neck dissection (removal of lateral lymph nodes with preservation of sternocleidomastoid muscle, internal jugular vein, and accessory nerve) was performed at total thyroidectomy. When lymph node metastases were not the presenting symptom, neck inspection was performed during thyroidectomy, and suspected lymph nodes were removed. When lymph node metastases became apparent during follow-up, a modified radical neck dissection was performed.

Follow-up was performed according to a standard protocol, consisting of unstimulated and at least one TSH-stimulated serum Tg measurement, diagnostic 185 MBq I-131 scintigraphy, and ultrasound. After initial therapy, levothyroxine therapy was started in a dose to suppress TSH levels (<0.1 mU/liter).

Cure 1 yr after therapy was defined as the absence of I-131 accumulation at diagnostic 185 MBq scintigraphy, Tg serum concentrations less than 2 µg/liter after TSH stimulation, and no other indication for disease (20). When Tg antibodies were present at evaluation of initial therapy, only those patients were considered cured in whom no tumor became discernible after prolonged follow-up.

Tumor presence during follow-up was defined as histological or radiological (x-ray, computed tomography, magnetic resonance imaging, 2-fluoro-2-deoxy-D-glucose positron emission tomography, or I-131 scintigraphy) proven DTC and stimulated Tg levels > 2 µg/liter (21). In case of recurrent disease or metastases, surgery was attempted if the lesion was solitary and accessible, followed by additional radioiodine therapy (6000 MBq). If the tumor could not be removed surgically, radioiodine therapy was given and repeated if necessary. All radioiodine therapies were followed after 7 d by whole body scintigraphy.

The following data were registered: age at diagnosis, sex, date of diagnosis, histology, Tumor-Node-Metastasis (TNM) stage, serum Tg, Tg antibodies and TSH levels at regular intervals, date of cure, disease state 1 yr after initial therapy, date of recurrence after cure, date of death, cause of death, and date of last follow-up. TNM stage was registered according to the fifth edition (22). This was done because most patients were analyzed before the latest edition of the TNM classification. We used the following end points of follow-up: date of death (82 patients), date of emigration (12), and date of most recent contact (272).

Death causes were analyzed in all 82 patients who had died during follow-up. Death cause was investigated using medical records, death certificates, inquiries with other physicians involved in the treatment of each patient, inquiries in other hospitals, inquiries with general practitioners, and autopsy findings. Death causes were divided into thyroid cancer-related death and other causes.

TSH analyses

Data from 6245 TSH measurements in 366 patients were retrieved from the Department of Clinical Chemistry. Of these, stimulated TSH

levels (verifying all TSH levels > 10 mU/liter) were discarded, which left 5680 measurements. Only patients were analyzed in whom at least four TSH measurements were available, leaving 4805 measurements in 310 patients.

After verifying that there was no time dependency of TSH in our patient group [the average slope of TSH in all patients during the observation period being -0.001 mU/liter*year (confidence interval (CI) $-0.002 - 0.000$ mU/liter*year)], and because from a biological point of view there is no indication that the relation between TSH and thyroid carcinoma cells does change over time, we chose to express TSH exposure using the following TSH summary parameters for each patient: the 25th, 50th, and 75th percentiles of all TSH measurements; and the percentage of all TSH levels less than 0.1, 0.4, and 4.5 mU/liter (13–16).

The prognostic significance of TSH for thyroid carcinoma-related death was analyzed in all patients as well as in patients who were cured 1 yr after initial therapy. The prognostic significance of TSH for tumor relapse was analyzed in patients who were cured 1 yr after initial therapy.

Laboratory measurements

Serum TSH was determined throughout the study period with Elecsys E-170 on a Modular Analytics E-170 system (Roche Diagnostic Systems, Basel, Switzerland; reference range 0.4–4.5 mU/liter, detection limit 0.005 mU/liter, intraassay variability 0.88–10.66%, and interassay variability 0.91–12.05%). Serum Tg was determined with IRMA (Tg kit; Brahms Diagnostica GmbH, Berlin, Germany) on a Wallac (Wallac, Turku, Finland; intraassay variability 0.14–13.9% and interassay variability 12.3–17.4%). Serum Tg antibodies were determined with IRMA (Sorin Biomedica, Amsterdam, The Netherlands) on a Wallac (intraassay variability 3.6–4.1% and interassay variability 11.6%).

Until January 1997, serum Tg was measured using an immunoradiometric assay (IRMA), the Dynotest TG (Brahms Diagnostica GmbH), with a sensitivity of 0.3 µg/liter. From January 1997, the Dynotest TG-s (Brahms Diagnostica GmbH) was used, with a sensitivity of 0.05 µg/liter and an interassay variability of 0.3 µg/liter. The comparability of the two methods was excellent: R^2 : 0.99, slope 0.99, intercept 0.09 (23). Serum Tg antibodies were also measured at these specific time points by the Ab-HTGK-3 IRMA (DiaSorin Biomedics, Saluggia, Vercelli, Italy).

Statistical analyses

Normally distributed data are presented as mean \pm sd. Data that are not distributed normally are expressed as median, and 25th and 75th percentiles. Categorical data are expressed as percentages. All statistical analyses were performed using SPSS for windows version 12.0 (SPSS, Inc., Chicago, IL). Prognostic indicators for recurrence or thyroid carcinoma-related death were identified using Cox regression analyses. Indicators that were identified as significant were entered into a stepwise model. A *P* value < 0.05 was considered significant.

Results

Characteristics of the patients are shown in Table 1. Mean age at time of surgery was 48 ± 18 yr. Median duration of follow-up was 8.85 yr (range 0.75–16.98). A total of 310 patients (75 males, 235 females) were available, in whom at least four unstimulated TSH measurements were available. Of these patients, 39 (13%) died of thyroid carcinoma. A total of 250 patients (81%) were cured 1 yr after initial therapy. Of the patients who were cured 1 yr after initial therapy, 39 (16%) developed a relapse, whereas 10 (4%) died because of thyroid carcinoma.

All patients

TSH-related parameters of all 310 patients are given in Table 2. The median of the individual percentages of TSH values below the lower limit of normal (0.4 mU/liter) was 73%, and the median of the percentages less than 0.1 mU/

TABLE 1. Patient characteristics

	No.	No. with ≥ 4 TSH measurements (%)	No. of thyroid carcinoma-related deaths (%)	No. of cured patients after 1 yr (%)	No. of patients with relapse after cure (%)	No. of thyroid carcinoma-related deaths after cure (%)
Total	366	310	39 (13)	250 (81)	38 (16)	10 (4)
Gender (male/female)	91/275	75 (24)/235 (76)	13 (14)/26 (14)	57 (76)/193 (82)	11 (19)/28 (15)	1 (2)/9 (5)
Stages						
T1	22	19	0 (0)	19 (100)	1 (5)	0 (0)
T2	188	164	8 (5)	153 (93)	17 (11)	4 (3)
T3	56	52	8 (15)	45 (87)	9 (20)	4 (9)
T4	96	75	23 (31) ^{a,b}	33 (44) ^{a,b}	12 (36) ^{a,b}	2 (6) ^{a,b}
N1	107	85	15 (18)	55 (65)	12 (22)	2 (4)
M1	52	42	19 (45) ^{a,b}	10 (24) ^{a,b}	10 (100) ^{a,b}	2 (20) ^a
Histology						
Papillary	203	171	18 (11)	141 (82)	25 (20)	4 (3)
Follicular	72	63	13 (21) ^a	50 (79)	10 (7)	5 (10)
Follicular variant papillary carcinoma	68	56	5 (9)	45 (80)	3 (7)	1 (2)
Hürthle cell	23	20	3 (15)	14 (70)	1 (7)	0 (0)
Age						
<55 yr	210	204	4 (2) ^{a,b}	188 (92) ^{a,b}	18 (10) ^{a,b}	1 (1) ^{a,b}
>55 yr	156	106	35 (33) ^{a,b}	62 (58) ^{a,b}	21 (34) ^{a,b}	9 (15) ^{a,b}

^a Significant at univariate analysis.^b Significant at multivariate analysis.

liter was 50%. No differences in these percentages were observed between the different TNM stages. According to univariate Cox regression analysis, significant indicators for thyroid carcinoma-related death were extrathyroidal tumor extension (T4), the presence of distant metastases, and older age (Table 1). Significant TSH-related predictors for thyroid carcinoma-related death were the 25th and 50th percentiles (median) of the serum TSH concentrations for each patient: the hazard ratio (HR) for the 25th percentile was 1.35 (a HR > 1, meaning a higher risk for the end point); and the HR for the median TSH was 1.22 (Table 3).

The 25th percentile for a patient indicates that 25% of the measurements are below (or equal) to this value, and 75% of the measurements are above (or equal) to this value. A higher 25th percentile value in a patient indicates that up to 75% of the TSH values are higher in this patient than in a patient with a lower 25th percentile.

When the significant variables assessed by univariate Cox regression analysis were introduced into a stepwise multivariate model, only T4, M1, and older age remained significant predictors (Tables 1 and 3).

TABLE 2. Summarizing data of serum TSH concentrations in 310 patients after initial therapy for DTC

Individual TSH-related parameters	All patients (n = 310)	Patients cured after 1 yr (n = 250)
Percentiles of TSH values per patient		
25th percentile (mU/liter)	0.0 (0.0–0.1)	0.0 (0.0–0.1)
50th percentile (mU/liter)	0.1 (0.0–0.4)	0.1 (0.0–0.4)
75th percentile (mU/liter)	0.4 (0.1–1.4)	0.4 (0.1–1.4)
Percentage of TSH values below the indicated values per patient		
<0.1 mU/liter	50 (30–73)	50 (29–73)
<0.4 mU/liter	73 (50–89)	72 (50–89)
<4.5 mU/liter	100 (90–100)	100 (90–100)

Data are expressed as median (25th–75th percentiles). TSH values are expressed with one digit.

Patients who were cured 1 yr after initial therapy

A total of 250 patients were cured 1 yr after initial therapy. When all 250 patients were analyzed, the median of the proportion of TSH values below the lower limit of normal (0.4 mU/liter) was 72%, and the median of the proportion less than 0.1 mU/liter was 50% (Table 2). No differences in these percentages were observed between the different TNM stages.

Thyroid cancer-related death. According to univariate Cox regression analysis, significant indicators for thyroid carcinoma-related death were extrathyroidal tumor extension (T4), the presence of distant metastases, and older age (Table 1). Significant TSH-related predictors for thyroid carcinoma-related death were the 50th percentile (HR: 2.03) and the percentage of TSH values above 4.5 mU/liter (HR: 1.06) (Table 3).

When the significant variables detected by univariate Cox regression analysis were introduced into a stepwise multivariate model, T4, M1, and older age remained significant predictors for thyroid carcinoma-related death (Table 1). For all cured patients, the 50th percentiles (HR: 2.14) of TSH values and the percentage of TSH values above 4.5 mU/liter (HR: 1.07) were significant independent predictors for thyroid carcinoma-related death (Table 3).

The effect of median TSH on thyroid carcinoma-related death became only discernable at a cutoff level of 2 mU/liter (Fig. 1). At cutoff levels of 0.1 and 0.4, no significant difference in thyroid carcinoma-related death was observed.

To investigate the relation of TSH in patients with recurrent and/or metastatic disease, whose tumor did or did not accumulate radioiodine, we studied the 38 patients with recurrence after initial cure. Of these patients, eight had metastases with radioiodine uptake. None of these patients died, whereas 12 of the 30 patients who had no uptake of radioiodine died. In an additional analysis in which we built an interaction term comprising TSH and radioiodine uptake,

TABLE 3. HRs of serum TSH levels for thyroid carcinoma-related death (A) and relapse (B) as calculated with Cox survival analysis

			Univariate analysis with single covariate		Stepwise analyses with significant covariates	
			P value	HR (CI)	P value	HR (CI)
A. Thyroid carcinoma-related death						
Total group	All stages combined	25th percentile	0.007	1.35 (1.08–1.69)	NS	
		Median TSH	0.028	1.22 (1.02–1.46)		
	T1–3 M0	Median TSH	0.044	1.63 (1.01–2.64)	NS	
Patients cured 1 yr after initial therapy	All stages combined	T4 M1	NS			
		NS				
	T1–3 M0	Median TSH	0.006	2.03 (1.22–3.37)	0.013	2.14 (1.18–3.89)
		Percentage TSH values > 4.5 mU/liter	0.009	1.06 (1.01–1.11)	0.021	1.07 (1.01–1.13)
T4 M1	NS					
B. Relapse						
	All stages combined	T1–3 M0	NS		0.033	1.41 (1.03–1.95)
		Median TSH	0.020	1.46 (1.06–2.01)		
		T4 M1	NS			

Only patients with ≥ 4 TSH values were included. NS, Not significant.

we found a HR for thyroid carcinoma-related death of 2.24 (CI 1.53–3.29) in patients without radioiodine uptake *vs.* patients in whom radioiodine uptake was present.

Relapse-free survival. According to univariate Cox regression analysis, significant indicators for relapse in patients who were cured 1 yr after initial therapy were extrathyroidal tumor extension (T4), the presence of distant metastases, and older age (Table 1). A significant TSH-related predictor was the 50th percentile (HR: 1.46) (Table 3).

When the significant variables obtained by univariate Cox regression analysis were introduced into a stepwise multivariate model, T4, M1, and older age remained significant predictors for relapse (Table 1). For all cured patients, the 50th percentile of TSH (HR: 1.41) was a significant independent predictor for thyroid carcinoma-related relapse (Table 3). The effect of median TSH on relapse became only discernable at a cutoff level of 2 mU/liter (Fig. 1). At cutoff levels of 0.1 and 0.4 mU/liter, no significant differences in relapse were observed (Fig. 1).

Discussion

In the present study we investigated the association between serum TSH concentrations in patients during follow-up for DTC, thyroid carcinoma-specific mortality and risk for recurrence. The study differed from earlier studies in the homogeneity of the patient group with respect to initial therapy (13, 15, 16), the study size, and duration of follow-up (14).

We found positive associations between serum TSH concentrations and risk for thyroid carcinoma-related death and relapse. In a multivariate Cox regression analysis model, in which tumor stage and age were also included, this association remained significant in patients who have been cured 1 yr after initial therapy. The median of the TSH concentrations in each patient appeared to be the best predictor for thyroid carcinoma-related death and relapse. However, subsequent analyses revealed that this effect became apparent at higher median TSH values (cutoff level of 2 mU/liter). No differences in risks for thyroid carcinoma-related death and relapse were observed between suppressed TSH levels (both

TSH < 0.4 and < 0.1 mU/liter) and unsuppressed TSH levels (TSH levels within the reference range). Even for initial tumor stage T1–3 and M0, median TSH was an independent predictor for thyroid carcinoma-related death. These results differ from the studies by Mazzaferri and Jhiang (13) and Cooper *et al.* (15), who did not find an independent relation between TSH and prognosis. Our patient group is comparable with the study by Pujol *et al.* (14). They found a difference in relapse between the extremes of TSH suppression (continuously undetectable *vs.* continuously unsuppressed). However, Pujol *et al.* (14) did not report the relation between TSH levels and thyroid carcinoma-related death. Our study results are in line with the recent report by Jonklaas *et al.* (16), who demonstrated that the degree of TSH suppression is a predictor of thyroid carcinoma-specific survival in high-risk patients, independent of radioiodine ablation therapy and the extent of thyroid surgery. Our analysis extends their findings in the respect that in patients who underwent total thyroidectomy and radioiodine ablation, and who were cured 1 yr after initial therapy, TSH remains an independent predictor for disease-specific survival. Our study confirms the findings of Jonklaas *et al.* (16), that this relation is only present at TSH levels in the higher normal range, so that sustained TSH suppression is not recommended in low-risk patients.

Because our study is based on retrospective data, the analyses might have been susceptible to bias. However, we could not find differences in summarizing parameters of serum TSH levels between high-risk and low-risk patients. In addition, differences in follow-up intensity between patients with higher and lower TSH levels could result in bias. However, the number of TSH measurements per year did not differ significantly between patients who died of thyroid carcinoma and who did not. Moreover, even if such a difference would have been present, lower, rather than higher, TSH levels would be expected in high-risk patients. Therefore, we believe that the results of our study are valid.

The percentage of patients reaching the target TSH range was lower than favorable (~73% below <0.4 mU/liter). We found no differences in TSH levels between high- and low-

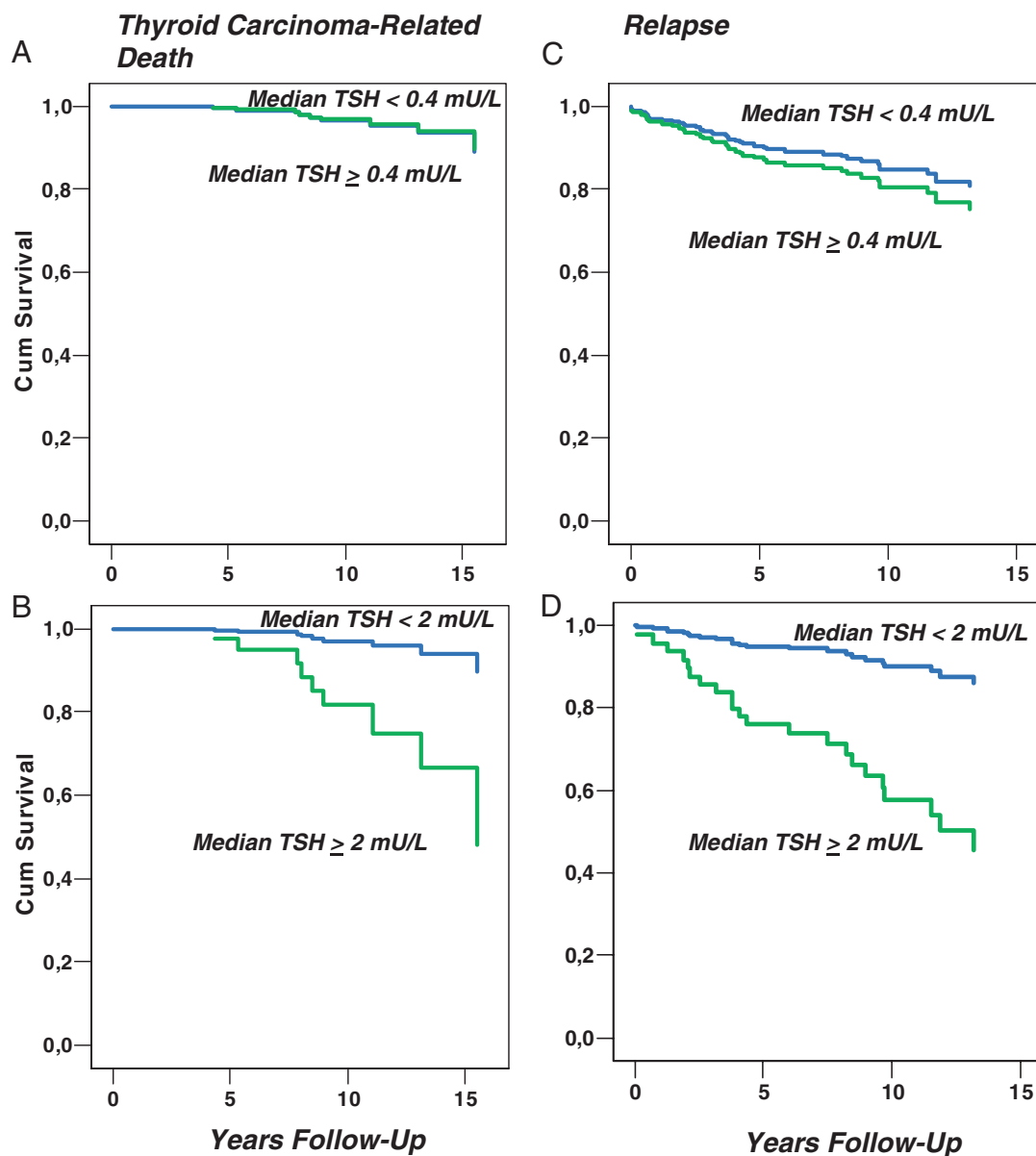


FIG. 1. Relation between the median (50th percentile) of serum TSH concentrations and thyroid carcinoma-related death and relapse in 250 patients who were cured 1 yr after initial therapy for DTC. A, Relation between a median serum TSH concentration cutoff value of 0.4 mU/liter and thyroid carcinoma-related death. B, Relation between a median serum TSH concentration cutoff value of 2 mU/liter and thyroid carcinoma-related death. C, Relation between a median serum TSH concentration cutoff value of 0.4 mU/liter and thyroid carcinoma relapse. D, Relation between a median serum TSH concentration cutoff value of 2 mU/liter and thyroid carcinoma-related relapse.

risk patients, so that physician-related differences in target TSH levels between high- and low risk patients is an unlikely explanation. Another explanation could be that over time, the physicians would have been less focused on keeping TSH at the target levels. However, we did not find any time dependency of TSH.

The results of our study, *e.g.* that the deleterious effects of TSH on thyroid carcinoma recurrence or thyroid carcinoma-related death become apparent above a median TSH of 2 mU/liter, provide a rationale for the advice in the recently published European and U.S. guidelines for the follow-up of thyroid carcinoma to aim at TSH levels in the lower normal

range (0.4–1 mU/liter) in low-risk DTC patients (19, 20) because unnecessary TSH suppression is associated with lower bone mineral density (17) and cardiac dysfunction (18, 24).

Although the relation between TSH levels and risk for thyroid carcinoma-related death or recurrence was also present in noncured patients and patients with an initially high risk, subgroup analysis did not reveal a safe TSH threshold in these patients. Because we found indications that the hazard of elevated TSH levels for thyroid carcinoma-related death is especially important in noniodine accumulating metastases, and given the findings of Jonklaas *et al.* (16), we

advise maintaining suppressed TSH levels (<0.1 mU/liter) in patient categories with initial high-risk and/or recurrent tumor.

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