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EDITORIAL

Prophylactic Central-Neck Dissection for Papillary Thyroid Carcinoma: A Thin Line between Benefit and Risk

In the September issue of *Thyroid*, Giordano and associates report a high rate of permanent hypoparathyroidism (16%) in patients undergoing prophylactic bilateral central-neck dissection (CND) during initial surgery for papillary thyroid carcinoma (PTC). (See the summary in this issue of *Clinical Thyroidology* on page 4.) (1). They propose a surgical strategy aimed at limiting prophylactic CND to the ipsilateral level VI compartment whenever possible. Prophylactic CND is currently the subject of vociferous debate among surgeons treating thyroid cancer, with valid arguments both for and against. Since the findings reported in the large, adequately powered, single-institution study by Giordano are a near-perfect reflection of the rest of the literature on the topic, this is an opportune moment to examine the benefits and risks of prophylactic CND in a distilled and dispassionate manner.

The central neck (level VI) contains approximately four to six lymph nodes per side. Though up to 70% of patients with PTC are observed to have microscopically positive nodes when prophylactic CND is performed routinely, only a small minority of these will manifest clinically as recurrences when CND is not performed routinely. The inferior parathyroid lies within the level VI territory and is jeopardized during CND; it can be accidentally removed or, more frequently, devascularized. Thus, autotransplantation of inferior parathyroid glands is standard practice when CND is performed. A technically well-executed parathyroid autotransplantation should result in a functional parathyroid within 6 weeks in 90% of cases. The recurrent laryngeal nerve runs obliquely through the center of the paratracheal area in the central neck. CND involves meticulous work right along the nerve to achieve compartmental clearance of the paratracheal nodes that flank the nerve. The above factors make CND technically demanding, so it is not surprising that most surgeons do not include prophylactic CND while performing thyroid cancer surgery.

The existing publications supporting prophylactic CND are all flawed to some degree. Because of the very large sample size and long-term follow-up required to demonstrate an oncologic benefit of prophylactic CND, a randomized, controlled trial on this topic is likely infeasible (2). So, retrospective studies are all we have for now. Several European studies have reported reduced cause-spe-

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cific mortality associated with prophylactic CND (3), though these results have been received with skepticism by many because of problems with study design and a sense that this conclusion may be biologically implausible. Recently, in a multicenter study involving 606 patients, Popadich et al. demonstrated that prophylactic ipsilateral CND reduced the rate of central-neck reoperation from 6.1% to 1.5% and was associated with lower stimulated thyroglobulin (Tg) levels (4). These beneficial effects were achieved without any increase in the long-term complication rate.

Arguments against prophylactic CND mainly concern hypoparathyroidism. Ipsilateral CND is associated with increased rates of temporary hypoparathyroidism but not permanent hypoparathyroidism. However, as reflected in the work by Giordano et al., bilateral CND is consistently associated with permanent hypoparathyroidism rates exceeding 5% or even 10%, figures that are generally considered unacceptable.

Like all surgical decisions, the issue of prophylactic CND boils down to the ratio of benefit to risk. But the key here is perspective: as survival rates in PTC are excellent, we are afforded the luxury of moving one rung up on Maslow's hierarchy of needs, into the realm of secondary end points such as recurrences, reoperations, Tg levels and hypoparathyroidism—all of which can be considered issues of convenience in comparison to the specter of cancer-specific mortality.

Patients who undergo prophylactic ipsilateral CND enjoy the convenience of avoiding reoperations and frequently enjoy the reassurance of undetectable stimulated Tg levels. In exchange, they take on the inconvenience of increased rates of temporary hypoparathyroidism. A growing minority of clinicians perceive this to be a trade that ends up in the patient's favor, particularly when considering that the surveillance process is often simplified in patients who have undergone prophylactic ipsilateral CND. In contrast, the risk:benefit profile of bilateral prophylactic CND is unfavorable. The high price of permanent hypoparathyroidism is not counterbalanced by any measurable oncologic gains (5).

Lastly, it is important to point out the influence of publication bias on this topic. The available evidence allows us only to conclude that ipsilateral prophylactic CND may be beneficial in the hands of expert surgeons. Given the technical challenges described above, CND should not be performed by the occasional thyroid surgeon. If it is to be performed at all, prophylactic CND should be performed ipsilaterally only, and by experts who will keep patients with thyroid cancer on the right side of the thin line between benefit and risk.

—Michael W. Yeh, MD
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Bilateral Central-Node Dissection with Total Thyroidectomy for Papillary Thyroid Cancer Often Results in Permanent Hypoparathyroidism

Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, Barbieri V. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 2012;22:911-7. Epub July 24, 2012.

SUMMARY

Background

Because the incidence of micrometastases to central lymph nodes in the neck is high in patients with papillary thyroid carcinoma (PTC), many surgeons perform routine prophylactic central-neck node dissection (CND) along with total thyroidectomy as the initial treatment for PTC. However, this is a controversial practice and is not recommended as routine surgery for PTC by any of the major societies concerned with this issue. The potential benefit is based on studies showing that lymph-node metastases may decrease survival and on the fact that many lymph-node metastases are microscopic and not evident grossly at surgery. However, CND may increase the frequency of recurrent laryngeal-nerve paralysis (RLNP) as well as hypoparathyroidism.

The aim of the current study was to characterize the frequency of temporary and permanent RLN damage and temporary and permanent hypoparathyroidism caused by CND in patients with PTC. In addition, the authors reviewed the literature on this controversial subject.

Methods

This is a retrospective study from a group of otolaryngologists at a single institution in Reggio Emilia, Italy. During 1980–1996, patients with PTC were treated with total thyroidectomy without CND unless there were clinically overt lymph nodes in the central or lateral neck. Since 1997, patients diagnosed by cytopathology as having PTC with clinically negative neck lymph nodes were treated by total thyroidectomy with concomitant prophylactic ipsilateral CND. Patients were excluded from the study if they had previous thyroid or parathyroid surgery or neck irradiation.

The study included 1097 patients divided into three groups. Group A comprised 394 patients who had total thyroidectomy alone; B, 385 patients who had total thyroidectomy and concomitant prophylactic ipsilateral CND without evidence of ipsilateral pretracheal and paratracheal lymph node metastasis on intraoperative frozen-section pathology; and C, 308 patients who had total thyroidectomy and concomitant prophylactic bilateral CND because of evidence of lymph-node metastases on intraoperative frozen-section pathology.

Vocal-cord motility was assessed preoperatively and postoperatively. The albumin-adjusted total serum calcium level was measured preoperatively and postoperatively. Transient hypoparathyroidism was defined as postoperative hypocalcemia with an albumin-adjusted total serum calcium level less than 8.0 mg/dl. Permanent hypoparathyroidism was defined as persistent hypocalcemia 6 months after surgery requiring calcium and vitamin D supplements.

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Table 1. Incidence of Transient and Permanent RLNP and Transient and Permanent Hypoparathyroidism (%).

Group	A	B	C	P Value*
Transient RLNP	3.6	3.9	5.5	0.40 (NS)
Permanent RLNP	1.0	0.5	2.3	0.10 (NS)
Transient hypoparathyroidism	28	36	52	See below
Permanent hypoparathyroidism	6	7	16	See below

* NS denotes not significant.

Results

There was no significant difference in the incidence of transient or permanent RLNP among the three groups (Table 1). There were no cases of bilateral permanent RLNP.

Transient hypoparathyroidism was significantly more frequent in groups B (P = 0.014) and C (P<0.001) than in group A. Permanent hypoparathyroidism was significantly more frequent in group C (P<0.001) than in group A or B.

Conclusions

Limiting prophylactic CND associated with total thyroidectomy for PTC to the ipsilateral side may represent an effective strategy for reducing the rate of permanent hypoparathyroidism.

ANALYSIS AND COMMENTARY

Prophylactic CND in patients with PTC is a contentious topic, as summarized in the discussion of this paper and in an excellent recent review (1) in which two prominent surgeons take divergent positions on this issue. In their review of the literature, the current authors found that the rate of transient RLN injury ranged from 0% to 7.3%, similar to the overall rate of 4.2% they reported in groups B and C together; the rate of transient hypoparathyroidism ranged from 14% to 60%, similar to their rate of 37.5%. In regard to the permanent complications, their rate of RLN damage was 1.2%, similar to the literature review, which showed 0 to 5%, and their rate of hypoparathyroidism of 9.4% was in line with the literature, which reports a rate ranging from 4% to 11%. In contrast with the current report, a meta-analysis of five studies, including 1132 patients studied by an English group, concluded that performing prophylactic CND at the same time as thyroidectomy resulted in no increased permanent morbidity (2).

It is important to note that, in the current study, the rate of permanent hypoparathyroidism increased only when bilateral CND was performed, and this procedure was necessitated by the finding of tumor in frozen sections of nodes that were sampled for this purpose. This prompts the question of whether the procedure is prophylactic when positive nodes led to the decision to perform bilateral CND. However,

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surgeons who do not favor CND probably do not perform sampling for frozen section of grossly normal nodes. Another limitation of this study is that the total thyroidectomy without CND in group A was performed in an earlier era, so that the groups are not truly comparable.

My current viewpoint is that I leave it to my excellent surgeon to make the decision about CND based on the findings at surgery, and I do not choose a surgeon for my patients based on this issue.

— Jerome M. Hershman, MD

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Are Hürthle-Cell Thyroid Cancers Really a More Aggressive Form of Thyroid Cancer?

Goffredo P, Roman S, Sosa JA. Hurthle cell carcinoma. Cancer. July 11, 2012 [Epub ahead of print]. doi: 10.1002/cncr.27770.

SUMMARY

Background

Hürthle-cell cancer (HCC) is an uncommon thyroid cancer. The World Health Organization (WHO) considers it a variant of follicular thyroid carcinoma. Because of the small numbers of tumors that present annually, there is very little data about the clinical outcome of patients with this cancer. Whether HCC is more aggressive than other forms of differentiated thyroid cancer has been debated for many years (1,2). The authors queried the Surveillance, Epidemiology, and End Results (SEER) database, which acquires data from 18 registries in the United States. These regions represent about 28% of the U.S. population and were selected to reflect the ethnic and socioeconomic characteristics of the entire country. The objectives of this study were to compare outcomes of patients with HCC with patients with other well-differentiated thyroid cancer (ODTC) and evaluate prognostic factors associated with survival at a population level.

Methods and Results

The SEER database was queried from 1988 to 2009. Patients prior to 1988 did not have complete data on the extent of surgery or use of radioactive iodine. Years of diagnosis were divided into 1988–1997, 1998–2006, and 2007–2009. A total of 3311 patients were identified with HCC and 59,585 patients with ODTC. HCC occurs more often in men (31.1% vs. 23% for ODTC, P<0.001) and older patients (mean age, 57.6 years, vs. 48.9 years for ODTC) than in patients with well-differentiated thyroid cancer (WDTC). SEER staging is defined as local (confined to the thyroid), regional (extends beyond the thyroid or has regional lymph nodes), and distant (metastases to extracervical nodes or organs). Patients with HCC presented at a higher SEER stage (P<0.001) and with larger tumors (36.1 mm vs. 20.2 mm for ODTC; P<0.001) than patients with WDTC. It is not clear why, but patients with HCC had total thyroidectomy less often than patients with WDTC (P = 0.028). Overall and disease-specific survival were lower for HCC as compared with WDTC (P<0.001) and have not improved over the past two decades (P = 0.689). The overall survival rate was 82.1% for patients with HCC and 89.2% for patients with ODTC. Disease-specific mortality occurred in 5.9% of patients with HCC and in 2.7% of patients with ODTC. When adjusted for age >45 years, poor prognosis was strongly associated with not having thyroid surgery and distant metastatic disease (hazard ratio, >3). Improved survival from HCC was associated with lower SEER stage, tumor confined to the thyroid, size <4 cm, and no lymph-node metastases. Administration of postoperative RAI was associated with reduced mortality (hazard ratio, 0.66; P = 0.005).

Conclusions

This population study based on the SEER database confirms that HCC has a more aggressive behavior and lower survival as compared with ODTC. Improved survival was associated with small tumors confined to the thyroid without local or distant metastases and with radioiodine therapy.

ANALYSIS AND COMMENTARY

This population study confirms that HCC is a more aggressive form of thyroid cancer. The information would have been more clinically relevant if the authors had compared HCC with follicular thyroid carcinoma rather than with all differentiated thyroid cancers (follicular and papillary thyroid carcinoma). The critical question is whether HCC is more aggressive

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than follicular thyroid carcinoma when compared by American Joint Committee on Cancer (AJCC) staging. Nevertheless, this population study confirms that HCC should be managed aggressively with the expectation of a worse disease-free survival than ODTC. It has always been a question whether RAI ablation therapy should be given for a tumor that is often not iodine-avid. At face value, this population study suggests that RAI ablation reduces mortality, but I suspect that patients who did not receive RAI also did not have thyroidectomy because of advanced local or distant metastatic spread. Thus, the patients who received RAI had lower-stage tumors and a better survival. This is supported by the authors who found after adjusting for "various" factors that RAI was not associated independently with long-term survival. I support the ATA guideline that suggests that RAI ablation of the thyroid remnant should be performed to improve early detection by revealing rising serum thyroglobulin levels (3).

— Stephanie L. Lee, MD, PhD

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The Prevalence of the BRAF(V600E) Mutation Is Increasing in Papillary Thyroid Cancers

Romei C, Fugazzola L, Puxeddu E, Frasca F, Viola D, Muzza M, Moretti S, Luisa Nicolosi M, Giani C, Cirello V, Avenia N, Rossi S, Vitti P, Pinchera A, Elisei R. Modifications in the papillary thyroid cancer gene profile over the last 15 years. J Clin Endocrinol Metab 2012;97:E1758-65. Epub June 28, 2012.

SUMMARY

Background

Activating mutations in the RET/RAS/RAF/MAPK signal-transduction pathways have been reported in a majority of papillary thyroid cancers (PTC) in recent years. RET rearrangements have been associated with radiation-related PTC, but BRAF mutations have not. However, BRAF mutations are associated with more aggressive disease and a worse outcome. The purpose of the current report was to evaluate the frequency of the BRAF(V600E) mutations and RET/PTC rearrangements in a large series of patients with PTC over a period of 15 years and to correlate these findings with other demographic and clinical characteristics.

Methods and Results

Patients with PTC treated in several Italian centers during the period from 1996 to 2010 were included and divided into three consecutive 5-year periods. In three centers, there were 401 patients who had analysis of their PTC for BRAF and RET/PTC as well as clinical and epidemiologic data. In addition, 459 patients with PTC from Sicily had only mutation analysis of the tumors. Individual and combined analysis of both groups showed a progressive increase in the frequency of BRAF mutations that was statistically significant. This was also true for the combined population of 860 patients. The prevalence of BRAF(V600E) mutations increased from 33.6% in 1996–2000 to 47.8% in 2001–2005 to 61.5% in 2006–2010 ($P<0.0001$) and the prevalence of RET/PTC rearrangements significantly decreased ($P<0.0001$) in the entire cohort.

During the 15-year period, there was a significant increase in age at diagnosis and a decrease in tumor size.

Conclusions

The oncogene profile of PTC has changed over the past 15 years, with a significant increase in the prevalence of BRAF(V600E) mutations and a decrease in RET/PTC rearrangements.

ANALYSIS AND COMMENTARY

The results in the current report from Italy confirm a report from California covering the period 1991–2005 in three 5-year periods; the prevalence of BRAF increased from 43% in the first 5-year period to 88% in the third (1) (reviewed in Clinical Thyroidology, July 2011). In a smaller cohort from Ireland of patients with PTC , an increase in prevalence of the BRAF mutation was found in tumors after 1997 versus those removed before 1997 (2).

For many years, it has been noted that iodine pro-

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phylaxis was associated with an increase in the ratio of papillary to follicular thyroid cancers. It should be noted that the mutations discussed above are found in PTC and not in follicular thyroid carcinoma. A higher prevalence of BRAF mutation was reported in regions of China with higher iodine intake as compared with regions with lower iodine intake (3). However, in the United States, the intake of iodine has been sufficient for many decades, so it is unlikely that higher iodine intake can explain the increased prevalence of the BRAF mutation in PTC. It is possible that thus far unrecognized environmental pollutants damage DNA, cause BRAF mutations, and are responsible for thyroid carcinogenesis, but this remains to be demonstrated.

— Jerome M. Hershman, MD

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Does TSH Directly Affect Serum Lipid Levels in Euthyroid Patients Whose TSH Levels Are in the Normal Range? A Review of Two Retrospective Studies Advocated in Support of this Concept

SUMMARY

Background

TSH regulates serum thyroid hormone levels, which in turn affect lipid synthesis, uptake, release, and degradation. However, can TSH affect lipid metabolism directly, independently of its effect on thyroid hormone levels? Clinically, one does sometimes see a patient with hypercholesterolemia whose TSH level is high, yet whose thyroid hormone levels are within the normal range, but many factors other than TSH could be involved. The TSH receptor can be detected in many cell types besides thyrocytes, and TSH does affect growth and functions in these cells in vitro. Several recent papers from Shandong University have been interpreted as showing that TSH directly affects serum lipid levels, even in patients with normal T_3 and T_4 levels. This group previously reported thought-provoking studies on rats, which showed that thyroidectomy raises the level of hepatic cholesterol and of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis. By giving L-T_4 to those rats, the serum cholesterol level was normalized, and the hepatic HMGCR level fell. However, if they also gave the rats TSH, hepatic HMGCR rose, indicating that TSH itself affects the expression of this protein in the liver (1). I review two recent retrospective clinical studies from the Shandong group that contend that TSH levels directly influence lipid levels in euthyroid patients.

STUDY 1

Wanjia X, Chenggang W, Aihong W, Xiaomei Y, Jiajun Z, Chunxiao Y, Jin X, Yinglong H, Ling G. A high normal TSH level is associated with an atherogenic lipid profile in euthyroid non-smokers with newly diagnosed asymptomatic coronary heart disease. Lipids Health Dis 2012;11:44.

Methods

Based on abnormalities noted on electrocardiograms (EKGs) and then confirmed by angiography, about 1000 asymptomatic patients (45 to 88 years old) were newly diagnosed to have coronary heart disease (CHD) between 2004 and 2010 in the Qianfoshan or Shandong Provincial Hospitals. Only patients who were clinically stable were candidates for study. Any patients taking medications that might affect thyroid or lipid metabolism; who had ever smoked; who were missing thyroid tests; who had renal, hepatic, or neurologic disease; or who had evidence of euthyroid sick syndrome (with a low reverse T_3) were excluded. This left 521 potential subjects, of whom 406 were used for the study. Thyroid-function tests were measured using an electrochemiluminescence detection assay (Roche Elecsys 2010). The laboratory reference range for TSH was given as 0.27 to 4.2 mIU/L, however the authors defined patients as euthyroid if their T_4 and T_3 levels were normal and their TSH was between 0.3 and 4.8 mIU/L. The patients were segregated into four (unequal) groups based on their TSH levels: 0.3 to 0.99 mU/L (79 patients); 1.0 to 1.89 (135), 1.9 to 2.49 (78), and 2.5 to 4.8 (114). Multiple linear regression and logistic-regression analyses were used to establish whether TSH levels within the euthyroid range were associated with total cholesterol, non–high density lipoprotein (HDL) cholesterol, and triglycerides.

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Does TSH Directly Affect Serum Lipid Levels in Euthyroid Patients Whose TSH Levels Are in the Normal Range? A Review of Two Retrospective Studies Advocated in Support of this Concept

Results

The FT_3 and FT_4 levels (all within the normal range) did not correlate significantly with log-transformed lipid levels in these asymptomatic patients with CHD, whereas the patients' TSH levels did correlate significantly with log-transformed total cholesterol, non–HDL cholesterol and triglyceride levels. The levels of FT_4, FT_3, uric acid, fasting blood glucose, diastolic or systolic blood pressure, and antibody positivity did not differ among the four TSH groups. Analysis of variance indicated that after adjusting for these potential confounding factors, each of the three groups with the higher TSH levels had significantly higher log-transformed cholesterol, triglyceride, and non–HDL cholesterol levels than those in the group with the lowest TSH levels. (One might note that the major rise occurred between the first and second TSH groups: the levels in the third and fourth groups were not much higher than in the second group. This was also true for the prevalence of cholesterol or triglyceride levels above 200 mg/dl).

Conclusions

After adjusting for sex, age, history of diabetes, fasting blood glucose, hypertension, alcohol intake, and uric acid (but not body-mass index), a logistic-regression analysis indicated that the TSH level was an independent factor predictive of increased lipid abnormality in these euthyroid nonsmokers with asymptomatic CHD. In some parts of the world, patients with a TSH level at the high end of the "normal range" cited in this paper would probably be categorized as having mild subclinical hypothyroidism; but even if this was the true diagnosis, the results do suggest that TSH levels are correlated with total cholesterol and triglyceride levels in a collection of euthyroid and almost-euthyroid patients with CHD. Obviously, lipid levels are only one of many actors, since even the patients in the group with the lowest TSH and lipid levels did have CHD, although they didn't have an "atherogenic lipid profile."

STUDY 2

Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, Zhang B, Guan Q, Xu J, Zhang J, Zhang D, Lin H, Yu C, Zhao J. Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. J Clin Endocrinol Metab 2012;97:2724-31. Epub June 22, 2012.

Methods

From 2004 to 2009, a total of 4848 patients came to the Shandong Provincial hospital for a routine health checkup. Thyroid-function tests were performed on blood obtained between 9 and 10 a.m., using an Advia Centaur Xp system (which others have found to give TSH results that closely agree with the results obtained with the Elecsys 2010 system used in the previous article). Patients were excluded if their TSH was outside the reference range (given as 0.27 to 5.5 mU/L); if FT_4, FT_3, total T_4, or total T_3 was outside its reference range; or if they were pregnant, had chronic liver or renal disease, or were taking medicine that might affect thyroid or lipid status. A total of 3709 subjects met these criteria; missing data were projected using expectation-maximization software, but the numbers for missing data were not provided. To offset the well-known correlations among FT_4, FT_3, total T_4 and total T_3, three "uncorrelated principal components" were derived from these four hormone determinations and accounted for almost 88% of variance, but they still correlated with the dependent variables. After the data were subjected to regression analysis involving two variables by one factor, 45 patients were excluded because the absolute value of their residual standard deviation was less than 3, leaving 3664 subjects in

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Does TSH Directly Affect Serum Lipid Levels in Euthyroid Patients Whose TSH Levels Are in the Normal Range? A Review of Two Retrospective Studies Advocated in Support of this Concept

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the study. The authors grouped the patients into six categories according to their TSH levels: in 3% of patients, the TSH was between 0.27 and 0.61 mU/L, in the next 24%, it was between 0.62 and 1.35, in the next 24% between 1.36 and 1.92, in the next 24% between 1.93 and 2.65, in the next 23% between 2.66 and 4.60, and in the last 2% between 4.61 and 5.50. Associations of TSH as a categorical variable with total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels were assessed using general linear analysis, after correcting for sex, age, body-mass index (BMI), smoking status, glucose levels, and thyroid-hormone levels. To validate results obtained with general linear analysis, a multivariable path analysis was also performed, which provided an assessment of both direct and indirect effects of each variable on total cholesterol levels.

Results

In the 95% of subjects comprising the four groups with TSH levels between 0.62 and 4.60 mU/L, the mean prevalence of hypercholesterolemia was about 15%. In the 2% with the highest TSH (4.6 to 5.5 mU/L), the prevalence of hypercholesterolemia was 26.7%, whereas in the 3% with the lowest TSH (0.27 to 0.61 mU/L), the prevalence was 10.7%. After adjusting for age, sex, BMI, smoking status, glucose levels, and thyroid-hormone levels, there was a slight but significant linear relation between the TSH levels and the log-transformed cholesterol ($P = 0.021$) and also the log-transformed triglyceride levels ($P<0.001$), independent of thyroid hormone levels. Multivariable path analysis to assess both direct and indirect effects of each variable indicated that FT_3, FT_4, sex, age, glucose level, BMI, and smoking had direct effects on total cholesterol levels. Total T_4 and T_3 had only indirect effects on the total cholesterol level (via FT_4 and FT_3). TSH had both a small direct effect on the total cholesterol level, as well as indirect components mediated via FT_3 and FT_4.

Conclusions

The complex multivariable pathway analysis indicates that a part of the effect of TSH on the cholesterol level in euthyroid patients is direct, which would support the contention that TSH can play an independent role in lipid metabolism, even when thyroid hormone levels are within the normal range.

ANALYSIS AND COMMENTARY

In the first clinical study, it is not clear why obesity was not included as a confounding variable, since it does appear to be associated with the TSH level in normal euthyroid individuals (2). In both studies, the ranges for normal TSH seem a bit wide, and thus the data obtained from patients whose TSH levels were near the outer limits could have influenced the results of the statistical analyses.

Several of the pathways involved in regulating the metabolism of intracellular and circulating lipids have been found to respond to TSH. Various cell types, including adipocytes, fibroblasts, monocytes, and vascular cells are also known to be TSH-responsive, so TSH could also be acting on lipid metabolism in many tissues in addition to the liver. One reason for studying hepatic HMGCR is that its gene's promoter does not contain a canonical thyroid-hormone response element, and the level of HMGCR messenger RNA in the liver takes 48 hours to respond to T_3. The HMGCR promoter does contain other response elements, including one for the cAMP response element (CRE) binding protein. The authors showed that a nuclear extract from hepatocytes treated with TSH used in an electrophoretic mobility assay caused

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more supershifting of HMGCR promoter by antibody to phosphorylated-CRE binding protein than nuclear extract from control cells (1).

Although the authors' previous laboratory study (1) is provocative, the two retrospective clinical analyses reviewed here do not yet provide unquestionable evidence that the TSH level in euthyroid patients regulates serum lipid levels and influences the prevalence of coronary heart disease.

— Stephen W. Spaulding, MD

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Clinical THYROIDOLOGY
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Serum TSH Levels in the Upper Normal Range Suggest That a Thyroid Nodule Is Malignant

McLeod DS, Watters KF, Carpenter AD, Ladenson PW, Cooper DS, Ding EL. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. J Clin Endocrinol Metab 2012;97(8):2682-92. Epub May 23, 2012.

SUMMARY

Background

Since Boelaert et al. in the United Kingdom first reported that serum TSH was a dose-related risk factor for thyroid carcinoma in thyroid nodules (1), there have been a large number of additional studies to evaluate this association. In the current study, the authors performed a systematic review of clinical studies that examined the relationship between serum TSH and the diagnosis of thyroid cancer.

Methods

The authors used MEDLINE and EMBASE to find appropriate articles. They required that each paper contain evidence of pathologically confirmed thyroid cancer as well as serum TSH concentrations and to have nested case controls in prospective, retrospective, or cross-sectional studies. Studies that consisted of only patients with thyroid cancer and no controls were excluded. To derive odds ratios (OR), they used the "aggregate generalized least squares for trend" method.

Results

Of the 6833 abstracts of articles obtained in the literature search, only 97 passed the screening phase and were read in full text. Of these, 28 studies were selected for systematic review; 22 of them included data that could be combined for meta-analyses. These 22 studies included 40,929 subjects and 5605 cases of thyroid cancer. Using a linear dose-response model, the pooled OR for higher serum TSH was 1.23 (95% CI, 1.11 to 1.37) per milliunit of TSH per liter. At a TSH of 3 mU/L, this model predicts an OR for thyroid cancer of 1.87 (95% CI, 1.36 to 2.55), and at 5 mU/L an OR of 2.83 (95% CI, 1.67 to 4.77). Because of considerable heterogeneity in the linear model, a spline model was constructed using data from 17 studies. The slope of OR vs. TSH was slightly steeper at a TSH of 0 to 1 mU/L, leading to the OR of a TSH <1.0 of 1.72 (95% CI ,1.42 to 2.07) per milliunit per liter; above a TSH of 1.0, the OR was lower, at 1.16 (95% CI, 1.12 to 1.21) per milliunit of TSH per liter in a spline analysis.

Interestingly, studies adjusting for autoimmune thyroiditis reported lower TSH-related OR for thyroid cancer; for TSH <2.5 mU/L , OR was 1.23 (95% CI, 1.02 to -1.47) per milliunit per liter and somewhat surprisingly, for TSH >2.5 mU/L, the OR was 0.98 (95% CI, 0.89 to 1.09) per milliunit per liter.

Conclusions

Higher serum TSH concentrations are generally associated with an increased risk of thyroid cancer.

ANALYSIS AND COMMENTARY

Presumably the data and conclusions apply to patients with thyroid nodules who are being evaluated for the possibility of thyroid cancer, but this assumption tended to get lost in the presentation of data. Nevertheless, the paper is a very useful and timely summary of the literature on this topic. In my analysis of their table summarizing the studies, I note that 15 of 25 studies show a TSH-related increase in the OR of cancer, frequently extending to supranormal serum TSH, but the lower confidence limit of the OR was often less than 1.0. As occurs with the additional power of meta-analysis, combining studies will often show significance that may be "lost" with smaller numbers of subjects. I like the linear analysis because it implies that the higher the TSH, the higher the chance of cancer in a nodule. The spline analysis showing that the OR per milliunit of TSH is higher with a TSH <1.0

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mU/L makes no clinical sense because in all but one of the various studies there is no increase in OR with TSH <1.0 mU/L; in fact, in most studies the authors set TSH <1.0 as the control OR of 1.0.

The authors carefully avoided recommending TSH suppression of nodules as a means of reducing the risk of thyroid cancer. However, one large study of 27,914 patients included in the analysis reported that patients with thyroid nodules treated with levothyroxine had a lower TSH and a lower frequency of papillary thyroid cancer than those not so treated (2). The authors also recommend that future studies should investigate the validity of using serum TSH for diagnostic nomograms in the evaluation of nodules. I think that the large body of data summarized by the authors already provides a basis for considering that a relatively low serum TSH suggests that a nodule is more likely to be benign and that a relatively high serum TSH, even if in the normal range or slightly above it, makes the nodule more worrisome, unless the patient has overt Hashimoto's disease. I also think the autoimmunity issue is fascinating and could well impact on the shape of the relationship between TSH and thyroid cancer. But, the fact that the TSH effect was attenuated after adjusting for thyroid autoimmunity suggests that thyroid autoimmunity, via hypothyroidism, may be driving the "TSH effect,", so it doesn't make Hashimoto's "less worrisome"; it just makes it an explanation for the TSH effect.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
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Differentiated Thyroid Carcinoma Is More Common in Reproductive Age Women but Is Not Clinically More Aggressive

Lee JC, Zhao JT, Clifton-Bligh RJ, Gill AJ, Gundara S, Ip J, Sywak MS, Delbridge LW, Robinson BG, Sidhu SB. Papillary thyroid carcinoma in pregnancy: a variant of the disease? Ann Surg Oncol. August 9, 2012 [Epub ahead of print]. doi: 10.1245/s10434-012-2556-3.

SUMMARY

Background

There are conflicting reports in the literature regarding the prognostic influence of pregnancy on patients with papillary thyroid carcinoma (PTC), and there is no literature on specific microRNA (miRNA) profiles of PTC in the context of pregnancy. The authors' aims were to determine whether pregnancy is an adverse factor in PTC and whether PTCs associated with pregnancy are biologically different from those in nonpregnant women in terms of their miRNA profiles. miRNAs are small molecules approximately 22 nucleotides in length; their profiles have been used to accurately identify the tissues of origin of poorly differentiated cancer tissues. In thyroid pathology, miRNA profiles have been used to classify thyroid tumor types and to differentiate malignant tumors from their benign counterparts.

Methods

Women diagnosed with PTC during or soon after becoming pregnant were recruited into the pregnancy group. Age-matched nonpregnant women were recruited into the nonpregnancy group. miRNA microarray was performed on the PTC tissue of pregnant patients (10), nonpregnant patients (10), and normal thyroids (5). There were 6 differentially expressed miRNAs from the microarray comparisons.

Results

There were 24 patients in the clinical pregnancy group (recruited between January 1995 and December 2010) and 30 in the nonpregnancy group (recruited between January 2004 and December 2005). Tumors from the pregnancy group were significantly larger and showed more regional lymph-node metastases. The microarray data showed a total of 27 miRNAs that were potential differentiators of PTC tissue samples from pregnant and nonpregnant patients. Of the 6 selected for validation, no significant difference in expression was found. There were no deaths in either group, and the disease-free survival rates were similar in the two groups (86.4 % in the pregnancy group vs. 91.3 % in the nonpregnancy group, P = 0.66), with mean lengths of follow-up of 44.7 and 44 months for the pregnancy and nonpregnancy groups, respectively. Also the rates of radioactive iodine ablation and mean doses given were similar in the two groups.

Conclusions

The data suggest that PTC during pregnancy may be more aggressive locoregionally. However, no difference in survival or recurrence is demonstrated. The miRNA profiles of the pregnancy-associated PTC have not been shown to be different from those of the nonpregnancy counterparts. This suggests that the differences seen clinically are related to patient factors rather than to the disease itself. The authors concluded that their data are in agreement with the majority of the published literature, which shows that pregnant women with PTC do not have a worse prognosis and that treatment can usually be delayed until postpartum, unless there are specific aggressive features or the malignancy is diagnosed very early in the pregnancy.

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Differentiated Thyroid Carcinoma Is More Common in Reproductive Age Women but Is Not Clinically More Aggressive

ANALYSIS AND COMMENTARY

About 10 % of thyroid cancers diagnosed during childbearing age occur during pregnancy or in the 12-month postpartum period (1). Thyroid cancer is reportedly the second most common malignancy diagnosed during pregnancy (second only to breast cancer), at a rate of 0.144 cases per 1000 births. Also, 75% of these women are diagnosed during the 12-month postpartum period (2). Based on current guidelines from the American Thyroid Association (3) and the Endocrine Society (4), thyroidectomy may be postponed until after delivery for patients diagnosed with PTC during pregnancy whose disease does not show any aggressive features, although surgery is recommended during the second trimester if aggressive features are present. The only long-term retrospective study with a significant number of patients to justify the above conclusions was published in 1997 by Moosa and Mazzaferri (5). The authors showed no difference in long-term outcome in a group of patients with PTC who were undergoing surgery during pregnancy, as compared with those who were treated surgically in the 12 months after delivery. Whether pregnancy by itself is a risk factor for increased aggressiveness of PTC is controversial. In women with no evidence of residual PTC, pregnancy by itself does not affect the natural course of the disease; however, patients with evidence of persistent disease may show progression during pregnancy (6,7). On the other hand, Vannucchi et al. reported on a small number of patients and showed the negative prognostic effect pregnancy has on patients with thyroid cancer, attributing it to the presence of estrogen receptor alpha (ERa) on the majority of pregnancy-associated thyroid cancers and its absence in papillary lesions in nulliparous women (8).

In summary, as the authors stated, in the presence of conflicting clinical data, prospective molecular studies may be helpful in determining whether PTC in association with pregnancy is a more aggressive variant of the disease. As with other thyroid pathologies in pregnancy, a prospective long-term multicenter clinical trial with the support of molecular markers could solve the present clinical dilemma confronting the physician advising a woman who is pregnant or planning a pregnancy about the best therapy for a newly diagnosed or previously treated differentiated PTC.

— Jorge H Mestman, MD

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Survivors of Childhood Malignant Hematopoietic Disorders Treated With Total-Body Irradiation Must Be Checked Periodically for the Appearance of Thyroid Abnormalities

Vivanco M, Dalle JH, Alberti C, Lescoeur B, Yakouben K, Carel JC, Baruchel A, Leger J. 2012. Malignant and benign thyroid nodules after total body irradiation preceding hematopoietic cell transplantation during childhood. Eur J Endocrinol 167:225-233. Epub May 22, 2012.

SUMMARY

Background

Many studies have documented a high frequency of benign or malignant thyroid nodules in children who have undergone irradiation for malignant diseases. Even though there is no unanimity, the prevailing opinion is that these nodules are more frequently malignant than nodules found in control populations. The risk increases with higher doses of irradiation. Additional unfavorable factors are young age at irradiation, the type of cancer treated, the type of chemotherapy, and the resulting immunodeficiency. Conceivably, the individual contribution of each of these factors can be more precisely defined by studying a rather homogeneous group of patients. Thus, the present study is focused on childhood malignant hematopoietic disorders who are receiving total-body irradiation (TBI) in advance of hematopoietic stem-cell transplantation. Even so, there is still some heterogeneity in this group of patients, since TBI can be given as one dose or as fractionated doses over 3 days.

Methods and Results

The retrospective study extended from 1989 to 2009. A total of 76 patients, representing 80% of the survivors, participated. The thyroid observation period varied from 2 to 19 years. The study included patients with major types of leukemia and one lymphoma. Fractionated doses of 1200 Gy were given over 3 days. In 12% of cases, the treatment included cranial irradiation. The criteria for performing thyroid investigations were not specified, and no protocol is provided. The patients were tracked by ultrasound. Nodules of less than 4 mm were considered micronodules. In those larger than 8 mm, fine-needle aspiration biopsy was performed.

During the observation period 21 patients (28%) with one or multiple thyroid nodules were identified. Children receiving TBI earlier in their life were more prone to the development of nodules, although this could be due to their being observed over a longer time span (9.9 years vs. 3.9 years). As illustrated in Figure 1 in the article, the incidence of thyroid nodules increased markedly during the 8 years following TBI, and this increase was mainly due to the appearance of benign nodules. There was no correlation between thyroid nodules and hypothyroidism; 71% of the nodules in the 21 affected patients were benign and 29% were malignant. The malignant nodules were larger than the benign ones, but over time all nodules grew. Therefore, the growth rate was not a reliable criterion for malignancy. Histology consistently revealed papillary cancer or the follicular variant of papillary cancer, and no follicular cancer was reported. Bilateral neck metastasis developed in one child, but no peripheral metastases were found. Treatment with ^{131}I was judged to be necessary in two cases. So far all patients are disease-free.

Conclusions

Short-term and lifelong monitoring, with ultrasound screening for nodules of the thyroid gland, is recommended for survivors who undergo TBI during childhood.

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Survivors of Childhood Malignant Hematopoietic Disorders Treated With Total-Body Irradiation Must Be Checked Periodically for the Appearance of Thyroid Abnormalities

Vivanco M, et al.

ANALYSIS AND COMMENTARY

Thyroid nodules in healthy children are extremely rare. They tend to appear in adolescents and are a common finding in adults. In patients followed after chemotherapy and/or irradiation for malignancies, benign and malignant thyroid nodules occur more frequently. Here we have the data for young patients who have undergone TBI for malignant hematopoietic disease. Since physical examination alone is unreliable, ultrasound investigation is required. The cumulative incidence of benign or malignant thyroid nodules increased greatly after the first 8 years of observation in this study. The growth rate for both benign and malignant nodules was similar; the doubling time varied between 2 and 8 years. No nodules remained unchanged in size.

This and other studies stress the point that thyroid nodules are much more frequent in patients, particularly children, who have been treated with TBI for a malignant hematopoietic disease. Since all patients received 1200 Gy, nothing can be said concerning the relationship between initial irradiation dose and the later risk of thyroid nodules developing, but it is known from the literature that the incidence of secondary cancers increases with increasing radiation dose. In this series, the occurrence of thyroid nodules over time was very high, reaching 28% at the end of the observation period. Approximately one third of all nodules were papillary thyroid cancers. In this small series the outcome of these cancers was excellent, which is in line with similar reports. There seemed to be a sudden rise in the cumulative incidence of thyroid nodules 8 to 10 years after irradiation. We do not know whether this is due to a more sophisticated ultrasound thyroid investigation, since during the years of observation this method had become a well-established routine.

In practice, it would appear to me that a routine ultrasound examination of patients such as those included in this study should be done every 2 to 3 years. For the moment, we do not know whether there is a reasonable upper time limit to the follow-up time. It is also important to include serum TSH measurement in the follow-up, so as not to miss hypothyroidism; this topic was mentioned only briefly in this article.

— Albert G. Burger, MD

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