The Prevalence of Occult Medullary Thyroid Carcinoma at Autopsy

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Context: The prevalence of occult medullary thyroid carcinoma (MTC) in the general population is unknown but may be important when considering strategies to diagnose clinically relevant MTC in nodular goiter or other populations.

Objective: Our objective was to determine the prevalence of occult MTC in a series of autopsies.

Design: We conducted a systematic review of autopsy series from 1970 to present using a PubMed search.

Patients: The patients came from 21 countries, ages ranged from 6–95 yr, both genders were represented, and none had clinical evidence of thyroid disease before autopsy.

Intervention: Three series were excluded based on tumor size less than 500 μm, non-English language, or insufficient information.

Main Outcome Measure: Prevalence of occult MTC was calculated.

Results: An average prevalence of 0.14 and 7.6% for occult MTC and papillary thyroid carcinoma, respectively, was found among 7897 autopsies from 24 published series. Greater than 75% of patients with MTC were more than 60 yr old, and male to female ratio was comparable. Tumor size was virtually all subcentimeter, and there was no lymph node spread, extrathyroidal extension, or distant metastases reported.

Conclusions: A small number of people in the general population, who do not have known thyroid disease, have occult MTC and die of other causes. This finding of untreated occult MTC without morbidity or mortality should be considered in population prevalence studies, when strategies to detect thyroid neoplasia are considered (*e.g.* serum calcitonin or ultrasound), and included in cost-effectiveness models of routine serum calcitonin screening for nodular thyroid disease. **(*J Clin Endocrinol Metab* 96: E109–E113, 2011)**

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor originating from the parafollicular C cells of the thyroid. C cells secrete calcitonin (Ct). Serum Ct levels are elevated in C-cell disorders, thus making it a sensitive clinical marker for MTC. MTC accounts for approximately 4% of all clinically detected thyroid malignancies (1, 2).

The natural history of occult sporadic MTC is largely unknown. However, once clinically apparent, the prognosis for MTC is mainly dependent on the age at diagnosis and the extent of the primary tumor, nodal disease, and distant metastases. The 10-yr survival rate for MTC for stages I, II, III, and IV disease is 100, 93, 71, and 21%, respectively (3), using a TNM (tumor-node-metastasis) staging system that predates the American Joint Committee on Cancer *Cancer Staging Manual, sixth edition* (47). Unfortunately, around 50% of patients at

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Abbreviations: C/E, Cost-effectiveness; Ct, calcitonin; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

initial presentation have lymph node involvement, and 20% of those patients have distant metastases (1, 4).

Since MTC was originally described, there has been minimal improvement in earlier detection of sporadic disease or in patient outcomes (2). Early detection is imperative for cure, which involves complete surgical resection and possible lymphadenectomy. Because of this, and the limitations of fine-needle aspiration biopsy to accurately diagnose MTC, there has been interest in the routine use of serum Ct level screening in the evaluation of nodular thyroid disease. Multiple studies in Europe have shown that routine serum Ct measurement in the initial evaluation of nodular thyroid disease may improve detection of earlier-stage MTC and possibly patient outcomes (5–9). Unfortunately, the positive predictive value for serum Ct screening is low, leading to concerns for unnecessary evaluation and possible treatment of patients without MTC. Rink *et al.* (10) found that using a higher cutoff value for serum Ct (15 ng/liter instead of 10 ng/liter) led to preserved sensitivity and reduced the false-positive rate. Still, 157 of their patients underwent thyroid surgery for suspected MTC, and only 28 cases were found with 15 of them measuring less than 1 cm in size.

Routine serum Ct screening is standard in the initial evaluation of thyroid nodules in Europe based on the 2006 European Thyroid Association guidelines and the 2010 American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association guidelines. The above guidelines state that measurement of basal serum Ct level may be a useful test in the initial evaluation of thyroid nodules (5, 11). Conversely, the 2009 American Thyroid Association guidelines for the management of thyroid nodules could not recommend for or against the routine measurement of Ct in the initial evaluation of thyroid nodules (12). This decision was based, in part, on a lack of convincing evidence that screening with serum Ct levels decreased MTC-related mortality, improved overall patient outcomes, or demonstrated cost-effectiveness (C/E).

An important decision model using hypothetical patients studied the C/E of adding routine serum Ct screening to the 2006 American Thyroid Association guidelines for nodular thyroid disease (13). The C/E in this model was found to be highly sensitive to patient age and gender, changes in disease prevalence, specificity of fine-needle aspiration and Ct testing, Ct screening level, costs of testing, and length of follow-up. It appears that correction of the overall disease prevalence for a background prevalence of clinically insignificant disease was not directly considered.

The prevalence of occult MTC in the general population is not well established. The purpose of this study was to better estimate the prevalence of occult MTC in the general population by analyzing published autopsy series. A background prevalence rate of occult MTC in the general population may suggest that some MTC never progresses to clinically significant disease. This may have implications when considering routine serum Ct screening and its C/E in nodular thyroid disease or other populations.

Materials and Methods

A systematic review of the autopsy literature was done via an extensive PubMed search. The keywords used to search were medullary thyroid carcinoma, occult thyroid cancer, occult papillary thyroid carcinoma, autopsy, and thyroid cancer. Only autopsy series published since 1970 were reviewed, 10 yr after the definitive histological description of MTC (2). Of the 27 autopsy series reviewed, 24 were included. Three were excluded based on tumors less than 500 μm (14), language other than English (14, 15), and insufficient information (16). An average prevalence of MTC was then calculated on the data from each included series.

Results

In the 24 autopsy series included, there was representation from 21 different countries from 1970–2006 (Table 1). The number of patients in each series ranged from 100-1167 for a combined total of 7897 patients. The patients' ages at autopsy were between 6 and 95 yr with 75% of patients over 60 yr. One autopsy series included only patients 20–40 yr old (17). The youngest patient with MTC was 28, and the oldest was 80, but most were between 60 and 80 yr old. On average, the ratio of men to women included in the autopsies was 3:2. There were insufficient data to determine any significant difference of MTC prevalence between the sexes. The size of MTC found was 1 cm or smaller. None of the patients had known thyroid disease before autopsy.

There were differences in the preparation and examination of the thyroid glands in several of the autopsy series. The most important differences were in size of slice thickness and how many slides were prepared from macroscopically normal tissue. The breakdown of slice thickness can be separated into three groups: 1–2 mm, 2–3 mm, and 3 mm or more. The percentage of autopsy series following these methods was 35% (18–23), 40% (17, 24–33), and 25% (28, 34–39), respectively. In all of the published series, gross abnormalities went to microscopy with routine hematoxylin and eosin staining. Only 9 of the 24 (37.5%) series performed a histological examination from each slice regardless of macroscopic appearance (17, 18, 27–32, 39). Additional staining for Ct was done in six series (17, 19, 23, 24, 28, 30). If a suspicious lesion was observed under the microscope, 16 of the 24 series used the World Health Organization classification system (40),

TABLE 1. Breakdown of prevalence, age, size, and country of origin by autopsy series

No. autopsy cases	No. MTC cases	% MTC	% PTC	Country (state)	Mean age (yr)	Size (mm)	Slice thickness (mm)	Year (Ref.)
100	0	0.0	24.0	U.S. (HI)	NA	NA	3[a]	1971 (39)
157	1	0.6	5.1	U.S. (MN)	64	<1.5	2–3	1974 (25)
274	1	0.4	2.9	Chile	78	10 × 5	2–3	1974 (33)
1167	0	0.0	12.0	Intl[b]	NA	NA	2–3[a]	1975 (32)
600	0	0.0	1.0	Portugal	NA	NA	3	1979 (34)
500	4	0.8	6.4	Sweden	75% > 60	<10	1–2	1981 (19)
260	0	0.0	4.2	Israel	NA	NA	1–2	1981 (21)
101	0	0.0	35.6	Finland	NA	NA	2–3[a]	1985 (27)
1020	1	0.1	6.1	Germany	ND	<10	1–2	1987 (23)
138	1	0.7	2.9	U.S. (WI)	28	8.0	2[a]	1988 (17)
300	0	0.0	1.0	Brazil	NA	NA	3	1989 (38)
100	0	0.0	11.0	Argentina	NA	NA	2	1989 (26)
408	0	0.0	15.7	Japan	NA	NA	3	1990 (35)
199	1	0.5	6.0	Iceland	ND	3.7	2–3[a]	1992 (30)
444	0	0.0	9.0	Singapore	NA	NA	1–2[a]	1992 (18)
625A	1	0.2	4.6	Spain	68	5.0	3	1993 (28)
100B	0	0.0	22.0	Spain	NA	NA	2–3[a]	1993 (28)
215	1	0.5	8.8	Belarus	62	2.6	2–3	1993 (24)
162	0	0.0	10.8	Ukraine	NA	NA	2–3[a]	1996 (29)
118	0	0.0	8.6	Austria	NA	NA	2–3[a]	2001 (31)
160	0	0.0	5.6	Greece	NA	NA	3–5	2002 (36)
150	0	0.0	2.0	Guatemala	NA	NA	1	2005 (20)
433	0	0.0	5.0	Hungary	NA	NA	1–2	2005 (22)
166	0	0.0	7.8	Brazil	NA	NA	3	2006 (37)

A and B denote two series done by Martinez-Tello *et al.* (28) to compare two separate methods of autopsy examination. ND, No data available; NA, not applicable.

[a] Entire gland sent for microscopy.

[b] Canada, Poland, Columbia, Japan, and U.S. (Hawaii).

four used the Hazard (41) criteria for carcinomas, and the remainder were not documented. There was no extrathyroidal spread of MTC tumors documented. Six series reviewed cervical lymph nodes microscopically if a carcinoma was found during autopsy (23, 26, 32, 34, 35, 39), two series explicitly stated that cervical lymph nodes were not examined (24, 36), whereas this was not clear in the remainder.

The MTC prevalence ranged from 0–0.8% (Table 1). The average MTC prevalence calculated from the autopsy data were 0.14% (number of MTC cases/total number of patients) (17–39). When each autopsy series is weighted equally, the average prevalence is 0.16%. For comparison, the average papillary thyroid cancer (PTC) prevalence calculated from the autopsy data were 7.6% (number of PTC cases/total number of patients). When each autopsy series is weighted equally, the average PTC prevalence is 9.0%. Sixteen of 24 autopsy series reported a 0% prevalence of MTC (18, 20–22, 26–29, 31, 32, 34–39). The average prevalence rate was also calculated with more strict exclusion criteria. When excluding series with slice thickness of 3 mm or more, absent immunohistochemistry for Ct detection, and lack of entire thyroid gland examination, the prevalence rates are 0.18% (28, 34–39), 0.33% (17, 19, 23, 24, 28, 36), and 0.08% (17, 18, 27–29, 31, 32, 39), respectively. For comparison, the PTC prevalence was 8.4 and 12.0% when excluding series with slice thickness of more than 3 mm and not examining the entire thyroid gland, respectively. The MTC prevalence was 0.42% including only the studies that examined the entire gland microscopically and used Ct staining (17, 28).

Discussion

Once MTC has metastasized, most patients are not able to be rendered free of disease (2). Currently, early detection and treatment appear imperative for a complete cure. Potential earlier detection of MTC and improvement in patient outcome by adding serum Ct screening to the evaluation of thyroid nodules continues to be controversial based on issues of C/E when no prospective randomized trial has been performed, and the hypothetical models must contend with the unknown natural history of small tumors. These concerns regarding the natural history of occult disease have seen recent significant changes in the approach to screening for several malignancies. Most notable are guideline changes regarding breast and prostate cancers that discourage detecting occult disease in populations that may not benefit from its treatment (42, 43).

This review of 24 autopsy series since 1970 was done to better estimate the prevalence rate of occult MTC in the general population. In this analysis of 7897 autopsies, an MTC prevalence of 0.14% was found, and the size of most MTC was subcentimeter. Data to determine the prevalence of MTC by decade of life were lacking. When only investigations that examined the entire thyroid gland microscopically and used Ct staining were included, the prevalence of MTC was 0.42% (17, 28).

There are limitations to analyzing and extrapolating from autopsy series, which include selection bias (older population age), operator and facility variability during the autopsy, lack of standardized diagnostic criteria and methods of autopsy examination, and inability to determine when disease first manifested or its rate of growth. It remains unknown whether the prevalence rates would change if all studies had systematically examined the entire gland with Ct staining (as was the case in only two of the 24 studies reviewed) and whether patients would have had clinically significant progression of their disease had they not died from other causes.

A recent important hypothetical model of C/E for routine Ct screening in nodular thyroid disease was published (13). This model for C/E is highly sensitive to changes in disease prevalence. A decrease in MTC prevalence results in decreased C/E. The authors used a disease prevalence of 0.78% in their base-case analysis. However, this prevalence was skewed by the inclusion of one series with a prevalence of 2.8% (44). Excluding the series with the highest and lowest prevalence would have given an overall prevalence of 0.59%. Including all series, had these authors calculated the disease prevalence using number cases/total patients, then their prevalence would have been 0.47%. If one assumes that occult MTC found in autopsy series represents clinically insignificant MTC in the general population (as it was for those patients autopsied) and subtracts this prevalence from the prevalence found in nodular goiter to determine the prevalence of possibly clinically significant MTC, then this adjusted prevalence would be $0.47 - 0.14 = 0.33\%$. Such a decrement in prevalence would make the C/E model nearly 2.4-fold less C/E and raise the cost per life-year saved to more than $27,000 compared with $11,793 per life-year saved when the prevalence estimate was 0.78%. The recent publications of Rink *et al.* (10) and Herrmann *et al.* (45) that report the prevalence MTC in the setting of nodular goiter as 0.18 and 0.20%, respectively, support the use of a lower prevalence estimate and demonstrate prevalence values very similar to those reported from autopsy series.

Knowing the prevalence of occult MTC in the general population may have implications in other areas as well. A newly approved (by the U.S. Food and Drug Administration) antidiabetic medication, liraglutide [a GLP-1 (glucagon-like peptide-1) receptor agonist], has been found to cause MTC in rodents who receive eight times the exposure amount that humans receive (46). The prevalence rate of occult MTC in the general population may be important in the evaluation of liraglutide and its potential to cause MTC, or its affect on occult MTC, or if clinicians elect to obtain baseline and/or serial Ct values and/or ultrasound examinations in these patients despite the Food and Drug Administration's warning that it is unknown whether such monitoring will mitigate risk and that such monitoring may lead to unnecessary interventions.

Conclusions

A small number of people in the general population have occult MTC and die of other causes. Whether or not these tumors would have eventually become clinically significant is unknown. The possibility that these tumors would have remained indolent suggests that such tumors should be taken into account when considering diagnostic tests that may detect both clinically relevant and irrelevant cases of MTC.

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