# Analysis of the lower incidence of medullary thyroid cancer in China

**Min Huang[1], Giuseppe Fanciulli[2], Shu-Qiong Wu[1], Zheng Zhang[1], Jing Zhang[1]**

[1]Department of Endocrinology, The Affiliated Xinhua Hospital of Hubei University of Chinese Medicine, Hubei Provincial Hospital of Integrated Chinese and Western Medicine, Wuhan, Hubei 430015, China;

[2]Neuroendocrine Unit, Department of Medical, Surgical and Experimental Medicine, University of Sassari, Sassari, Viale San Pietro, 07100 Sassari, Italy.

*To the Editor:* Thyroid cancer, which is one of the most common diseases of the endocrine system, can be divided into four primary types, including papillary thyroid cancer (PTC) accounting for 80% to 90% of cases, follicular thyroid cancer accounting for 10% to 15% of cases, medullary thyroid cancer (MTC) accounting for 3% to 10% of cases, and anaplastic thyroid cancer accounting for 1% to 2% of cases. Typically, patients diagnosed with PTC or follicular thyroid cancer have better prognoses and overall survival rates than patients diagnosed with MTC or anaplastic thyroid cancer. The incidence of thyroid cancer has been rapidly growing in the world [Supplementary Figure S1, http://links.lww.com/CM9/A99].[1] During the last 20 years, China has experienced significant growth in the number of annual thyroid cancer diagnoses. According to the Dataset Records for National Central Cancer Registry of China, thyroid cancer incidences have steadily increased in China from 2010 to 2014, yet the mortality rate has remained stable during the same period [Supplementary Tables S1 and S2, http://links.lww.com/CM9/A99]. As of 2015, China accounts for approximately 16% of all new thyroid cancer cases and 14% of thyroid cancer-associated deaths in the world.[2]

MTC is a neuroendocrine tumor that arises from the uncontrolled proliferation of thyroid C cells. There are two primary forms of MTC, including sporadic MTC accounting for 75% to 80% of cases and hereditary MTC (hMTC) accounting for 20% to 25% of cases. hMTC is caused by germline-activating mutations of the rearranged during transfection (RET) proto-oncogene. In addition, hMTC can be further classified as multiple endocrine neoplasia type 2A (MEN2A) or multiple endocrine neoplasia type 2B (MEN2B), with each type arising from different mutations within the RET proto-oncogene. Given the genetic background of MTC, the search for genes associated with this disease is of critical importance to identify patients and families more likely to develop MTC. Genetic screening should be recommended for the direct family members and offspring of patients with MTC, yet some physicians do not recommend genetic screening due to financial or availability concerns. Many lower-income family members are unable to afford genetic testing, while other patients do not want to know their status.

The standard diagnostic method for MTC was previously established [Figure 1]. Despite some advances, the early detection of MTC remains a hindrance to its successful treatment and eradication in the clinic. While other thyroid cancers primarily affect middle-aged adults, MTC occurs in younger adults (18–25 years of age) with more than 90% of patients being diagnosed before 50 years of age. However, some patients with MTC can go undiagnosed for decades as the disease progresses slowly with minimal physical symptoms, until the tumor has metastasized or grown large enough to affect the surrounding vasculature. Advanced-stage MTC is characterized by dysphagia, dysphasia, and dyspnea, which are symptoms produced by the mass impingement, extension, and invasion of the tumor into the adjacent organs. Nearly two-thirds of patients with MTC show signs of metastatic disease when initially diagnosed with the majority of patients presenting with cervical or mediastinal lymph node metastases. In addition, approximately 5% of cases have distant metastases of the liver, lungs, bones, brain, or skin when initially diagnosed.

The incidence of MTC varies across countries. MTC accounts for 1% to 2% of thyroid cancers in the United States and 1% to 3% in the United Kingdom. In China, it was reported that the proportion of patients diagnosed with PTC had increased from 2004 to 2013 in the Guangzhou. However, the percentage of MTC cases decreased during this same period, ranging from 2.03% in 2004 to 0.42% in 2013.[2] In another study, Du *et al*[3] reported a significant increase in the proportion of PTC

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000463

**Correspondence to:** Dr. Jing Zhang, Department of Endocrinology, The Affiliated Xinhua Hospital of Hubei University of Chinese Medicine, Hubei Provincial Hospital of Integrated Chinese and Western Medicine, 11 Lingjiaohu Road, Wuhan, Hubei 430015, China
E-Mail: 1025823309@qq.com



Chinese Medical Journal 2019;132(20)

**Received:** 02-07-2019 **Edited by:** Yi Cui

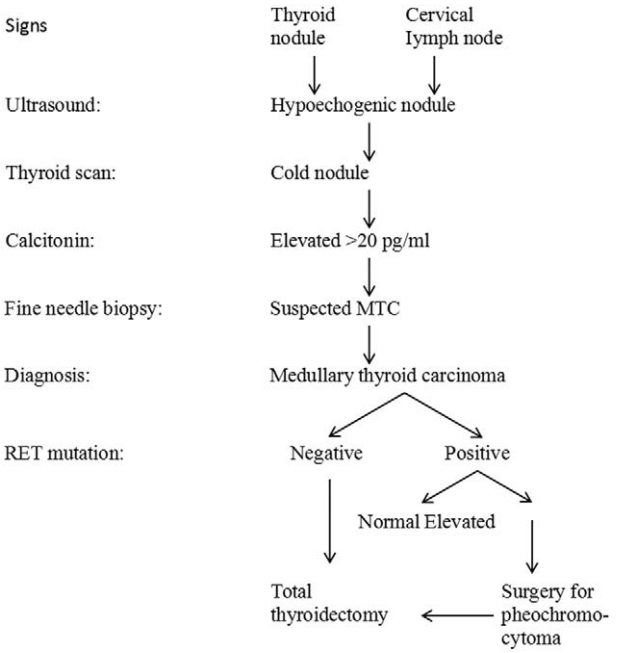


**Figure 1:** Clinical evaluation of patients with suspected MTC. MTC: Medullary thyroid carcinoma; RET: Rearranged during transfection.

between 1972 and 2014, along with a reduced percentage of MTC cases.

As a subtype of PTC, papillary thyroid microcarcinoma (PTMC) was first introduced by the World Health Organization in 1989. PTMC often has a maximum diameter of 1.0 cm and comprises more than 50% of new thyroid cancer cases diagnosed each year. PTMC is commonly found during autopsies of patients who died from non-thyroid-related diseases. Recently, the over-diagnosis and over-treatment of PTMC were debated by leading researchers in the field. However, the over-discrimination of PTMC has always existed.

In comparison to PTMC, MTC often goes undiagnosed for years as most patients are asymptomatic. In addition, patients with early stage MTC may have normal results from thyroid function tests, which hinder the diagnosis and treatment of the disease. For example, only a portion of patients with MTC secrete adrenocorticotropic hormone, which can lead to Cushing syndrome, during the early stages of MTC. Previously, Gordon *et al*[4] described a male patient who was initially diagnosed and treated for non-small-cell lung adenocarcinoma, yet genomic profiling revealed a well-known RET point mutation associated with MTC. In another study, Mass *et al*[5] reported a case of an 11-month-old child having MEN2B that was misdiagnosed as familial dysautonomia. The child was not accurately diagnosed with MEN2B until the age of 6. These case studies demonstrate the importance of correctly identifying thyroid cancers in patients.

For this study, we conducted a literature search of MTC cases to determine why the incidence of MTC is lower in China when compared with other developed countries. Using PubMed and Embase, we uncovered 199 articles through September 2018. Although there are many limitations such as the quantity and quality of the included paper in this review, from our findings, the lower incidence of MTC in China may be attributed to a combination of three factors. First, there are more cases of PTMC (tumors less than 1.0 cm) diagnosed in China than Western countries, which effectively reduces the portion of MTC cases. Second, high-risk patients in China are less likely to undergo genetic screening for MTC. Last, China lacks a large-scale national statistical analysis of MTC.

In China, the prevalence of thyroid cancer was 9.29/100,000 in 2014. Currently, there is a need for improved strategies to detect early stage MTC. The diagnosis and treatment of MTC require multidepartment collaborations in endocrinologists, general surgeons, pediatricians, nuclear medicine physicians, radiologists, oncologists, pathologists, and clinical laboratory specialists. The multidisciplinary team provides an opportunity for improved patient care and the development of personalized treatment plans. This interdisciplinary approach can lead to improved patient care worldwide.

## Funding

This study was supported by a grant from the Health Commission of Hubei Province Scientific Research Project (No. WJ2019F166).

## Conflicts of interest

None.

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**How to cite this article:** Huang M, Fanciulli G, Wu SQ, Zhang Z, Zhang J. Analysis of the lower incidence of medullary thyroid cancer in China. Chin Med J 2019;132:2516–2517. doi: 10.1097/CM9.0000000000000463