THYROID NODULES: GLOBAL, ECONOMIC AND PERSONAL BURDEN

[1]Khalimova Z.Yu., [2]Dadakhanova M.B.

[1,2]Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan named after academician. Y.H.Turakulov, Tashkent Pediatric Medical Institute, Department of Endocrinology, Pediatric Endocrinology

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Abstract. *Thyroid nodules have received attention due to changes in population surveillance systems and growing concerns about the associated financial burden on health care systems, payers, and patients. In this review, we found that prevalence rates vary widely depending on detection method and may be particularly pronounced in asymptomatic patients undergoing routine screening. Incidence rates may particularly increase in low- and middle-income countries and may decrease in higher-income countries. Over the past few decades, the evaluation and treatment of thyroid nodules has become more complex with the advent of fine-needle aspiration biopsy, specialized biomarkers, and molecular testing. However, gaps remain in risk stratification, which can lead to significant treatment costs. Some molecular tests, such as the Afirma Gene Sequencing Classifier, can result in diagnostic costs of US$17,873 while achieving only a modest reduction in the number of diagnostic lobectomies performed on patients (from 11.6% to 9.7% in one research). The out-of-pocket costs associated with treating thyroid nodules continue to result in significant financial toxicity for patients, especially for people with thyroid cancer. Additional cost-effectiveness analysis is needed to improve current treatment systems for thyroid nodules, and new clinical tools are needed to avoid unnecessary testing and treatment.*

Keywords: *thyroid gland, nodules, formations.*

Thyroid nodules have received attention due to changes in population surveillance systems and growing concerns about the associated financial burden on health care systems, payers, and patients. In this review, we found that prevalence rates vary widely depending on detection method and may be particularly pronounced in asymptomatic patients undergoing routine screening. Incidence rates may particularly increase in low- and middle-income countries and may decrease in higher-income countries.

Despite the high incidence rate, survival rate for papillary thyroid cancer is still as high as 97%. Over the past few decades, the evaluation and treatment of thyroid nodules has become more complex with the advent of fine-needle aspiration biopsy, specialized biomarkers, and molecular testing. However, gaps remain in risk stratification, which can lead to significant treatment costs. Some molecular tests, such as the Afirma Gene Sequencing Classifier, can result in diagnostic costs of US$17,873 while achieving only a modest reduction in the number of diagnostic lobectomies performed on patients (from 11.6% to 9.7% in one research).

The out-of-pocket costs associated with treating thyroid nodules continue to result in significant financial toxicity for patients, especially for people with thyroid cancer. Financial toxicity is defined as a term that describes how the direct and indirect medical costs of cancer treatment place a burden on patients and households through decreased income, assets, and spending on essential items. Recent research suggests that such toxicity can lead to adverse financial consequences such as foreclosure and bankruptcy. Additional cost-effectiveness analysis

is needed to improve current treatment systems for thyroid nodules, and new clinical tools are needed to avoid unnecessary testing and treatment.

Increasing rates of thyroid nodule detection have prompted an assessment of the global, economic, and patient burden associated with the evaluation and treatment of benign and malignant diseases. The global burden of thyroid nodules reflects differences in population surveillance among countries, which has resulted in differences in the incidence of thyroid nodules.

For payers, disparate healthcare coverage systems present unique economic considerations related to funding the costs of testing and treating thyroid nodules. . High out-of-pocket costs also lead to patient concerns about diagnostic testing and treatment of thyroid nodules. Here we describe what is known about the global, economic, and patient burden associated with the treatment of thyroid nodules and outline strategies to mitigate the social and financial consequences associated with potentially unnecessary or unrelated care.

The prevalence of thyroid nodules in the general population is estimated to be more than 67% depending on the method of detection (palpation, ultrasound, or autopsy) and varies widely between countries (1–3). Prevalence ranges from 34% to 66% depending on ultrasound detection rates or autopsy findings (2, 4). Female gender, higher body mass index (BMI), and older age are associated with an increased prevalence of thyroid nodules (5, 6). Although high prevalence rates suggest a significant disease burden, most thyroid nodules are benign or lack ultrasound features suggestive of malignancy and are thus largely clinically insignificant (7, 8). In assessing the mechanism of nodule diagnosis globally, Sajisevi et al. found differences across participating countries (9).

Rates of diagnosis of nodules secondary to symptomatic manifestations were much higher in South Africa and Denmark, at 79% and 54%, respectively, whereas rates were similar and much lower in the United States and Canada, around 30% (9). However, in the United States and Canada, thyroid surgery has been performed more frequently in asymptomatic patients, which has significant implications when considering effective treatment of nodules without overtreatment (9).

The widespread adoption of sensitive imaging techniques has contributed to an increase in the detection rate of incidental thyroid nodules (10). Because of the relatively indolent nature of thyroid nodules, the major clinical challenge is to exclude malignancy. Thus, comprehensive diagnostic evaluation of thyroid nodules primarily aims to determine clinical significance while avoiding overdiagnosis and overtreatment (11, 12). Of the nodules detected, 10–15% are malignant (11). Worldwide, the incidence of thyroid cancer has increased substantially with the proliferation of thyroid ultrasound, raising concerns about overdiagnosis of subclinical thyroid disease. In the United States, the incidence of thyroid cancer tripled from 1975 to 2009 (13), which is reminiscent of trends in other countries such as South Korea (14, 15). The increase is primarily due to increased detection of low-risk subclinical papillary thyroid microcarcinoma (14). Survival rates remain at 97% for papillary thyroid cancer, the most common type of thyroid cancer (16). From 1978 to 2007, mortality rates declined steadily in most countries, with mortality rates reported to have declined by 43.2% for men and 50% for women (17). Additionally, it was noted that during this time, the largest reductions in mortality rates were observed in men in China and women in Australia (17). Taking into account the declining mortality rate, despite rising incidence,

further supports concerns about overdiagnosis and overtreatment of thyroid cancer on a global scale (16).

The upward trend in incidence began to reverse first in South Korea in 2014. when the number of nodules detected decreased by 30% in response to fewer screenings and resulting fewer diagnoses (15).

Similarly, recent results from the Global Burden of Disease Study showed that between 2011 and 2019, incidence rates began to stabilize in the EU15+ countries and the United States (18).

However, in low- and middle-income countries, incidence rates continue to rise (19). Although the incidence may be declining in high-income countries, the overall incidence of thyroid cancer remains highest in these countries, with the largest number of cases occurring in China, the United States, and India (18, 20). In addition, there are significant differences in reported rates around the world. For example, there is a fivefold difference in the incidence of thyroid cancer in women in different regions of the world (17). Despite regional differences in incidence by sex, the observed female to male ratio is relatively stable across all regions at 3:1 (17).

Possible factors contributing to regional differences include barriers to access to health care, higher levels of radiation exposure, and iodine deficiency present in some low- and middle-income countries (20, 21). This suggests that while over screening and overdiagnosis may contribute to high incidence in high-income countries, variability in other parts of the world may be a true increase in incidence due to environmental exposures or modifiable risk factors. However, recent work examining trends in thyroid cancer mortality in the United States found that incidence mortality may increase by as much as 1.1% annually for all patients with thyroid cancer and by 2.9% for advanced papillary thyroid cancer (22). Thus, to accurately characterize the burden of thyroid nodules, additional studies of thyroid cancer incidence and mortality that control for demographic and tumor characteristics may be required.

Economic burden of treating thyroid nodules

Although the global burden of disease is frequently reported, the economic burden associated with thyroid nodules is only partially understood. By 2030, differentiated treatment costs for thyroid cancer in the United States are projected to exceed $3.5 billion for nodules presenting with malignant disease (23). The majority (41%) of healthcare costs are spent on newly diagnosed patients.

Initial diagnosis and evaluation, including primary care visits, endocrinologist/surgeon consultations, ultrasound imaging, and fine-needle aspiration (FNA) biopsies contribute to the economic burden of treating thyroid nodules in both benign and malignant conditions.

American Thyroid Association (ATA) guidelines suggest that FNA is the most cost-effective method for evaluating thyroid nodules and also recommend ultrasound guidance, which has been shown to provide better diagnostic accuracy than palpation alone (24–26). For incidental thyroid nodules smaller than 2 centimeters, the cost-effectiveness of FNA appears to be low compared with observation ($542 versus $412 in direct costs) (27).

Previous cost-effectiveness analyzes estimated that screening and treating all thyroid nodules in the United States would cost $25.1 billion, and adding specialized biomarkers such as serum calcitonin for medullary thyroid cancer to current ATA recommendations could add 1.4 dollar. billion in costs, amounting to an average of $11,793 per life-year saved (28).

Instead of routinely using additional testing, other studies of the cost of thyroid nodule evaluation have considered adding molecular testing only for individuals with indeterminate thyroid nodules based on initial FNA cytology results (29), which account for 20–30% of FNA results. Yip et al found that although molecular testing added $104 per patient to the cost of diagnosing thyroid nodules, cost savings were achieved by reducing the proportion of diagnostic lobectomies compared with standard care (from 11.6% to 9.7%) (29). Afirma Gene Sequencing Classifier™ and ThyroSeq™ are two nucleic acid-based molecular tests that use gene expression profiling and/or genotyping of tumor-associated genetic mutations to attempt to determine the likelihood that samples represent malignancies (28–31).

The cost-effectiveness of molecular testing also varies between Afirma, which may be more costly than lobectomy (30), and ThyroSeq v3, which was shown in a single-center Canadian study to reduce the number of diagnostic lobectomies (31).

A comparison study of both molecular testing options found that for indeterminate nodules, both Afirma and ThyroSeq v3 were more cost-effective than lobectomy, but ThyroSeq v3 gave a cost per diagnosis of US$14,277 compared to US$17,873 for the gene sequencing classifier Afirma (32). Molecular tests may be used more often in the United States than in other countries. However, due to the relatively recent emergence and development of molecular testing, the extent to which the use of such tests varies across countries has not yet been fully characterized.

Although intraoperative frozen section analysis is not routinely performed, it may also contribute to the economic burden of treating thyroid nodules and includes potential costs for testing, labor, lengthy operating room time, and in some cases, completed thyroidectomy (33, 34).

One meta-analysis found that frozen section analysis has only moderate diagnostic value (sensitivity, 95% CI: 43%, 34%-53%), and its routine use is not recommended for follicular neoplasms (34).

Instead, a separate cost analysis found that routine use of frozen sections for patients with cytology "suspicious for malignancy" at the time of thyroid lobectomy could actually reach a cost of $474 per case, primarily due to a significant reduction in the rate of subsequent total thyroidectomy compared with standard treatment (7.7% vs. 26.1%) (35).

The financial burden of treating thyroid nodules falls on the patient

Finally, the financial burden of thyroid disease on the patient was assessed using both out-of-pocket costs and perceived financial toxicity as primary indicators. Out-of-pocket costs are driven by surgical treatment of thyroid disease, which are substantial for both benign and malignant conditions and are pronounced even for commercially insured patients (15). However, out-of-pocket costs for patients who do not undergo surgical treatment of thyroid nodules remain due to the diagnostic implications of incidental discovery, including active surveillance that includes laboratory testing and repeat imaging. Patients who self-identify as over diagnosed with thyroid cancer but choose nonintervention are at risk for refusal of care and decreased quality of life (36). Current estimates of perceived financial burden are based primarily on cohort and cross-sectional studies of thyroid cancer patients, which showed that 46.1% of patients endorsed psychological financial burden and 28.1% of patients endorsed material financial burden (37). There is also evidence of home strain associated with patients' thyroid cancer diagnosis and treatment: 48% of patients reported a decrease in income, 9% lost insurance coverage, and 18.1% reported unemployment for at least 6 months (38, 39).

Treatment for thyroid cancer is also associated with adverse financial outcomes, including a higher likelihood of notice of default, foreclosure, and bankruptcy compared to other types of cancer (40, 41). Notably, the bankruptcy rate is estimated to be 41% 5 years after diagnosis, despite high survival rates (98% 5 years after diagnosis) (42).

We previously summarized the financial burden of thyroid cancer and outlined a framework for improving research aimed at measuring and mitigating the financial burden of treatment (43).

Additionally, evidence suggests that overdiagnosis and overtreatment of thyroid cancer may also worsen patients' health-related quality of life (HRQoL).

Thyroid cancer survivors report decreased psychological and emotional well-being due to treatment-related anxiety and depression, and these symptoms may persist during remission as patients often fear cancer recurrence (44). For patients undergoing thyroidectomy, the costs of surveillance may also contribute to decreased quality of life and excessive out-of-pocket costs, especially since the cost of detecting a single recurrence is estimated to be US$147,819 (45, 46). As we have summarized previously, the costs of diagnosing and treating thyroid cancer cause many patients to delay care and may risk the costs of treating other diseases that contribute significantly to improving health, quality of life, and length of life (43).

Conclusion. A recent retrospective analysis found that 41% of patients undergoing surgical treatment of thyroid nodules had no thyroid-related symptoms at the time of discovery, and the mean tumor size was smaller in asymptomatic patients (2.1 cm) compared with symptomatic patients (3.2 cm). (9). An additional meta-analysis found that 68.8% of all thyroid nodules undergoing surgical excision were benign (47). This suggests that increased detection of benign and subclinical diseases may lead to excess healthcare costs. Diagnostic workup of thyroid nodules usually includes ultrasound imaging and FNA for nodules considered suspicious for malignancy based on sonographic features.

In the United States, the American College of Radiology Risk Stratification System (TIRADS) is used to guide the subsequent management of thyroid nodules undergoing sonographic evaluation (48). This scoring system creates categories and biopsy thresholds for FNA consideration based on malignancy risk, but does not additionally include cost-effectiveness estimates or stratify by thyroid cancer subtype. The latter is especially important given the significant differences in 5-year relative survival between patients with follicular and medullary thyroid cancer compared with papillary thyroid cancer (49).

Thus, there are likely many patients with borderline radiographic features (i.e., TR2 and TR3 classifications) who still undergo unnecessary FNA despite the low risk of malignancy and potentially little benefit from earlier detection of indolent types of follicular thyroid cancer. Likewise, the Bethesda classification system for thyroid cytopathologies may lead to unnecessary thyroid surgery in many patients with indeterminate typical FNA findings (50), and controversy remains about whether molecular testing significantly reduces the cost of treating indeterminate nodules, the high cost testing Afirma and ThyroSeq v3. One potential factor is the clinical concern that the risk of malignancy in pathologically analyzed specimens is underestimated (50). Although thyroid cancer incidence rates in the United States have begun to stabilize following changes in ATA guidelines, disability-adjusted life years have not yet improved, which may reflect suboptimal risk stratification and higher average health care costs compared with other countries (18).

High treatment costs suggest a different risk calculus to evaluate the risks and benefits of thyroid cancer treatment, especially since patients incur significant out-of-pocket costs for diagnostic testing, surgery, and follow-up. It is important to note that patients with thyroid cancer continue to be at risk for adverse financial, physical, and psychological consequences. difficulties that may impair quality of life more than some untreated forms of thyroid cancer, such as papillary thyroid microcarcinoma, which are unlikely to cause symptoms or metastasize. Moreover, these risks do not appear to decrease during remission, as patients continue to incur costs due to surveillance and experience the burden associated with fear of relapse

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