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Thyroid nodules: Global, economic, and personal burdens

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Thyroid nodules have garnered attention due to changes in population surveillance systems and rising concerns about the associated financial burden on healthcare systems, payers, and patients. In this review, we find that prevalence rates vary widely based on method of detection and may particularly pronounced in asymptomatic patients undergoing routine screening. Incidence rates may be particularly rising in lower-income and middle-income countries and may be declining in higher-income countries. Despite high incidence rates, survival rates continue to be as high as 97% for papillary thyroid cancer. Over the last few decades, thyroid nodule workup and management has grown more sophisticated with the advent of fine-needle aspiration biopsy, specialized biomarkers, and molecular testing. However, gaps remain in risk stratification that can lead to substantial costs of care. Certain molecular tests, such as the Afirma Gene Sequencing Classifier can lead to a cost per diagnosis of \$17,873 while achieving only mild decreases in diagnostic lobectomies for patients (11.6% to 9.7% in one study). Out-of-pocket costs associated with thyroid nodule management continue to drive significant financial toxicity for patients, especially for individuals with thyroid cancer. Financial toxicity has been defined as a term that describes how direct and indirect medical costs of cancer care strain patients and households via decreased income, assets, and spending on basic necessities. Recent studies suggest that such toxicity can lead to adverse financial outcomes, such as foreclosure and bankruptcy. Additional cost-effectiveness analyses are needed to improve existing thyroid nodule management systems and new clinical tools are needed to avoid unnecessary workup and management.

KEYWORDS

thyroid nodule, cost effectiveness, financial burden, healthcare policy and management, economic impact

Introduction

Increasing rates of thyroid nodule detection has prompted assessment of the global, economic, and patient-borne burden associated with the evaluation and treatment of benign and malignant disease. The global burden of thyroid nodules reflects differences in population surveillance across countries that has led to variation in thyroid nodule

incidence rates. For payers, disparate systems for covering healthcare costs yields unique economic considerations associated with financing the costs of thyroid nodule workup and management. High out-of-pocket costs also lead to patient concerns with managing diagnostic workup and treatment of thyroid nodules. Here, we describe what is known about the global, economic, and patient-borne burdens of thyroid nodule management and outline strategies for mitigating the societal and financial implications associated with potentially unnecessary or extraneous care.

Global burden of thyroid nodules

The prevalence of thyroid nodules among the general population has been estimated as upwards of 67% depending on mode of detection (palpation, ultrasound or autopsy) and varies widely by country (1–3). Prevalence ranges between 34% to 66% depending on ultrasound detection rates or autopsy findings (2, 4). Female sex, 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 burden of disease, most thyroid nodules are benign or have no ultrasound features to suggest malignancy and thus are largely clinically insignificant (7, 8). When evaluating mechanism of nodule diagnosis on a global scale, Sajisevi et al. found variation across participating countries (9). Rates of nodule diagnosis secondary to symptomatic presentation were much higher in South Africa and Denmark at 79% and 54%, respectively, while rates were similar and much lower in the United States and Canada at around 30% (9). However, thyroid surgery was performed more often in asymptomatic patients in the United States and Canada which has substantial impact when considering the effective management of nodules without overtreatment (9).

The widespread adoption of sensitive imaging techniques has contributed to the increasing frequency of detection of incidental thyroid nodules (10). Due to the relatively indolent nature of thyroid nodules, the primary clinical concern is excluding malignancy. Thus, the complex diagnostic assessment of thyroid nodules largely pertains to determining clinical significance while avoiding overdiagnosis and overtreatment (11, 12). Of detected nodules, 10–15% represent malignant disease (11). Globally, incidence rates of thyroid cancer have grown substantially with the adoption of widespread thyroid ultrasound use, which has raised concerns of the overdiagnosis of subclinical thyroid disease. In the United States, the incidence of thyroid cancer tripled from 1975 to 2009 (13), which resembles trends in other countries, such as South Korea (14, 15). Increases are largely due to increasing detection of low-risk subclinical papillary thyroid microcarcinoma (14). Survival rates have remained as high as 97% for papillary thyroid cancer, the most common type of thyroid cancer (16). From 1978 to 2007, mortality rates steadily declined in most countries with reported mortality rate reductions of 43.2% for men, and 50% for women (17). Further, men in China and women in Australia were noted to have the largest decreases in mortality rates during this time (17). Consideration of the falling mortality rates despite the rising incidence further supports the concern for overdiagnosis and overtreatment of thyroid cancer on a global scale (16).

The trend of rising incidence began to regress first in South Korea in 2014 with a 30% reduction in nodule detection in response to less screening, and as a result, less diagnosis (15). Similarly, recent findings from the Global Burden of Disease Study found that incidence rates have started to plateau in EU15+ nations and in the US between 2011 and 2019 (18). However, in low- and middle-income countries, incidence rates have continued to rise (19). Although the incidence in high-income countries may be decreasing, overall rates of thyroid cancer are still highest in these countries with the most incident cases in China, the United States, and India (18, 20). Further, significant variability in reported rates exists globally. For instance, there is a fivefold difference in thyroid cancer incidence rates in women across various regions of the world (17). Despite the regional variation in incidence by sex, the observed female to male ratio is relatively consistent across all regions at 3:1 (17). Possible contributing factors to the regional variation include barriers to access to health care, higher levels of radiation exposure, and iodine deficiency present in certain low- and middle-income countries (20, 21). This suggests that although over screening and overdiagnosis could be contributing to the high incidence in high-income countries, the variability in other parts of the world may be a true rise in incidence due to environmental exposures or modifiable risk factors. However, recent work on US trends in thyroid cancer mortality has suggested that incidence-based mortality may be growing by as much as 1.1% annually for all thyroid cancer patients and 2.9% for advanced-stage papillary thyroid carcinoma (22). Therefore, robustly characterizing the burden of thyroid nodules may require additional research on thyroid cancer incidence and mortality that accounts for demographic and tumor characteristics.

Economic burden of thyroid nodule care

While the global burden of disease has been frequently reported, the economic burden associated with thyroid nodules is only partially understood. For nodules representing malignant disease, the costs of well-differentiated thyroid cancer care in the United States are projected to exceed \$3.5 billion by 2030 (23). The plurality (41%) of healthcare expenditures is incurred for newly diagnosed patients. Initial diagnosis and evaluation, including primary care provider visit, endocrinology/surgical consultations, ultrasound imaging, and fine-needle aspiration biopsy (FNA) drive the economic burden of thyroid nodule management for both benign and malignant disease. American Thyroid Association (ATA) guidelines suggest that FNA is the most cost-effective method for evaluating thyroid nodules and further recommends ultrasound guidance, which has been shown to achieve better diagnostic accuracy than palpation alone (24–26). For incidental thyroid nodules that are less than 2 centimeters, the cost-effectiveness of FNA appears poor compared to observation (\$542 vs. \$412 in direct costs) (27).

Prior cost-effectiveness analyses have estimated that the screening and management of all thyroid nodules in the United States would incur \$25.1 billion in costs, and the addition of specialized biomarkers, such as serum calcitonin for medullary thyroid cancer, to current ATA guidelines could add \$1.4 billion in costs, which

would represent a mean \$11,793 per life-year saved (28). Rather than routine use of adjunct testing, other studies of the cost of thyroid nodule evaluation considered adding molecular testing only for individuals with indeterminate thyroid nodules based on initial FNA cytology results (29), which represent 20–30% of FNA results. Yip et al. found that while molecular testing added \$104 per patient to the costs of thyroid nodule diagnostic workup, cost savings were realized by a decrease in the proportion of diagnostic lobectomies compared to standard care (11.6% to 9.7%) (29). The 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 malignancy (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 comparative study of both molecular testing options suggested that for indeterminate nodules, both Afirma and ThyroSeq v3 were more cost-effective than lobectomy, but ThyroSeq v3 yielded a cost per diagnosis of \$14,277 compared to \$17,873 for the Afirma Gene Sequencing Classifier (32). Molecular tests may be used more often in the United States than in other countries. However, due to the relatively recent emergence and evolution of molecular testing, the particular extent to which the use of such tests varies between countries has not yet been fully characterized.

Although not routinely performed, intraoperative frozen section analysis can also be a driver of the economic burden of thyroid nodule management and includes potential costs from testing, labor, extended operating room time, and completion thyroidectomies in some cases (33, 34). One meta-analysis suggested that frozen section analysis offered only moderate diagnostic utility (sensitivity, 95% CI: 43%, 34%–53%) and routine use should be discouraged for follicular neoplasms (34). A separate cost analysis instead suggested that routine use of frozen section for patients with “suspicious for malignancy” cytology during thyroid lobectomy could actually achieve costs of \$474 per case, primarily due to a large reduction in rates of subsequent total thyroidectomy compared to standard care (7.7% vs. 26.1%) (35).

Patient-borne financial burden of thyroid nodule management

Finally, the patient-borne financial burden of thyroid disease has been assessed using both out-of-pocket costs and perceived financial toxicity as primary metrics. Out-of-pocket costs are driven by the surgical management of thyroid disease, which are substantial for both benign and malignant conditions and pronounced even for commercial insured patients (15). However out-of-pocket costs for patients who do not undergo surgical management for thyroid nodules remain due to the diagnostic sequelae of incidental detection, including active surveillance which includes lab testing and recurrent imaging. Patients who self-identify with overdiagnosed thyroid cancer but opt for nonintervention are at risk for healthcare disengagement and lower quality-of-life (36). Current estimates of the perceived financial burden rely primarily on cohort and cross-

sectional studies of thyroid cancer patients, which have shown that 46.1% of patients endorse a psychological financial burden and 28.1% of patients endorse a material financial burden (37). There is also evidence of household strain associated with thyroid cancer diagnosis and treatment on patients with 48% patients reporting reduced income, 9% losing insurance coverage as well as 18.1% reporting unemployment for at least 6 months (38, 39). Thyroid cancer care has also been associated with adverse financial outcomes, including a higher likelihood of notice of default and foreclosure and bankruptcy compared to other cancer types (40, 41). Notably, bankruptcy rates have been estimated to be as high as 41% at 5 years after diagnosis despite high survival rates (98% at 5 years after diagnosis) (42). Previously, we have summarized the financial burden of thyroid cancer and outlined frameworks for improving research designed to measure and mitigate the financial burden of care (43).

Evidence further suggests that overdiagnosis and overtreatment of thyroid cancer can also impair health-related quality of life (HRQoL) for patients. Thyroid cancer survivors cite declines in psychological and emotional well-being due to anxiety and depression associated with treatment, and these symptoms may persist during remission because patients often fear recurrence of cancer (44). For patients who have undergone thyroidectomy, surveillance costs can also contribute to reduced quality of life and excess out-of-pocket spending, especially since the cost to detect 1 recurrence has been estimated at \$147,819 (45, 46). As we have summarized previously, the costs of thyroid cancer diagnosis and treatment lead many patients to delay care and may risk spending on other medical conditions that contribute substantially to improved health, quality of life, and lifespan (43).

Discussion

Recent retrospective analyses have found that 41% of patients undergoing surgical treatment for thyroid nodules have no thyroid-referable symptoms at the time of detection, and the mean tumor size is smaller in asymptomatic patients (2.1 cm) compared to symptomatic patients (3.2 cm) (9). An additional meta-analysis showed that 68.8% of all thyroid nodules undergoing surgical excision represented benign disease (47). This suggests that increasing detection of benign and subclinical disease may be generating excess healthcare costs. The thyroid nodule diagnostic workup routinely involves ultrasound imaging and FNA for nodules considered suspicious for malignancy based on sonographic features. In the United States, the American College of Radiology Thyroid Imaging Reporting and Data System (TIRADS) risk stratification system is used to guide subsequent management of thyroid nodules undergoing sonographic evaluation (48). This points system creates categories and biopsy thresholds for consideration of FNA based on risk of malignancy but does not additionally incorporate cost-effectiveness estimates nor stratifies by thyroid cancer subtype. The latter is particularly important considering the significant differences in 5-year relative survival rates between patients with follicular and medullary thyroid cancer compared to 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 low malignancy risk and potentially little benefit from earlier detection of indolent follicular

thyroid cancer types. In an analogous fashion, the Bethesda classification system for thyroid cytopathology may lead to unnecessary thyroid surgery in many patients with indeterminate typical findings from FNA (50), and there remains debate as to whether molecular testing substantially reduces the costs of care for indeterminate nodules given the high costs of Afirma and ThyroSeq v3 testing. One potential driver is clinical concern that the risk of malignancy for pathologically analyzed samples is underestimated (50). Although thyroid cancer incidence rates have started to plateau in the US after changes in ATA recommendations, disability-adjusted life years have not yet improved which may reflect suboptimal risk stratification and higher average healthcare expenditures relative to other countries (18).

The high costs of care in the United States imply a different risk calculus for assessing the risks and benefits of thyroid cancer care, especially since patients bear substantial out-of-pocket costs for diagnostic workup, surgical management, and surveillance. Importantly, thyroid cancer patients remain at risk for adverse financial outcomes and material and psychological hardship that could impair quality of life more than certain untreated forms of thyroid cancer, such as papillary thyroid microcarcinoma, that are unlikely to produce symptoms or metastasize. Furthermore, these risks do not appear to abate during remission, as patients continue to incur costs due to surveillance and experience burden associated with the fear of recurrence. Therefore, thyroid nodule management may need to be tailored in the United States to the unique healthcare system reimbursement structure and high patient-borne costs of care compared to countries with single-payer systems or alternative

payment schemes in which patients pay a smaller proportion of household income towards medical care.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

Author NU reports income from Ironwood Medical Information Technologies, Quantified Ventures, and BrightEdge within the prior 3 years that is outside of the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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