Addressing Thyroid Cancer Overdiagnosis with Diagnostic Changes and Individualized Treatments

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Writer's Comment: The scientific research community has made great strides in uncovering the mechanism of cancer development at the molecular level over the past two decades. The challenge now faced by researchers is determining how this knowledge can be applied to the development of robust cancer treatments. My literature review, written for Amy Goodman-Bide's UWP 102B course, addresses recent therapeutic discoveries in the context of treating papillary thyroid carcinomas. This form of malignancy is accompanied by a very low risk of mortality, yet has become increasingly prevalent in developed countries like the United States. Surgical removal of the affected thyroid gland has long been considered the "best" treatment for papillary thyroid cancer; however, I believe that the burden associated with the management of this cancer can be significantly mitigated by further investigation into potentially less invasive pharmacological options. Optimization and expansion of the treatment profile for papillary thyroid carcinoma is more possible than ever before given our continually growing knowledge of the interplay between molecular and cell biology.

Instructor's Comment: Lucas Hallman's final literature review for UWP 102B asks a timely question about the impact of expanding diagnostic capabilities in medicine. When he began researching the topic, Lucas wanted to explore current treatments for thyroid cancer, but soon discovered that there was a greater question of whether the very tools that have helped diagnose papillary thyroid carcinoma may also have led to overdiagnosis and possibly unnecessary treatment.

Throughout the term, Lucas was willing to be flexible with his initial interest and go where the literature led, including researching the history of diagnostics for thyroid cancer and changes in treatment over time. Doing that required many extra hours researching, reading articles, and revising, but the outcome was worth it. Lucas has written a strong, clear review that is a great example of what happens when writers dive into the process of researching and writing.

—Amy Goodman-Bide, University Writing Program

Abstract

Widespread public fear was the result of a dramatic increase in thyroid cancer incidence initially documented in the early 1990s. The response in many developed countries was the implementation of extensive thyroid cancer screening programs without consideration of the potential for overdiagnosis. Overdiagnosis of thyroid cancer is of particular concern because the treatment often involves surgical removal of the thyroid gland, which carries the risk of complications. In cases of low-risk thyroid cancer, this aggressive form of treatment does not adequately reflect the severity of the disease. This review addresses the potential cause for overdiagnosis of thyroid cancer, the adjustments that have been made to diagnosis of the disease, and alternative therapeutics being developed to expand treatment options. There is strong evidence that the advancement of diagnostic capabilities of ultrasound and fine-needle aspiration have uncovered an increasing number of small, indolent papillary thyroid carcinomas. Between 29 and 69 percent of these cancers are caused by mutational activation of the signaling molecule $BRAF^{V600E}$ in thyroid papillary cells. This mutation can be identified by performing genetic profiling on a biopsied specimen of a suspicious thyroid nodule. Treatment of patients with $BRAF^{V600E}$ positive papillary thyroid cancer without thyroidectomy is increasing in possibility as a greater array of targeted therapeutics are developed. In addition, an assortment of homeopathic medicines are being explored as a means to oppose the onset of malignancy. Risk of overdiagnosis may be reduced as treatment options expand and are tailored to the specific histology of each thyroid cancer.

Introduction

Thyroid cancer incidence has rapidly increased over the last few decades and is projected to be the fourth most common cancer in the world by 2030 (Jegerlehner et al., 2017). The increase in incidence is primarily attributed to diagnoses of papillary thyroid carcinoma (PTC). PTC is the least aggressive and often indolent histologic subtype of thyroid cancer (Raue & Frank-Raue, 2016). The overdiagnosis of PTC is a possibility because many patients with this low-risk disease will opt to undergo unnecessary, high-risk thyroidectomies (Haymart et al., 2019). In order to mitigate the damage associated with overdiagnosis, researchers are searching for the underlying cause of the increase in PTC incidence. Empirical evidence has supported the hypothesis that the cause is the enhanced ability of diagnostic capabilities to detect PTC (Haymart et al., 2019, and Nagar et al., 2014). These diagnostic technologies, which include ultrasound paired with fine-needle aspiration (FNA), were clinically standardized only as recently as the early 1990s (Nagar et al., 2014). This timing is consistent with the time frame in which thyroid cancer incidence began to rise sharply. In response to this knowledge, the American Thyroid Association has adjusted diagnostic criteria for PTC to safely address the growing number of new cases (Haugen et al., 2016). Molecular profiling of PTC is now widely used in clinical practice due to recent discoveries into the genetic mutations that cause the disease (Raue & Frank-Raue, 2016). The specific mutations that are uncovered can be treated with novel targeted pharmaceuticals and homeopathic medications. These emergent treatment options have the potential to reduce the psychological, financial, and physical burden associated with a PTC diagnosis. In this review, I will explain how PTC is being overdiagnosed, the refinements being made to the diagnostic criteria and diagnosis, and the potential of new treatment options.

Evidence and implications of overdiagnosis

In their 1933 article, Black and Welch correctly predicted that the increased use of diagnostic imaging would result in the overdiagnosis of thyroid cancer (Schnadig, 2018). Schnadig defines overdiagnosis as the detection of a medical condition that is essentially harmless. In their analysis of thyroid cancer registry data from Switzerland between 1998–2012, Jegerlehner et al. (2017) found that the increase in the incidence

rate of thyroid cancer was essentially attributable to diagnoses of PTC. PTC carries an excellent prognosis with a 95 percent survival rate after thirty-five years (Raue & Frank-Raue, 2016). As a result, Jegerlehner et al. (2017) concluded that the population of Switzerland is at serious risk for thyroid cancer overdiagnosis because PTC incidence rates increased concurrently with thyroidectomy rates. Similar findings were reported in countries where intensive thyroid cancer screening programs were established in the 1990s (Schnadig, 2018).

Researchers have conducted several experiments to confirm whether thyroid cancer overdiagnosis is the result of the increased detection of small, indolent PTCs using enhanced diagnostic capabilities. Haymart et al. (2019) explored the use of ultrasound as the initial imaging test for thyroid cancer in the elderly (>65 years) U.S. population. Selection of this demographic was appropriate because it has seen the greatest increase in incidence and has the most disease-associated risks. It was found that the rate of thyroid ultrasound as initial imaging increased 20.9 percent per year between 2002 and 2013 and that thyroid cancer incidence and use of diagnostic ultrasound were significantly associated in this population (Haymart et al., 2019). In another retrospective study, Nagar et al. (2014), used physician age as a surrogate to test the relationship between increased incidence and use of ultrasound with FNA. In the late 2000s, younger physicians (<35 years) would have trained well after the popularization of ultrasound with FNA and would use these tools extensively in practice. On the other hand, older physicians (>55 years) trained well before the addition of these powerful diagnostic tools and would rely on palpation to diagnose thyroid cancer. Nagar et al. (2014) determined that areas with higher concentrations of younger physicians had significantly higher rates of thyroid cancer incidence between 2006 and 2009. This led Nagar et al. to arrive at a similar conclusion as that of the experiment conducted by Haymart et al. (2019). The results of these experiments support the findings of Jegerlehner et al. (2017) and support the claim that overdiagnosis is the result of increasing diagnostic capabilities.

Takano (2020) addresses the "epidemic of fear" that resulted from the extensive use of ultrasound with FNA to screen for PTC. Many people who are unaware of thyroid cancer overdiagnosis and scared by news of increased incidence opt to undergo screening. A portion of patients who receive a PTC diagnosis go on to have a thyroidectomy

when it may not be necessary. Those who do have a thyroidectomy run the risk of facing complications such as infection, bleeding, recurrent laryngeal nerve damage, and secondary hypoparathyroidism (Rosato et al., 2004). As an increasing number of patients receive a PTC diagnosis, it becomes more important to refine diagnostics and optimize treatments to reduce the burden of disease.

Refinement to the diagnostic criteria using molecular profiling

In response to the increasing incidence of PTC and scientific advancements, the American Thyroid Association updated the management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (which is primarily PTC) in 2015 (Haugen et al., 2016). These guidelines expressly state that a goal is to minimize the harm associated with overdiagnosis of low-risk thyroid cancer while offering the optimal treatment for those with high-risk thyroid cancer. It is recommended that samples collected by FNA are tested according to the Bethesda System for Reporting Thyroid Cytopathology. The Bethesda system has the capacity in 89–95 percent of cases to reveal whether a suspicious thyroid nodule is benign or malignant. If malignancy is detected, further analysis can be done to test for specific genetic mutations (Raue & Frank-Raue, 2016). The ability to test for mutational changes specific to certain subtypes of PTC gives researchers the opportunity to develop individualized therapies.

Development of individualized therapies expands treatment options

Over the past two decades, research has elucidated many of the molecular drivers responsible for the development of thyroid cancer (Raue & Frank-Raue, 2016). Mutational activation of the mitogen-activated protein kinase (MAPK) pathway has been implicated as the main driver of PTC (Naoum et al., 2018). A mutation in $BRAF^{V600E}$, a signaling molecule within the MAPK pathway, is present in 29 to 69 percent of PTC cases (White et al., 2017). PTC that carry this mutation are more prone to metastasis, are more likely to develop resistance to radioactive iodine (RAI) treatment, and have a higher mortality rate (Brose et al., 2016). The multiple-kinase inhibitor (MKI) vemurafenib, which

specifically targets $BRAF^{V600E}$, was initially used in the management of $BRAF^{V600E}$ positive melanoma. Brose et al. conducted a clinical trial of vemurafenib treatment on primarily U.S. patients with metastatic PTC that is both $BRAF^{V600E}$ positive and RAI-refractory. After a 14.4–month treatment course, 73 percent of the twenty-six patients who had not received prior MKI treatment had achieved disease control with a median progression-free survival of 18.2 months. Based on these results, Brose et al. (2016) concluded that vemurafenib may represent a potentially effective treatment for these patients.

Use of vemurafenib paired with dabrafenib has shown promise in the treatment of patients with $BRAF^{V600E}$-positive PTC, but the onset of drug resistance and adverse effects limit long-term efficacy (White et al., 2017). It was found that continuous treatment with vemurafenib induced dependence of resistant cells on this drug to continue proliferation. In response to this discovery, new trials were arranged where dabrafenib dosing was intermittent and done in conjunction with another MKI called trametinib. White et al. (2017) performed a case study on two patients with RAI-refractory, $BRAF^{V600E}$-positive PTC that underwent this treatment course. It was reported that intermittent dosing of dabrafenib with trametinib was both more well-tolerated than continuous dosing and stabilized cancer progression over twenty-seven months. This is one example of clinical research in this field that builds upon that done prior. As more research into mutation-specific treatments is performed, the effectiveness and safety of these drugs will continue to improve.

Homeopathic options may further improve outcomes

Alternative treatments in development for patients with PTC are not limited to pharmaceuticals. Homeopathic options are being explored that exploit nature's ability to manufacture organic compounds capable of serving a medicinal role. One example is curcumin, a naturally occurring polyphenol found in the common household spice turmeric (Zhang et al., 2018). Curcumin is capable of inducing apoptosis in PTC cells. Zhang et al. (2018) conducted an experiment in order to determine the mechanism of this action. They determined that curcumin disrupts calcium homeostasis in PTC cells by inducing endoplasmic reticulum stress that triggers the release of stored calcium ions into the cytosol. The result is depolarization of the mitochondrial membrane, which prevents

the production of adenosine triphosphate (an organic compound that provides energy) and ultimately leads to cell death. Other tannins have the ability to promote PTC cell apoptosis as well (Yang et al., 2020). Epigallocatechin-3-gallate, commonly found in tea, inhibits PTC cell proliferation and induces apoptosis. Punicalagin extracted from pomegranates has a similar effect. Patients have easy access to these affordable organic compounds, which makes them very promising potential supplements to the prevention and treatment of PTC.

Conclusion

Overdiagnosis of thyroid cancer is a self-perpetuating issue in that concerns about increased incidence motivates more people to undergo thyroid ultrasound, which in turn leads to additional new diagnoses. Currently, there is no significant evidence to suggest that the incidence rate will level off or decline. As such, it is exceedingly important that researchers and clinicians continue to refine diagnostic criteria and treatment options for patients with PTC. The exact mechanism of PTC development has been detailed by research over the last two decades. These discoveries increase the possibility of broadening the scope of treatment options for PTC beyond the standard thyroidectomy. Targeted therapies specific to molecular drivers of PTC are in development and clinical trials continue to enhance their efficacy. The ability of naturally derived compounds to combat PTC development represents another method to supplement treatment. The expansion of treatment options affords patients diagnosed with PTC greater freedom to decide how they want to approach disease management. In addition, the availability of increasingly individualized therapies aids in the reduction of the risks associated with enhanced detection of low-risk thyroid cancers.

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