Differentiated thyroid cancer: millions spent with no tangible gain?

Luis Furuya-Kanamori1, Art Sedrakyan2-3, Adedayo A Onitilo4, Nasser Bagheri2, Paul Glasziou5 and Suhail A R Doi1

1Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar
2Research School of Population Health, Australian National University, Canberra, ACT, Australia
3Department of Healthcare Policy and Research, Weill Cornell Medicine, New York, New York, USA
4Department of Hematology/Oncology, Marshfield Clinic Weston Center, Weston, Wisconsin, USA
5Centre for Research in Evidence Based Practice, Bond University, Gold Coast, QLD, Australia

Correspondence should be addressed to S A R Doi: sardoi@gmx.net

Abstract

The incidence of differentiated thyroid cancer (DTC) has rapidly increased worldwide over the last decades. It is unknown if the increase in diagnosis has been mirrored by an increase in thyroidectomy rates with the concomitant economic impact that this would have on the health care system. DTC and thyroidectomy incidence as well as DTC-specific mortality were modeled using Poisson regression in New South Wales (NSW), Australia per year and by sex. The incidence of 2002 was the point from which the increase in rates was assessed cumulatively over the subsequent decade. The economic burden of potentially avoidable thyroidectomies due to the increase in diagnosis was estimated as the product of the additional thyroidectomy procedures during a decade attributable to rates beyond those reported for 2002 and the national average hospital cost of an uncomplicated thyroidectomy in Australia. The following results were obtained. The incidence of both DTC and thyroidectomy doubled in NSW between 2003 and 2012, while the DTC-specific mortality rate remained unchanged over the same period. Based on the 2002 incidence, the projected increase over 10 years (2003–2012) in thyroidectomy procedures was 2196. This translates to an extra cost burden of over AUD$ 18,600,000 in surgery-related health care expenditure over one decade in NSW. Our findings suggest that, if this rise is solely attributable to overdetection, then the rising expenditure serves no additional purpose. Reducing unnecessary detection and a conservative approach to managing DTC are sensible and would lead to millions of dollars in savings and reduced harms to patients.

Key Words

thyroid
thyroidectomy
over detection

Introduction

The incidence of thyroid cancer has increased worldwide 3- to 15-fold over the last two decades, but with no significant increase in mortality (Pellegriti et al. 2013, Ahn et al. 2014). The increase in incidence is largely attributable to increased detection of differentiated thyroid cancer (DTC) – i.e. papillary and follicular cancer (Burgess & Tucker 2006, Davies & Welch 2006, Enewold et al. 2011). Studies have found that the penetrance of thyroid cancer screening and fine-needle aspiration (FNA) strongly correlate with the observed increase in incidence (Burgess & Tucker 2006, Ahn et al. 2014). Our recent investigation has also found that the increasing incidence...
of DTC is not mirrored by the prevalence of incidental DTC in autopsy studies, which has remained stable since 1970 (Furuya-Kanamori et al. 2016). These findings, especially given the latter, establish the case for the absence of a true population level increase in tumorigenesis and supports the notion that the increasing burden is driven by increasing detection (Davies & Welch 2006, Welch & Black 2010, Brito et al. 2014, Furuya-Kanamori et al. 2016).

Alongside this increase in DTC incidence, there are reports that suggest that subsequent surgical intervention (i.e. thyroidectomy) is also increasing (Sung et al. 2014, Ahn & Welch 2015). For example, DTC overdetection in small papillary carcinomas is leading to unnecessary thyroidectomies with no real survival advantage delivered to patients (Davies & Welch 2006, Enewold et al. 2011). After surgery, most patients would require lifelong thyroid-replacement therapy, while some patients may have complications from the surgical procedure such as hypoparathyroidism and paralysis of recurrent or superior laryngeal nerves (Hartl & Schlumberger 2013). Therefore, in March 2014, a Physician Coalition for Prevention of Overdiagnosis of Thyroid Cancer in South Korea wrote an open letter to the public discouraging routine ultrasonographic screening, this recommendation led to a 40% decrease in thyroidectomies within the country in the subsequent year (Ahn & Welch 2015).

Similar to other countries, DTC incidence has rapidly increased over the last two decades in Australia (Burgess 2002, Haggar et al. 2012, Pandeya et al. 2016, Cancer Australia 2017); however, it is unknown if this has been paralleled by an increase in surgical intervention rates. We therefore undertook an evaluation of the diagnostic, surgical and mortality trend data for DTC from New South Wales (NSW) to estimate the increase in economic burden of these surgical interventions to the Australian health care system and its impact on DTC-specific mortality rates during the last decade.

Materials and methods

The study was approved by the Australian National University – Science & Medical Delegated Ethics Review Committee (#2016/030) and conforms to the data-use agreement from the NSW Health Department.

Data sources and study population

Aggregated data from patients diagnosed with thyroid cancer (Cancer Institute NSW 2016b) and thyroid cancer-specific deaths (Cancer Institute NSW 2016c) in NSW between January 1982 and December 2012 were retrieved from the Cancer Institute NSW. The NSW Cancer Registry (NSWCR) is managed by the Cancer Institute NSW. The NSWCR is a population-based cancer registry that contains records of people with malignant neoplasms in NSW since 1972. Notification of new cancer cases and cancer deaths is legally required in NSW and the NSWCR receives data from public and private hospitals, nursing homes, public and private pathology laboratories and the Registry of Births, Deaths and Marriage.

Data from patients with thyroid gland malignancies (ICD-10-CM C73) that underwent partial (ICD-10-AM 30306-00, 30306-01, 30308-00, 30310-00, 90046-00) or total (ICD-10-AM 30296-00, 30296-01, 90046-01, 90046-02) thyroidectomies between January 2002 and December 2012 in NSW were extracted from the Admitted Patient Data Collection (APDC). Thyroidectomies with indications other than thyroid cancer (i.e. thyrotoxicosis ICD-10-AM 30309-00) were excluded from the analysis. To avoid the inclusion of recurrent cases of surgical procedures (e.g. partial thyroidectomy followed by a total thyroidectomy – ICD-10-AM 30297-00, 30297-01, 30297-02) and overestimating the incidence of patients that underwent a thyroidectomy; if a patient had more than one surgical procedure, only the first procedure was included for the analysis. The APDC is administered by the NSW Health Department. The APDC data provide reasonably accurate information on procedures and comorbidities (Goldsbury et al. 2011, 2012). A detailed description of the APDC scope, collection methodology, maintenance and data accuracy is described elsewhere (Australian Bureau of Statistics 2008).

Statistical analyses

Thyroid cancer cases, thyroidectomy procedures and thyroid cancer-specific mortality in NSW were categorized by year of event (diagnosis or surgical procedure) and sex. New events were counted within these categories. The population at risk, the population in NSW, was extracted from the Australian Bureau of Statistics (ABS) and stratified by year and sex. It should be noted that differentiation of DTC from all thyroid cancers was not possible, and this applies to thyroidectomy as well. Although the analyses were not DTC specific; yet, the estimated incidence rates reported are deemed to be those for DTC as they should closely match the DTC-specific incidence due to the small proportion (10% or less) of other histological types of cancers (i.e. medullary and anaplastic) expected in such cohorts during the same period (Pandeya et al. 2016).
This seems justified since an analysis of a previous dataset of ours with only DTC confirms that DTC mortality trends remain comparable to those reported here (Mankarios et al. 2014). All subsequent references to DTC should be understood to refer to DTC without exclusion of the other thyroid cancers.

Poisson regression models using robust standard errors and the population as the exposed population at risk were built to model the rates for incident DTC, incident thyroidectomies and thyroid cancer-specific mortality in NSW by including an interaction term for continuous year and sex. The predicted number of cases per year and by sex from the fitted models was used to estimate the incidence of DTC and DTC-specific mortality from 1982 to 2012 and thyroidectomy procedures from 2002 to 2012 in NSW per 100,000 population.

The rate observed in 2002 was deemed the baseline from which the increase in the rate of thyroidectomy was computed over the subsequent decade. The increase in thyroidectomy rates was therefore estimated for the period 2003–2012 as the difference from the baseline had it remained at the 2002 levels. To compute the additional number of surgical procedures over the last decade, the modeled difference in rates (from 2002 levels) was multiplied by the population at risk in NSW during each year.

The national average hospital cost of uncomplicated thyroidectomy for 2012–2013 in Australia was AUD$8500 (Independent Hospital Pricing Authority 2015). The economic burden of potentially avoidable thyroidectomy due to the increase in diagnosis to the Australian health care system was estimated as the product of the additional thyroidectomy within the decade after 2002 and the national average hospital cost of an uncomplicated thyroidectomy. We did not estimate the costs of complications or ongoing treatment such as thyroid replacement. All statistical analyses were conducted using Stata SE, version 14 (Stata Corporation; College Station, TX, USA).

Results

Between 1982 and 2012, 13,131 patients were diagnosed with DTC in NSW and 859 had a thyroid cancer-specific mortality. The majority of diagnosed patients were females (n=9877; 75.1%). 6790 thyroidectomies were recorded among patients with DTC between 2002 and 2012 in NSW hospitals. The majority of the thyroidectomy procedures were performed in women (n=5485; 80.89%), and the median age of the patients was 50 years (IQR 40–62 years) (Table 1).

The estimated DTC incidence per 100,000 population increased from 3.4 (females) and 1.2 (males) in 1982 to 20.6 (females) and 6.8 (males) in 2012. The estimated thyroidectomy incidence per 100,000 population increased from 9.1 (females) and 3.0 (males) in 2002 to 18.6 (females) and 6.0 (males) in 2012, while the estimated thyroid cancer-specific mortality rate demonstrated no change over this period or indeed the prior two decades (Figs 1 and 2 & Supplementary Table 1, see section on supplementary data given at the end of this article).

During the decade of interest (2003–2012), there was a twofold increase in both DTC and thyroidectomies among females and males. Since the percentage of DTC diagnosed patients getting a thyroidectomy has remained stable, it follows therefore that watchful waiting is not happening at a greater rate than previously despite DTC incidence steeply rising (Figs 1 and 2). Based on this increasing

<table>
<thead>
<tr>
<th>Year</th>
<th>Thyroid cancer cases (n=13,131)</th>
<th>Thyroidectomies (n=6790)</th>
<th>Thyroid cancer-specific mortality (n=859)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female sex</td>
<td>Age in years, median (IQR)</td>
<td>Type of thyroidectomy</td>
</tr>
<tr>
<td></td>
<td>9877 (75.2%)</td>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td></td>
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<td>Total</td>
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<td></td>
<td>Year</td>
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<td>1982–1985</td>
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<td>1986–1989</td>
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<td>1998–1901</td>
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<td>2006–2009</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2010–2012</td>
<td>2845</td>
<td></td>
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</tr>
</tbody>
</table>

IQR, inter-quartile range.
incidence, the projected increase in thyroidectomy was 2196 (1667 females; 529 males) cases more than would have happened if thyroidectomy rates had remained stable subsequent to 2002. This translates to an increase of AUD$ 18,666,000 ($14,169,500 in females; $4,496,500 in males) in surgery-related health care expenditure over one decade in NSW (Figs 1 and 2).

Discussion

DTC incidence has increased to epidemic proportions worldwide over the last few decades. Overdetection has not only increased DTC incidence, but it has also led to a concurrent increase in thyroidectomy procedures with a huge economic burden on the health care system (Table 2).

Over the last decade, we estimate that the number of potentially avoidable thyroidectomies performed in NSW was 2196. The increase in thyroidectomy procedures in NSW over this decade actually approximates the total estimated number of new cases of thyroid cancer diagnosed throughout Australia in 2016 (2098 new cases) (Cancer Australia 2017). DTC-specific mortality in Australia however has remained essentially unchanged over the last 30 years (Cancer Australia 2017), and among the thyroid cancer-specific deaths recorded in 2012 in NSW, half of them occurred in patients aged 80 years or above (Cancer Institute NSW 2016a). These figures amount to a huge excess in diagnosis and intervention that do not lead to increased survival for patients (Davies & Welch 2006, Ito et al. 2010, 2014, Sugitani et al. 2010, Welch & Black 2010, Furuya-Kanamori et al. 2016, Cancer Australia 2017).

It should be emphasized that we base our conclusion regarding the lack of tangible clinical gain only on the specific mortality rate having remained unchanged. There is, however, no expectation that intervention may decrease morbidity that does not lead to death. Unfortunately, these interventions themselves have been associated with morbidities. In fact, paradoxically, there is likely to be an increase in morbidity related to treatment if patients subject to such (over)diagnosis are given the standard management for thyroid cancer, which includes surgical resection and/or radioiodine therapy (Doi & Woodhouse 2000, Doi et al. 2007, Haugen et al. 2015). Surgical complications may arise and include hypoparathyroidism, a life-threatening condition that requires intensive monitoring and therapy with calcium and vitamin D; laryngeal nerve palsy which will result in voice change and/or require tracheotomy in cases of bilateral nerve damage. Even when the surgery is complication free, most of the patients will require lifelong surveillance, and thyroid hormone suppression or replacement, which may have longer term metabolic implications (Hartl & Schlumberger 2013).

It could be argued that the increased thyroid cancer diagnosis in recent years is associated with stable mortality because of improvement in diagnosis and management over time. However, Davies and Welch have pointed out that this is not likely to be true (Davies & Welch 2014) because for mortality to remain stable, improvements (in diagnostic techniques and disease management) have to precisely mirror the increase in thyroid incidence. Thus, improvements occurring at a faster or slower rate than changes in incidence rate would certainly alter mortality rates and to assume an exact match between the rising
incidence and the improvements over 30 years is highly implausible. In a previous study, we demonstrated that the reservoir of incidental DTC has remained stable since 1970 suggesting that population level of tumorigenesis has remained unchanged (Furuya-Kanamori et al. 2016). Therefore, the most reasonable explanation for the rising thyroid cancer incidence with stable mortality is that subclinical DTC is increasingly being detected due to the improvements in diagnostic techniques, but these newly discovered subclinical cases may not progress or will progress so slowly that the patient is more likely to die from other causes.

Overdetection of indolent DTC microcarcinomas could lead to unnecessary economic burden, while late diagnosis of clinically significant thyroid cancer could worsen clinical outcome. The current evidence does make the case for the development of strategies to reduce overdetection (the thyroid should not be examined without a specific indication) as well as implementation of a more conservative approach to nodule diagnosis through active surveillance leading on to intervention if thyroid nodules demonstrate progression (i.e. size and/or characteristics) (Leboulleux et al. 2016). At this point, it is not clear which patients are eligible for active surveillance, further studies are required to accurately discriminate patients who need to undergo thyroid nodule biopsy or active surveillance, as well as to recognize prognostic factors that would warrant early intervention among the subset of thyroid cancer patients with more aggressive disease. Currently, nodule size is an important factor in such decision making, along with family history, exposure to radiation and age of the patient (>45 years) (Onitilo et al. 2009, Mankarios et al. 2014, Haugen et al. 2015, Hoang et al. 2015). Although differentiation of DTC histopathology (papillary vs follicular) does not seem to play a major role in decision making, FNA cytology may be indicated if there are signs of progression or to differentiate DTC from other types of carcinomas (i.e. medullary and anaplastic) given the different prognosis associated with the latter.

In terms of health services expenditure, thyroid gland surgeries in Australia cost on average AUD$ 8500; however, when there are surgical complications, this amount rapidly increases to over AUD$ 15,000 (Independent Hospital Pricing Authority 2015). We used the average cost of uncomplicated thyroidectomies, which provides a conservative economic estimate of the burden of increasing diagnosis. Future economic evaluations would need to take into account additional costs such as diagnosis (e.g. FNA and histopathology examination), complications during the surgical intervention (e.g. ICU admission), hormone replacement therapy and outpatient consultations. Thus, a deferral of surgery can be expected to lead to significant savings in projected health care expenditure of at least AUD$ 4 million per year in the state of NSW. This cost saving over 10 years is weighted heavily toward the later part of the decade and is a very conservative estimate as it does not take into account the treatment factors mentioned previously and of course the emotional burden on patients. Furthermore, given that the DTC incidence rise has been ongoing since the 1980s, our estimate over only the last decade is probably a considerable underestimate of the economic burden as overdetection/thyroidectomy may have increased 4-fold rather than just 2-fold. While the data suggest a clear economic case for surveillance rather than intervention, and accumulated evidence from several studies suggest that this would be a safe approach (Ito et al. 2010, 2014, Sugitani et al. 2010, Brito et al. 2014), the exact process that should be adopted requires further evidence from prospective clinical studies, and funding for such studies must be made a priority.

Our findings should be considered in the light of a few limitations. An important one was the inability to conduct sub-group analyses by age group, patient ethnicity, tumor size and histopathology. However, we were able to stratify the analyses by sex, which is known to be one of the strongest predictors of DTC incidence and thyroidectomy. We also make the assumption based on our previous work that the rising trends are representative

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**Table 2** Worldwide trends in thyroid cancer incidence, thyroidectomy rate and mortality rate.

<table>
<thead>
<tr>
<th>Country</th>
<th>Thyroid cancer incidence</th>
<th>Thyroidectomy rate</th>
<th>Mortality rate</th>
</tr>
</thead>
</table>

*Number of thyroidectomies, not rates.

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http://erc.endocrinology-journals.org
https://doi.org/10.1530/ERC-17-0397
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Published by Bioscientifica Ltd.
Printed in Great Britain
of overdiagnosis (Furuya-Kanamori et al. 2016). There have been studies that seem to disagree, and for example, from a SEER database analysis by Enewold and coworkers among white women, the rate of increase for papillary thyroid carcinoma >5 cm was similar to that for smaller thyroid cancer (Enewold et al. 2009). Another study from Spain by Rego-Iraeta and coworkers also reported that the rate of rise in thyroid cancer was observed across all tumor sizes (Rego-Iraeta et al. 2009). We agree with the latter that the incidence of all sizes are rising but a re-analysis of our previous data (Mankarios et al. 2014) stratified by tumor size and gender clearly demonstrates that the rate of rise decreases with increasing size, though all sizes are increasingly detected (data not shown). We believe that this again is consistent with overdiagnosis. Nevertheless, it is important to distinguish indolent tumors from clinically significant tumors (where delays in diagnosis are important), and this requires guidance from future studies regarding delineation of criteria for patients who need to undergo thyroid nodule biopsy for diagnosis of thyroid cancer (to avoid overdiagnosis of indolent thyroid cancer). Such criteria would likely be prognostic factors that would assist in the identification of more advanced thyroid cancers, thus avoiding fears that clinicians may delay treatment and increase recurrent/persistent disease within a selected subset of thyroid cancer patients with more aggressive disease.

In conclusion, the evidence base for avoidable costs to health care is clear and savings expected are substantial from a conservative approach to both thyroid examination (only when indicated) and management of thyroid cancer when detected. Current evidence suggests that watchful waiting is a safe route for management of many of the latter patients if due surveillance is properly managed. What remains to be mapped out is who exactly should be offered active surveillance and the criteria for subsequent intervention.

Author contribution statement
L F K and S A R D contributed to the conception and design of the study. A S and L F K assisted with data acquisition. L F K conducted the statistical analyses. L F K and S A R D drafted the manuscript. A S, A A O, N B, and P G critically revised the manuscript. L F K, A S, A A O, N B, P G and S A R D read and approved the final version of the manuscript and agreed to be fully accountable for ensuring the integrity and accuracy of the work.

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Received in final form 5 October 2017
Accepted 17 October 2017
Accepted preprint published online 17 October 2017