Society for Endocrinology
ENDOCRINE-RELATED CANCER

Differentiated thyroid cancer: Millions spent with no tangible gain?

Journal:	*Endocrine-Related Cancer*
Manuscript ID	ERC-17-0397.R1
Manuscript Type:	Research Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	Furuya-Kanamori, Luis; Qatar University, Public Health Sedrakyan, Art; Australian National University, Research School of Population Health Onitilo, Adedayo; Marshfield Clinic Weston Center, Hematology/Oncology; University of Queensland, School of Population Health Bagheri, Nasser; Australian National University, Research School of Population Health Glasziou, Paul; Bond University, Centre for Research in Evidence-Based Practice Doi, Suhail; University of Queensland, School of Population Health
Keywords:	Thyroid, thyroidectomy, over detection

Original Research

Differentiated thyroid cancer: Millions spent with no tangible gain?

Running title: Increase in DTC incidence and thyroidectomy

Luis Furuya-Kanamori *PhD*[1], Professor Art Sedrakyan *PhD*[2,3], Adedayo A. Onitilo *PhD*[4], Nasser Bagheri *PhD*[2], Professor Paul Glasziou *PhD*[5], Professor Suhail A.R Doi *PhD*[1*]

[1] Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

[2] Research School of Population Health, Australian National University, Canberra, ACT, Australia

[3] Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, NY, USA

[4] Department of Hematology/Oncology, Marshfield Clinic Weston Center, Weston, WI, USA

[5] Centre for Research in Evidence Based Practice, Bond University, Gold Coast, QLD, Australia

* Post-publication correspondence to:

Professor Suhail A.R. Doi *MBBS, MMed, MClinEpid, PhD, FRCP*

Department of Population Medicine, College of Medicine, Qatar University

2713, Al Hala St, Doha, Qatar

sardoi@gmx.net

Word count: 2821

Abstract

Background: 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 healthcare system.

Methods: DTC and thyroidectomy incidence as well as DTC specific mortality were modelled 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 were 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.

Results: 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 2,196. This translates to an extra cost burden of over AUD$ 18,600,000 in surgery-related healthcare expenditure over one decade in NSW.

Conclusions: 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.

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 and Tucker, 2006, Davies and 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 and 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 and Welch, 2006, Welch and 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 and Welch, 2015). For example, DTC overdetection in small papillary carcinomas is leading to unnecessary thyroidectomies with no real survival advantage delivered to patients (Davies and 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 and 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 and 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); 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 healthcare 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 over estimating 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 provides reasonably accurate information on procedures and comorbidities (Goldsbury et al., 2011, Goldsbury et al., 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 regressions 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 were 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 modelled 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$ 8,500 (Independent Hospital Pricing Authority, 2015). The economic burden of potentially avoidable thyroidectomy due to the increase in diagnosis to the Australian healthcare 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).

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=9,877; 75·1%). 6,790 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=5,485; 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 (Figures 1 and 2 & Supplementary material).

During the decade of interest (2003-2012), there was a two-fold 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 (Figures 1 & 2). Based on this increasing incidence, the projected increase in thyroidectomy was 2,196 (1,667 females; 529 males) cases more than would have happened if thyroidectomies 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 healthcare expenditure over one decade in NSW (Figures 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 healthcare system (Table 2). Over the last decade, we estimate that the number of potentially avoidable thyroidectomies performed in NSW was 2,196. The increase in thyroidectomy procedures in NSW over this decade actually approximates the total estimated number of new cases of thyroid cancer diagnosed Australia-wide in 2016 (2098 new cases) (Cancer Australia). DTC specific mortality in Australia however has remained essentially unchanged over the last 30 years (Cancer Australia) 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 and Welch, 2006, Ito et al., 2010, Sugitani et al., 2010, Welch and Black, 2010, Ito et al., 2014, Furuya-Kanamori et al., 2016, Cancer Australia).

It should be emphasised 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 and 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 results 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 and 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 and 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 diagnosed 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 recognise 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 versus 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$ 8,500; 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 healthcare expenditure of at least AUD$ 4 million per year in the state of NSW. This cost saving over 10 years is weighted heavily towards 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, Sugitani et al., 2010, Brito et al., 2014, Ito 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, tumour 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 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 et al. (2009) amongst White women, the rate of increase for papillary thyroid carcinoma >5cm was similar to that for smaller thyroid cancer. Another study from Spain by Rego-Iraeta et al. (2009) also reported that the rate of rise in thyroid cancer was observed across all tumour sizes. 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 tumour 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 tumours from clinically significant tumours (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 over-diagnosis of indolent thyroid cancer). Such criteria would likely be prognostic factors that would assist in identification of more advanced thyroid cancers thus avoiding fears that clinicians may delay treatment and increase recurrent/persistent disease within a selected sub-set of thyroid cancer patients with more aggressive disease.

In conclusion, the evidence base for avoidable costs to healthcare 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.

Declaration of interest

The authors have no conflicts of interest in the authorship or publication of this article.

Funding

None

Authors' contributions

LFK and SARD contributed to the conception and design of the study. AS and LFK assisted with data acquisition. LFK conducted the statistical analyses. LFK and SARD drafted the manuscript. AS, AAO, NB, and PG critically revised the manuscript. LFK, AS, AAO, NB, PG, and SARD read and approved the final version of the manuscript and agreed to be fully accountable for ensuring the integrity and accuracy of the work.

References

AHN, H. S., KIM, H. J. & WELCH, H. G. 2014. Korea's thyroid-cancer "epidemic"-screening and overdiagnosis. *N Engl J Med* **371**: 1765-7.

AHN, H. S. & WELCH, H. G. 2015. South Korea's thyroid-cancer "Epidemic"- Turning the tide. *N Engl J Med* **373**: 2389-90.

AUSTRALIAN BUREAU OF STATISTICS. 2008. *NSW Health Department, Admitted Patient Data Collection* [Online]. Available: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007 [Accessed September 2017].

BRITO, J. P., DAVIES, L., ZEBALLOS-PALACIOS, C., MORRIS, J. C. & MONTORI, V. M. 2014. Papillary lesions of indolent course: reducing the overdiagnosis of indolent papillary thyroid cancer and unnecessary treatment. *Future Oncol* **10**: 1-4.

BURGESS, J. R. 2002. Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). *Thyroid* **12**: 141-9.

BURGESS, J. R. & TUCKER, P. 2006. Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine-needle aspirate cytology. *Thyroid* **16**: 47-53.

CANCER AUSTRALIA. *Thyroid cancer* [Online]. Available: https://canceraustralia.gov.au/affected-cancer/cancer-types/thyroid-cancer/thyroid-cancer-statistics [Accessed September 2017].

CANCER INSTITUTE NSW. 2016a. *Thyroid cancer* [Online]. Available: https://www.cancerinstitute.org.au/understanding-cancer/cancer-in-nsw/thyroid-cancer [Accessed September 2017].

CANCER INSTITUTE NSW. 2016b. *Thyroid cancer - Age Standardised Incidence Rates* [Online]. Available: http://www.statistics.cancerinstitute.org.au/trends/trends_incid_C73_extall_NSW.htm [Accessed September 2017].

CANCER INSTITUTE NSW. 2016c. *Thyroid cancer - Age Standardised Mortality Rates* [Online]. Available:

http://www.statistics.cancerinstitute.org.au/trends/trends_mort_C73_extall_NSW.htm [Accessed September 2017].

DAVIES, L. & WELCH, H. 2014. Davies and welch draw unfounded conclusions about thyroid cancer from epidemiological data—reply. *JAMA Otolaryngol Head Neck Surg* **140**: 679.

DAVIES, L. & WELCH, H. G. 2006. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* **295**: 2164-7.

DOI, S. A. & WOODHOUSE, N. J. 2000. Ablation of the thyroid remnant and 131I dose in differentiated thyroid cancer. *Clin Endocrinol (Oxf)* **52**: 765-73.

DOI, S. A. R., WOODHOUSE, N. J., THALIB, L. & ONITILO, A. 2007. Ablation of the Thyroid Remnant and I-131 Dose in Differentiated Thyroid Cancer: A Meta-Analysis Revisited. *Clin Med Res* **5**: 87-90.

ENEWOLD, L., ZHU, K., RON, E., MARROGI, A. J., STOJADINOVIC, A., PEOPLES, G. E. & DEVESA, S. S. 2009. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev* **18**: 784-91.

ENEWOLD, L. R., ZHOU, J., DEVESA, S. S., BERRINGTON DE GONZALEZ, A., ANDERSON, W. F., ZAHM, S. H., STOJADINOVIC, A., PEOPLES, G. E., MARROGI, A. J., POTTER, J. F., MCGLYNN, K. A. & ZHU, K. 2011. Thyroid cancer incidence among active duty U.S. military personnel, 1990-2004. *Cancer Epidemiol Biomarkers Prev* **20**: 2369-76.

FURUYA-KANAMORI, L., BELL, K. J., CLARK, J., GLASZIOU, P. & DOI, S. A. 2016. Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis. *J Clin Oncol* **34**: 3672-9.

GOLDSBURY, D. E., ARMSTRONG, K., SIMONELLA, L., ARMSTRONG, B. K. & O'CONNELL, D. L. 2012. Using administrative health data to describe colorectal and lung cancer care in New South Wales, Australia: a validation study. *BMC Health Serv Res* **12**: 1472.

GOLDSBURY, D. E., SMITH, D. P., ARMSTRONG, B. K. & O'CONNELL, D. L. 2011. Using linked routinely collected health data to describe prostate cancer treatment in New South Wales, Australia: a validation study. *BMC Health Services Res* **11**: 253.

HAGGAR, F. A., PREEN, D. B., PEREIRA, G., HOLMAN, C. D. & EINARSDOTTIR, K. 2012. Cancer incidence and mortality trends in Australian adolescents and young adults, 1982-2007. *BMC Cancer* **12**: 151.

HARTL, D. M. & SCHLUMBERGER, M. 2013. Extent of Thyroidectomy and Incidence of Morbidity: Risk-appropriate Treatment. *In:* MICCOLI, P., TERRIS, D. J., MINUTO, M. N. & SEYBT, M. W. (eds.) *Thyroid Surgery: Preventing and Managing Complications.* Oxford: Wiley-Blackwell.

HAUGEN, B. R. M., ALEXANDER, E. K., BIBLE, K. C., DOHERTY, G., MANDEL, S. J., NIKIFOROV, Y. E., PACINI, F., RANDOLPH, G., SAWKA, A., SCHLUMBERGER, M., SCHUFF, K. G., SHERMAN, S. I., SOSA, J. A., STEWARD, D., TUTTLE, R. M. M. & WARTOFSKY, L. 2015. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **26**: 1-133.

HOANG, J. K., LANGER, J. E., MIDDLETON, W. D., WU, C. C., HAMMERS, L. W., CRONAN, J. J., TESSLER, F. N., GRANT, E. G. & BERLAND, L. L. 2015. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *J Am Coll Radiol* **12**: 143-50.

INDEPENDENT HOSPITAL PRICING AUTHORITY. 2015. *National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2012-2013, Round 17* [Online]. Available: https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-2013_round_17_0.pdf [Accessed September 2017].

ITO, Y., MIYAUCHI, A., INOUE, H., FUKUSHIMA, M., KIHARA, M., HIGASHIYAMA, T., TOMODA, C., TAKAMURA, Y., KOBAYASHI, K. & MIYA, A. 2010. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* **34**: 28-35.

ITO, Y., MIYAUCHI, A., KIHARA, M., HIGASHIYAMA, T., KOBAYASHI, K. & MIYA, A. 2014. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* **24**: 27-34.

LEBOULLEUX, S., TUTTLE, R. M., PACINI, F. & SCHLUMBERGER, M. 2016. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? *Lancet Diabetes Endocrinol* **4**: 933-42.

MANKARIOS, D., BAADE, P., YOUL, P., MORTIMER, R. H., ONITILO, A. A., RUSSELL, A. & DOI, S. A. 2014. Validation of the QTNM staging system for cancer-specific survival in patients with differentiated thyroid cancer. *Endocrine* **46**: 300-8.

ONITILO, A. A., ENGEL, J. M., LUNDGREN, C. I., HALL, P., THALIB, L. & DOI, S. A. 2009. Simplifying the TNM system for clinical use in differentiated thyroid cancer. *J Clin Oncol* **27**: 1872-8.

PANDEYA, N., MCLEOD, D. S., BALASUBRAMANIAM, K., BAADE, P. D., YOUL, P. H., BAIN, C. J., ALLISON, R. & JORDAN, S. J. 2016. Increasing thyroid cancer incidence in Queensland, Australia 1982-2008 - true increase or overdiagnosis? *Clin Endocrinol* **84**: 257-64.

PELLEGRITI, G., FRASCA, F., REGALBUTO, C., SQUATRITO, S. & VIGNERI, R. 2013. Worldwide increasing incidence of thyroid cancer: Update on epidemiology and risk factors. *J Cancer Epidemiol* **2013**: 965212.

REGO-IRAETA, A., PEREZ-MENDEZ, L. F., MANTINAN, B. & GARCIA-MAYOR, R. V. 2009. Time trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. *Thyroid* **19**: 333-40.

SUGITANI, I., TODA, K., YAMADA, K., YAMAMOTO, N., IKENAGA, M. & FUJIMOTO, Y. 2010. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg* **34**: 1222-31.

SUNG, M. W., PARK, B., AN, S. Y., HAH, J. H., JUNG, Y. H. & CHOI, H. G. 2014. Increasing thyroid cancer rate and the extent of thyroid surgery in Korea. *PLoS One* **9**: e113464.

WELCH, H. G. & BLACK, W. C. 2010. Overdiagnosis in cancer. *J Natl Cancer Inst* **102**: 605-13.

Table Title

Table 1. Patient's characteristics

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

Figure Legend

Figure 1. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in females. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the last decade and the excess in surgery-related healthcare expenditure associated with this.

Figure 2. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in males. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the last decade and the excess in surgery-related healthcare expenditure associated with this.

Table 1. Patient's characteristics

	Thyroid cancer cases (n=13,131)	Thyroidectomies (n=6,790)	Thyroid cancer specific mortality (n=859)
Female sex	9,877 (75·2%)	5,147 (75·8%)	513 (59·7%)
Age in years, median (IQR)	-	50 (40-62)	-
Type of thyroidectomy			
Partial	-	1,305 (19·2%)	-
Total	-	5,485 (80·8%)	-
Year			
1982-85	552	-	90
1986-89	693	-	96
1990-93	977	-	92
1994-97	1290	-	103
1998-01	1675	-	107
2002-05	2217	1823	132
2006-09	2872	2453	134
2010-2012	2845	2514	105

IQR inter-quartile range

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

Country	Thyroid cancer incidence	Thyroidectomy rate	Mortality rate
Canada	Increased 5-fold (1970-2012)	Increased 13% (2003-2011)	Remained stable (1970-2012)
South Korea	Increased 13-fold (1993-2011)	Increased 10-fold* (2001-2012)	Remained stable (1993-2011)
Switzerland	Increased 2- and 1.5- fold in females and males, respectively (1998-2012)	Increased 4- and 3-fold in females and males, respectively (1998-2012)	Decreased by 30% (1998-2012)
USA	Increased 3.6-fold (1974-2013)	Increased 39%* (1996-2006)	Increased 15% (1994-2013)
UK	Increased 2.2-fold (1993-2014)	Not available	Remained stable (1993-2014)

* Number of thyroidectomies, not rates

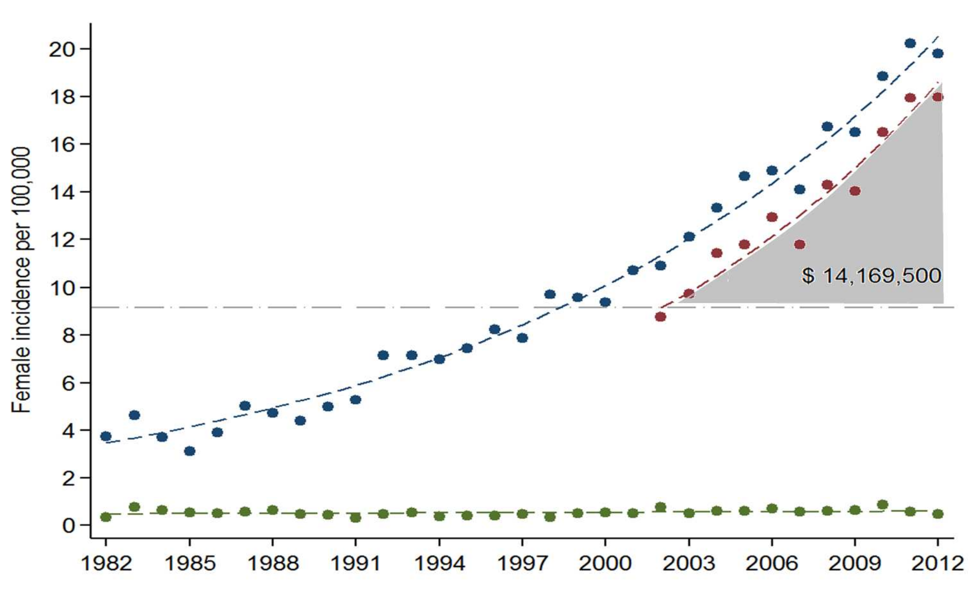

Figure 1. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in females. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the last decade and the excess in surgery-related healthcare expenditure associated with this.

1765x1051mm (96 x 96 DPI)

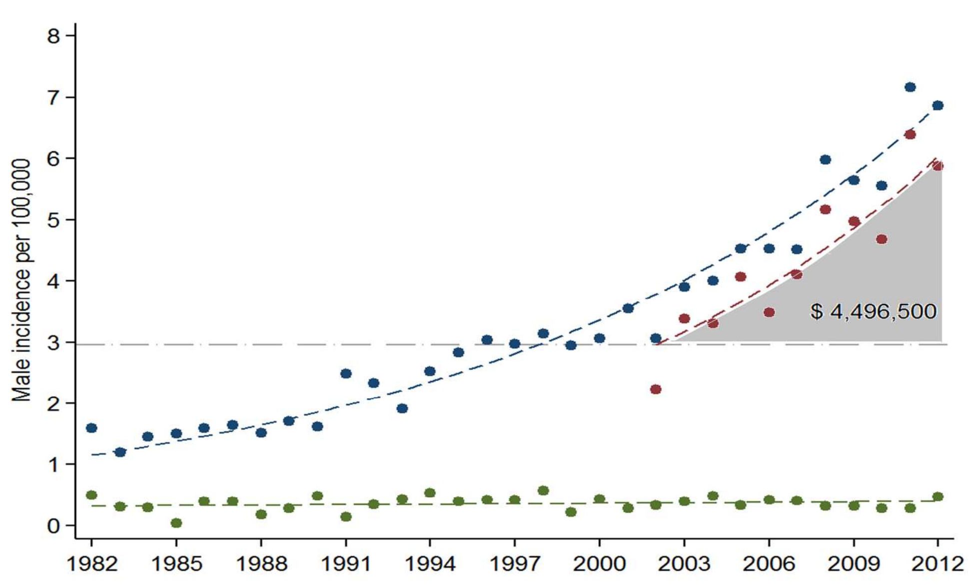

Figure 2. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in males. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the last decade and the excess in surgery-related healthcare expenditure associated with this.

1765x1051mm (96 x 96 DPI)

Supplementary material

Table S1. Estimated incidence and its 95% confidence interval of thyroid cancer, thyroidectomy, and thyroid cancer specific mortality per 100,000 population by sex.

Year	Female			Males		
	Thyroid cancer	Thyroidectomy	Thyroid cancer mortality	Thyroid cancer	Thyroidectomy	Thyroid cancer mortality
1982	3·5 (3·2-3·7)	-	0·5 (0·4-0·6)	1·2 (1·1-1·2)	-	0·3 (0·3-0·4)
1983	3·7 (3·5-3·9)	-	0·5 (0·4-0·6)	1·2 (1·2-1·3)	-	0·3 (0·3-0·4)
1984	3·9 (3·7-4·1)	-	0·5 (0·4-0·6)	1·3 (1·2-1·4)	-	0·3 (0·3-0·4)
1985	4·1 (3·9-4·4)	-	0·5 (0·4-0·6)	1·4 (1·3-1·5)	-	0·3 (0·3-0·4)
1986	4·4 (4·2-4·6)	-	0·5 (0·4-0·6)	1·5 (1·4-1·6)	-	0·3 (0·3-0·4)
1987	4·7 (4·4-4·9)	-	0·5 (0·4-0·6)	1·6 (1·5-1·6)	-	0·3 (0·3-0·4)
1988	4·9 (4·7-5·2)	-	0·5 (0·4-0·6)	1·6 (1·6-1·7)	-	0·3 (0·3-0·4)
1989	5·2 (5·0-5·5)	-	0·5 (0·4-0·6)	1·8 (1·7-1·8)	-	0·3 (0·3-0·4)
1990	5·6 (5·3-5·8)	-	0·5 (0·4-0·6)	1·9 (1·8-2·0)	-	0·3 (0·3-0·4)
1991	5·9 (5·7-6·2)	-	0·5 (0·5-0·6)	2·0 (1·9-2·1)	-	0·3 (0·3-0·4)
1992	6·3 (6·0-6·5)	-	0·5 (0·5-0·6)	2·1 (2·0-2·2)	-	0·3 (0·3-0·4)
1993	6·6 (6·4-6·9)	-	0·5 (0·5-0·6)	2·2 (2·1-2·3)	-	0·3 (0·3-0·4)
1994	7·1 (6·8-7·3)	-	0·5 (0·5-0·6)	2·4 (2·3-2·5)	-	0·3 (0·3-0·4)
1995	7·5 (7·2-7·7)	-	0·5 (0·5-0·6)	2·5 (2·4-2·6)	-	0·4 (0·3-0·4)
1996	7·9 (7·7-8·2)	-	0·5 (0·5-0·6)	2·7 (2·5-2·8)	-	0·4 (0·3-0·4)
1997	8·4 (8·2-8·7)	-	0·5 (0·5-0·6)	2·8 (2·7-2·9)	-	0·4 (0·3-0·4)
1998	8·9 (8·7-9·2)	-	0·5 (0·5-0·6)	3·0 (2·9-3·1)	-	0·4 (0·3-0·4)

1999	9·5 (9·3-9·7)	-	0·5 (0·5-0·6)	3·2 (3·1-3·3)	-	0·4 (0·3-0·4)
2000	10·1 (9·8-10·3)	-	0·5 (0·5-0·6)	3·4 (3·2-3·5)	-	0·4 (0·3-0·4)
2001	10·7 (10·4-10·9)	-	0·5 (0·5-0·6)	3·6 (3·4-3·7)	-	0·4 (0·3-0·4)
2002	11·3 (11·1-11·6)	9·1 (8·6-9·7)	0·5 (0·5-0·6)	3·8 (3·7-3·9)	3·0 (2·7-3·2)	0·4 (0·3-0·4)
2003	12·0 (11·8-12·3)	9·8 (9·3-10·3)	0·5 (0·5-0·6)	4·0 (3·9-4·2)	3·2 (2·9-3·4)	0·4 (0·3-0·4)
2004	12·8 (12·5-13·1)	10·5 (10·0-11·0)	0·5 (0·5-0·6)	4·3 (4·1-4·4)	3·4 (3·2-3·7)	0·4 (0·3-0·4)
2005	13·6 (13·3-13·9)	11·3 (10·8-11·8)	0·6 (0·5-0·6)	4·5 (4·4-4·7)	3·7 (3·4-3·9)	0·4 (0·3-0·4)
2006	14·4 (14·1-14·7)	12·1 (11·7-12·6)	0·6 (0·5-0·6)	4·8 (4·6-5·0)	3·9 (3·7-4·2)	0·4 (0·3-0·4)
2007	15·3 (14·9-15·6)	13·0 (12·6-13·5)	0·6 (0·5-0·6)	5·1 (4·9-5·3)	4·2 (4·0-4·5)	0·4 (0·3-0·4)
2008	16·2 (15·8-16·6)	14·0 (13·6-14·4)	0·6 (0·5-0·6)	5·4 (5·2-5·6)	4·5 (4·3-4·8)	0·4 (0·3-0·4)
2009	17·2 (16·7-17·7)	15·0 (14·6-15·5)	0·6 (0·5-0·6)	5·7 (5·5-6·0)	4·9 (4·6-5·2)	0·4 (0·3-0·4)
2010	18·2 (17·7-18·8)	16·2 (15·6-16·7)	0·6 (0·5-0·6)	6·1 (5·8-6·4)	5·2 (4·9-5·6)	0·4 (0·3-0·4)
2011	19·4 (18·8-19·9)	17·4 (16·7-18·0)	0·6 (0·5-0·7)	6·5 (6·2-6·8)	5·6 (5·3-6·0)	0·4 (0·3-0·4)
2012	20·5 (19·9-21·2)	18·6 (17·8-19·5)	0·6 (0·5-0·7)	6·9 (6·6-7·2)	6·0 (5·6-6·5)	0·4 (0·3-0·5)

Original Research

Differentiated thyroid cancer: Millions spent with no tangible gain?

Running title: Increase in DTC incidence and thyroidectomy

Luis Furuya-Kanamori *PhD*[1], Professor Art Sedrakyan *PhD*[2,3], Adedayo A. Onitilo *PhD*[4], Nasser Bagheri *PhD*[2], Professor Paul Glasziou *PhD*[5], Professor Suhail A.R Doi *PhD*[61]*

[1] Department of Populationublic MedicineHealth, College of MedicineHealth Sciences, Qatar University, Doha, Qatar

[2] Research School of Population Health, Australian National University, Canberra, ACT, Australia

[3] Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, NY, USA

[4] Department of Hematology/Oncology, Marshfield Clinic Weston Center, Weston, WI, USA

[5] Centre for Research in Evidence Based Practice, Bond University, Gold Coast, QLD, Australia

[6] Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

* Post-publication correspondence to:

Professor Suhail A.R. Doi *MBBS, MMed, MClinEpid, PhD, FRCP*

Department of Population Medicine, College of Medicine, Qatar University

2713, Al Hala St, Doha, Qatar

sardoi@gmx.net

Word count: 2574

Abstract

Background: 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 healthcare system.

Methods: DTC and thyroidectomy incidence as well as DTC specific mortality were modelled 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 were 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.

Results: 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 2,196. This translates to an extra cost burden of over AUD$ 18,600,000 in surgery-related healthcare expenditure over one decade in NSW.

Conclusions: 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.

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 and Tucker, 2006, Davies and 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 and 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 and Welch, 2006, Welch and 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 and Welch, 2015). For example, DTC overdetection, in small papillary carcinomas, is leading to unnecessary thyroidectomies with no real survival advantage delivered to patients (Davies and 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 and 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 ultrasonographicy screening, this recommendation led to a 40% decrease in thyroidectomies within the country in the subsequent year (Ahn and 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); 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 healthcare 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 over estimating 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 provides reasonably accurate information on procedures and comorbidities (Goldsbury et al., 2011, Goldsbury et al., 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 ~~In addition, we~~ an analysis~~ed~~ of a previous dataset of ours with only DTC ~~and~~ confirms~~ed~~ that DTC mortality trends ~~indeed remained~~ remain comparable ~~identical with~~ to those~~at~~ 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 regressions 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 were 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 modelled 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$ 8,500 (Independent Hospital Pricing Authority, 2015). The economic burden of potentially avoidable thyroidectomy due to the increase in diagnosis to the Australian healthcare 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).

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=9,877; 75·1%). 6,790 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=5,485; 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 (Figures 1 and 2 & Supplementary material).

During the decade of interest (2003-2012), there was a two-fold increase in both, DTC and thyroidectomies among females and males. Since, the percentage of DTC diagnosed patients getting a thyroidectomy has remained stable~~,~~ ~~therefore~~ it follows therefore that watchful waiting is not happening at a greater rate than previously despite DTC incidence steeply rising (Figures 1 & 2). Based on this increasing incidence, the projected increase in thyroidectomy was 2,196 (1,667 females; 529 males) cases more than would have happened if thyroidectomies 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 healthcare expenditure over one decade in NSW (Figures 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 healthcare system (Table 2). Over the last decade, we estimate that the number of potentially avoidable thyroidectomies performed in NSW was 2,196. The increase in thyroidectomy procedures in NSW over this decade actually approximates the total estimated number of new cases of thyroid cancer diagnosed Australia-wide in 2016 (2098 new cases) (Cancer Australia). DTC specific mortality in Australia however has remained essentially unchanged over the last 30 years (Cancer Australia) 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 and Welch, 2006, Ito et al., 2010, Sugitani et al., 2010, Welch and Black, 2010, Ito et al., 2014, Furuya-Kanamori et al., 2016, Cancer Australia).

It should be emphasised 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 and 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 results 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 and 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 and 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 diagnosed 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 recognise 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 versus 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$ 8,500; 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 healthcare expenditure of at least AUD$ 4 million per year in the state of NSW. This cost saving over 10 years is weighted heavily towards 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, Sugitani et al., 2010, Brito et al., 2014, Ito 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, tumour 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 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 et al. (2009) amongst White women, the rate of increase for papillary thyroid carcinoma >5cm was similar to that for smaller thyroid cancer. Another study from Spain by Rego-Iraeta et al. (2009) also reported that the rate of rise in thyroid cancer was observed across all tumour sizes. 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 tumour 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 tumours from clinically significant tumours (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 over-diagnosis of indolent thyroid cancer). Such criteria would likely be prognostic factors that would assist in identification of more advanced thyroid cancers thus avoiding fears that clinicians may delay treatment and increase recurrent/persistent disease within a selected sub-set of thyroid cancer patients with more aggressive disease.

In conclusion, the evidence base for avoidable costs to healthcare 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.

Declaration of interest

The authors have no conflicts of interest in the authorship or publication of this article.

Funding

None

Authors' contributions

LFK and SARD contributed to the conception and design of the study. AS and LFK assisted with data acquisition. LFK conducted the statistical analyses. LFK and SARD drafted the manuscript. AS, AAO, NB, and PG critically revised the manuscript. LFK, AS, AAO, NB, PG, and SARD read and approved the final version of the manuscript and agreed to be fully accountable for ensuring the integrity and accuracy of the work.

References

AHN, H. S., KIM, H. J. & WELCH, H. G. 2014. Korea's thyroid-cancer "epidemic"- screening and overdiagnosis. *N Engl J Med* **371**: 1765-7.

AHN, H. S. & WELCH, H. G. 2015. South Korea's thyroid-cancer "Epidemic"- Turning the tide. *N Engl J Med* **373**: 2389-90.

AUSTRALIAN BUREAU OF STATISTICS. 2008. *NSW Health Department, Admitted Patient Data Collection* [Online]. Available: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007 [Accessed September 2017].

BRITO, J. P., DAVIES, L., ZEBALLOS-PALACIOS, C., MORRIS, J. C. & MONTORI, V. M. 2014. Papillary lesions of indolent course: reducing the overdiagnosis of indolent papillary thyroid cancer and unnecessary treatment. *Future Oncol* **10**: 1-4.

BURGESS, J. R. 2002. Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). *Thyroid* **12**: 141-9.

BURGESS, J. R. & TUCKER, P. 2006. Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine-needle aspirate cytology. *Thyroid* **16**: 47-53.

CANCER AUSTRALIA. *Thyroid cancer* [Online]. Available: https://canceraustralia.gov.au/affected-cancer/cancer-types/thyroid-cancer/thyroid-cancer-statistics [Accessed September 2017].

CANCER INSTITUTE NSW. 2016a. *Thyroid cancer* [Online]. Available: https://www.cancerinstitute.org.au/understanding-cancer/cancer-in-nsw/thyroid-cancer [Accessed September 2017].

CANCER INSTITUTE NSW. 2016b. *Thyroid cancer - Age Standardised Incidence Rates* [Online]. Available: http://www.statistics.cancerinstitute.org.au/trends/trends_incid_C73_extall_NSW.htm [Accessed September 2017].

CANCER INSTITUTE NSW. 2016c. *Thyroid cancer - Age Standardised Mortality Rates* [Online]. Available:

http://www.statistics.cancerinstitute.org.au/trends/trends_mort_C73_extall_NSW.htm [Accessed September 2017].

DAVIES, L. & WELCH, H. 2014. Davies and welch draw unfounded conclusions about thyroid cancer from epidemiological data—reply. *JAMA Otolaryngol Head Neck Surg* **140**: 679.

DAVIES, L. & WELCH, H. G. 2006. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* **295**: 2164-7.

DOI, S. A. & WOODHOUSE, N. J. 2000. Ablation of the thyroid remnant and 131I dose in differentiated thyroid cancer. *Clin Endocrinol (Oxf)* **52**: 765-73.

DOI, S. A. R., WOODHOUSE, N. J., THALIB, L. & ONITILO, A. 2007. Ablation of the Thyroid Remnant and I-131 Dose in Differentiated Thyroid Cancer: A Meta-Analysis Revisited. *Clin Med Res* **5**: 87-90.

ENEWOLD, L., ZHU, K., RON, E., MARROGI, A. J., STOJADINOVIC, A., PEOPLES, G. E. & DEVESA, S. S. 2009. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev* **18**: 784-91.

ENEWOLD, L. R., ZHOU, J., DEVESA, S. S., BERRINGTON DE GONZALEZ, A., ANDERSON, W. F., ZAHM, S. H., STOJADINOVIC, A., PEOPLES, G. E., MARROGI, A. J., POTTER, J. F., MCGLYNN, K. A. & ZHU, K. 2011. Thyroid cancer incidence among active duty U.S. military personnel, 1990-2004. *Cancer Epidemiol Biomarkers Prev* **20**: 2369-76.

FURUYA-KANAMORI, L., BELL, K. J., CLARK, J., GLASZIOU, P. & DOI, S. A. 2016. Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis. *J Clin Oncol* **34**: 3672-9.

GOLDSBURY, D. E., ARMSTRONG, K., SIMONELLA, L., ARMSTRONG, B. K. & O'CONNELL, D. L. 2012. Using administrative health data to describe colorectal and lung cancer care in New South Wales, Australia: a validation study. *BMC Health Serv Res* **12**: 1472.

GOLDSBURY, D. E., SMITH, D. P., ARMSTRONG, B. K. & O'CONNELL, D. L. 2011. Using linked routinely collected health data to describe prostate cancer treatment in New South Wales, Australia: a validation study. *BMC Health Services Res* **11**: 253.

HAGGAR, F. A., PREEN, D. B., PEREIRA, G., HOLMAN, C. D. & EINARSDOTTIR, K. 2012. Cancer incidence and mortality trends in Australian adolescents and young adults, 1982-2007. *BMC Cancer* **12**: 151.

HARTL, D. M. & SCHLUMBERGER, M. 2013. Extent of Thyroidectomy and Incidence of Morbidity: Risk-appropriate Treatment. *In:* MICCOLI, P., TERRIS, D. J., MINUTO, M. N. & SEYBT, M. W. (eds.) *Thyroid Surgery: Preventing and Managing Complications.* Oxford: Wiley-Blackwell.

HAUGEN, B. R. M., ALEXANDER, E. K., BIBLE, K. C., DOHERTY, G., MANDEL, S. J., NIKIFOROV, Y. E., PACINI, F., RANDOLPH, G., SAWKA, A., SCHLUMBERGER, M., SCHUFF, K. G., SHERMAN, S. I., SOSA, J. A., STEWARD, D., TUTTLE, R. M. M. & WARTOFSKY, L. 2015. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **26**: 1-133.

HOANG, J. K., LANGER, J. E., MIDDLETON, W. D., WU, C. C., HAMMERS, L. W., CRONAN, J. J., TESSLER, F. N., GRANT, E. G. & BERLAND, L. L. 2015. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *J Am Coll Radiol* **12**: 143-50.

INDEPENDENT HOSPITAL PRICING AUTHORITY. 2015. *National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2012-2013, Round 17* [Online]. Available: https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-2013_round_17_0.pdf [Accessed September 2017].

ITO, Y., MIYAUCHI, A., INOUE, H., FUKUSHIMA, M., KIHARA, M., HIGASHIYAMA, T., TOMODA, C., TAKAMURA, Y., KOBAYASHI, K. & MIYA, A. 2010. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* **34**: 28-35.

ITO, Y., MIYAUCHI, A., KIHARA, M., HIGASHIYAMA, T., KOBAYASHI, K. & MIYA, A. 2014. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* **24**: 27-34.

LEBOULLEUX, S., TUTTLE, R. M., PACINI, F. & SCHLUMBERGER, M. 2016. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? *Lancet Diabetes Endocrinol* **4**: 933-42.

MANKARIOS, D., BAADE, P., YOUL, P., MORTIMER, R. H., ONITILO, A. A., RUSSELL, A. & DOI, S. A. 2014. Validation of the QTNM staging system for cancer-specific survival in patients with differentiated thyroid cancer. *Endocrine* **46**: 300-8.

ONITILO, A. A., ENGEL, J. M., LUNDGREN, C. I., HALL, P., THALIB, L. & DOI, S. A. 2009. Simplifying the TNM system for clinical use in differentiated thyroid cancer. *J Clin Oncol* **27**: 1872-8.

PANDEYA, N., MCLEOD, D. S., BALASUBRAMANIAM, K., BAADE, P. D., YOUL, P. H., BAIN, C. J., ALLISON, R. & JORDAN, S. J. 2016. Increasing thyroid cancer incidence in Queensland, Australia 1982-2008 - true increase or overdiagnosis? *Clin Endocrinol* **84**: 257-64.

PELLEGRITI, G., FRASCA, F., REGALBUTO, C., SQUATRITO, S. & VIGNERI, R. 2013. Worldwide increasing incidence of thyroid cancer: Update on epidemiology and risk factors. *J Cancer Epidemiol* **2013**: 965212.

REGO-IRAETA, A., PEREZ-MENDEZ, L. F., MANTINAN, B. & GARCIA-MAYOR, R. V. 2009. Time trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. *Thyroid* **19**: 333-40.

SUGITANI, I., TODA, K., YAMADA, K., YAMAMOTO, N., IKENAGA, M. & FUJIMOTO, Y. 2010. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg* **34**: 1222-31.

SUNG, M. W., PARK, B., AN, S. Y., HAH, J. H., JUNG, Y. H. & CHOI, H. G. 2014. Increasing thyroid cancer rate and the extent of thyroid surgery in Korea. *PLoS One* **9**: e113464.

WELCH, H. G. & BLACK, W. C. 2010. Overdiagnosis in cancer. *J Natl Cancer Inst* **102**: 605-13.

Table Title

Table 1. Patient's characteristics

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

Figure Legend

Figure 1. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in females. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the last decade and the excess in surgery-related healthcare expenditure associated with this.

Figure 2. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in males. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the last decade and the excess in surgery-related healthcare expenditure associated with this.