



**ENDOCRINE-RELATED
CANCER**



Differentiated thyroid cancer: Millions spent with no tangible gain?

Journal:	<i>Endocrine-Related Cancer</i>
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

SCHOLARONE™
Manuscripts

Only

1 Original Research

2

3 **Differentiated thyroid cancer: Millions spent with no tangible gain?**

4

5 Running title: Increase in DTC incidence and thyroidectomy

6

7 Luis Furuya-Kanamori *PhD*¹, Professor Art Sedrakyan *PhD*^{2,3}, Adedayo A. Onitilo *PhD*⁴,

8 Nasser Bagheri *PhD*², Professor Paul Glasziou *PhD*⁵, Professor Suhail A.R Doi *PhD*^{1*}

9

10

11 ¹ Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

12 ² Research School of Population Health, Australian National University, Canberra, ACT,
13 Australia

14 ³ Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, NY,
15 USA

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

17 ⁵ Centre for Research in Evidence Based Practice, Bond University, Gold Coast, QLD,
18 Australia

19

20

21 * Post-publication correspondence to:

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

23 Department of Population Medicine, College of Medicine, Qatar University

24 2713, Al Hala St, Doha, Qatar

25 sardo@mx.net

26

27

28 Word count: 2821

29 **Abstract**

30 **Background:** The incidence of differentiated thyroid cancer (DTC) has rapidly increased
31 worldwide over the last decades. It is unknown if the increase in diagnosis has been mirrored
32 by an increase in thyroidectomy rates with the concomitant economic impact that this would
33 have on the healthcare system.

34

35 **Methods:** DTC and thyroidectomy incidence as well as DTC specific mortality were
36 modelled using Poisson regression in New South Wales (NSW), Australia per year and by
37 sex. The incidence of 2002 was the point from which the increase in rates were assessed
38 cumulatively over the subsequent decade. The economic burden of potentially avoidable
39 thyroidectomies due to the increase in diagnosis was estimated as the product of the
40 additional thyroidectomy procedures during a decade attributable to rates beyond those
41 reported for 2002 and the national average hospital cost of an uncomplicated thyroidectomy
42 in Australia.

43

44 **Results:** The incidence of both DTC and thyroidectomy doubled in NSW between 2003 and
45 2012, while the DTC specific mortality rate remained unchanged over the same period. Based
46 on the 2002 incidence, the projected increase over 10 years (2003-2012) in thyroidectomy
47 procedures was 2,196. This translates to an extra cost burden of over AUD\$ 18,600,000 in
48 surgery-related healthcare expenditure over one decade in NSW.

49

50 **Conclusions:** Our findings suggest that, if this rise is solely attributable to overdiagnosis, then
51 the rising expenditure serves no additional purpose. Reducing unnecessary detection and a
52 conservative approach to managing DTC are sensible and would lead to millions of dollars in
53 savings and reduced harms to patients.

54

55 Introduction

56 The incidence of thyroid cancer has increased worldwide 3- to 15-fold over the last
57 two decades, but with no significant increase in mortality (Pellegriti et al., 2013, Ahn et al.,
58 2014). The increase in incidence is largely attributable to increased detection of differentiated
59 thyroid cancer ([DTC] – i.e. papillary and follicular cancer) (Burgess and Tucker, 2006,
60 Davies and Welch, 2006, Enewold et al., 2011). Studies have found that the penetrance of
61 thyroid-cancer screening and fine-needle aspiration (FNA) strongly correlate with the
62 observed increase in incidence (Burgess and Tucker, 2006, Ahn et al., 2014). Our recent
63 investigation has also found that the increasing incidence of DTC is not mirrored by the
64 prevalence of incidental DTC in autopsy studies which has remained stable since 1970
65 (Furuya-Kanamori et al., 2016). These findings, especially given the latter, establish the case
66 for the absence of a true population level increase in tumorigenesis and supports the notion
67 that the increasing burden is driven by increasing detection (Davies and Welch, 2006, Welch
68 and Black, 2010, Brito et al., 2014, Furuya-Kanamori et al., 2016).

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

79 to a 40% decrease in thyroidectomies within the country in the subsequent year (Ahn and
80 Welch, 2015).

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

88 **Materials and methods**

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

92

93 ***Data sources and study population***

94 Aggregated data from patients diagnosed with thyroid cancer (Cancer Institute NSW,
95 2016b) and thyroid cancer specific deaths (Cancer Institute NSW, 2016c) in NSW between
96 January 1982 and December 2012 were retrieved from the Cancer Institute NSW. The NSW
97 Cancer Registry (NSWCR) is managed by the Cancer Institute NSW. The NSWCR is a
98 population-based cancer registry that contains records of people with malignant neoplasms in
99 NSW since 1972. Notification of new cancer cases and cancer deaths is legally required in
100 NSW and the NSWCR receives data from public and private hospitals, nursing homes, public
101 and private pathology laboratories, and the Registry of Births, Deaths and Marriage.

102 Data from patients with thyroid gland malignancies (ICD-10-CM C73) that underwent
103 partial (ICD-10-AM 30306-00, 30306-01, 30308-00, 30310-00, 90046-00) or total (ICD-10-
104 AM 30296-00, 30296-01, 90046-01, 90046-02) thyroidectomies between January 2002 and
105 December 2012 in NSW were extracted from the Admitted Patient Data Collection (APDC).
106 Thyroidectomies with indications other than thyroid cancer (i.e. thyrotoxicosis ICD-10-AM
107 30309-00) were excluded from the analysis. To avoid the inclusion of recurrent cases of
108 surgical procedures (e.g. partial thyroidectomy followed by a total thyroidectomy – ICD-10-
109 AM 30297-00, 30297-01, 30297-02) and over estimating the incidence of patients that
110 underwent a thyroidectomy; if a patient had more than one surgical procedure, only the first
111 procedure was included for the analysis. The APDC is administered by the NSW Health
112 Department. The APDC data provides reasonably accurate information on procedures and

113 comorbidities (Goldsbury et al., 2011, Goldsbury et al., 2012). A detailed description of the
114 APDC scope, collection methodology, maintenance, and data accuracy is described
115 elsewhere (Australian Bureau of Statistics, 2008).

116

For Review Only

117 *Statistical analyses*

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

131 Poisson regressions models using robust standard errors and the population as the
132 exposed population at risk were built to model the rates for incident DTC, incident
133 thyroidectomies, and thyroid cancer specific mortality in NSW by including an interaction
134 term for continuous year and sex. The predicted number of cases per year and by sex from the
135 fitted models were used to estimate the incidence of DTC and DTC specific mortality from
136 1982 to 2012 and thyroidectomy procedures from 2002 to 2012 in NSW per 100,000
137 population.

138 The rate observed in 2002 was deemed the baseline from which the increase in the
139 rate of thyroidectomy was computed over the subsequent decade. The increase in
140 thyroidectomy rates was therefore estimated for the period 2003-2012 as the difference from
141 the baseline had it remained at the 2002 levels. To compute the additional number of surgical

142 procedures over the last decade, the modelled difference in rates (from 2002 levels) was
143 multiplied by the population at risk in NSW during each year.

144 The national average hospital cost of uncomplicated thyroidectomy for 2012-2013 in
145 Australia was AUD\$ 8,500 (Independent Hospital Pricing Authority, 2015). The economic
146 burden of potentially avoidable thyroidectomy due to the increase in diagnosis to the
147 Australian healthcare system was estimated as the product of the additional thyroidectomy
148 within the decade after 2002 and the national average hospital cost of an uncomplicated
149 thyroidectomy. We did not estimate the costs of complications or ongoing treatment such as
150 thyroid replacement. All statistical analyses were conducted using Stata® SE, version 14
151 (Stata Corporation; College Station, TX).

152 Results

153 Between 1982 and 2012, 13,131 patients were diagnosed with DTC in NSW and 859
154 had a thyroid cancer specific mortality. The majority of diagnosed patients were females
155 (n=9,877; 75.1%). 6,790 thyroidectomies were recorded among patients with DTC between
156 2002 and 2012 in NSW hospitals. The majority of the thyroidectomy procedures were
157 performed in women (n=5,485; 80.89%) and the median age of the patients was 50 years
158 (IQR 40-62 years) (Table 1).

159 The estimated DTC incidence per 100,000 population increased from 3.4 (females)
160 and 1.2 (males) in 1982 to 20.6 (females) and 6.8 (males) in 2012. The estimated
161 thyroidectomy incidence per 100,000 population increased from 9.1 (females) and 3.0
162 (males) in 2002 to 18.6 (females) and 6.0 (males) in 2012; while the estimated thyroid cancer
163 specific mortality rate demonstrated no change over this period or indeed the prior two
164 decades (Figures 1 and 2 & Supplementary material).

165 During the decade of interest (2003-2012), there was a two-fold increase in both,
166 DTC and thyroidectomies among females and males. Since, the percentage of DTC
167 diagnosed patients getting a thyroidectomy has remained stable, it follows therefore that
168 watchful waiting is not happening at a greater rate than previously despite DTC incidence
169 steeply rising (Figures 1 & 2). Based on this increasing incidence, the projected increase in
170 thyroidectomy was 2,196 (1,667 females; 529 males) cases more than would have happened
171 if thyroidectomies rates had remained stable subsequent to 2002. This translates to an
172 increase of AUD\$ 18,666,000 (\$14,169,500 in females; \$4,496,500 in males) in surgery-
173 related healthcare expenditure over one decade in NSW (Figures 1 and 2).

174 **Discussion**

175 DTC incidence has increased to epidemic proportions worldwide over the last few
176 decades. Overdetection has not only increased DTC incidence, but it has also led to a
177 concurrent increase in thyroidectomy procedures with a huge economic burden on the
178 healthcare system (Table 2). Over the last decade, we estimate that the number of potentially
179 avoidable thyroidectomies performed in NSW was 2,196. The increase in thyroidectomy
180 procedures in NSW over this decade actually approximates the total estimated number of new
181 cases of thyroid cancer diagnosed Australia-wide in 2016 (2098 new cases) (Cancer
182 Australia). DTC specific mortality in Australia however has remained essentially unchanged
183 over the last 30 years (Cancer Australia) and among the thyroid cancer specific deaths
184 recorded in 2012 in NSW, half of them occurred in patients aged 80 years or above (Cancer
185 Institute NSW, 2016a). These figures amount to a huge excess in diagnosis and intervention
186 that do not lead to increased survival for patients (Davies and Welch, 2006, Ito et al., 2010,
187 Sugitani et al., 2010, Welch and Black, 2010, Ito et al., 2014, Furuya-Kanamori et al., 2016,
188 Cancer Australia).

189 It should be emphasised that we base our conclusion regarding the lack of tangible
190 clinical gain only on the specific mortality rate having remained unchanged. There is,
191 however, no expectation that intervention may decrease morbidity that does not lead to death.
192 Unfortunately, these interventions themselves have been associated with morbidities. In fact,
193 paradoxically there is likely to be an increase in morbidity related to treatment if patients
194 subject to such (over)diagnosis are given the standard management for thyroid cancer which
195 includes surgical resection and/or radioiodine therapy (Doi and Woodhouse, 2000, Doi et al.,
196 2007, Haugen et al., 2015). Surgical complications may arise and include
197 hypoparathyroidism, a life-threatening condition that requires intensive monitoring and
198 therapy with calcium and vitamin D; laryngeal nerve palsy which will results in voice

199 change; and/or require tracheotomy in cases of bilateral nerve damage. Even when the
200 surgery is complication free, most of the patients will require lifelong surveillance, and
201 thyroid hormone suppression or replacement which may have longer term metabolic
202 implications (Hartl and Schlumberger, 2013).

203 It could be argued that the increased thyroid cancer diagnosis in recent years is
204 associated with stable mortality because of improvement in diagnosis and management over
205 time. However, Davies and Welch have pointed out that this is not likely to be true (Davies
206 and Welch, 2014) because for mortality to remain stable, improvements (in diagnostic
207 techniques and disease management) have to precisely mirror the increase in thyroid
208 incidence. Thus, improvements occurring at a faster or slower rate than changes in incidence
209 rate would certainly alter mortality rates and to assume an exact match between the rising
210 incidence and the improvements over 30 years is highly implausible. In a previous study, we
211 demonstrated that the reservoir of incidental DTC has remained stable since 1970 suggesting
212 that population level of tumorigenesis has remained unchanged (Furuya-Kanamori et al.,
213 2016). Therefore, the most reasonable explanation for the rising thyroid cancer incidence
214 with stable mortality is that subclinical DTC is increasingly being detected due to the
215 improvements in diagnostic techniques, but these newly diagnosed subclinical cases may not
216 progress or will progress so slowly that the patient is more likely to die from other causes.

217 Overdetection of indolent DTC microcarcinomas could lead to unnecessary economic
218 burden, while late diagnosis of clinically significant thyroid cancer could worsen clinical
219 outcome. The current evidence does make the case for the development of strategies to
220 reduce overdetection (the thyroid should not be examined without a specific indication) as
221 well as implementation of a more conservative approach to nodule diagnosis through active
222 surveillance leading on to intervention if thyroid nodules demonstrate progression (i.e. size
223 and/or characteristics) (Leboulleux et al., 2016). At this point, it is not clear which patients

224 are eligible for active surveillance, further studies are required to accurately discriminate
225 patients who need to undergo thyroid nodule biopsy or active surveillance; as well as to
226 recognise prognostic factors that would warrant early intervention among the subset of
227 thyroid cancer patients with more aggressive disease. Currently, nodule size is an important
228 factor in such decision making, along with family history, exposure to radiation, and age of
229 the patient (>45 years) (Onitilo et al., 2009, Mankarios et al., 2014, Haugen et al., 2015,
230 Hoang et al., 2015). Although, differentiation of DTC histopathology (papillary versus
231 follicular) does not seem to play a major role in decision making, FNA cytology may be
232 indicated if there are signs of progression or to differentiate DTC from other types of
233 carcinomas (i.e. medullary and anaplastic) given the different prognosis associated with the
234 latter.

235 In terms of health services expenditure, thyroid gland surgeries in Australia cost on
236 average AUD\$ 8,500; however when there are surgical complications, this amount rapidly
237 increases to over AUD\$ 15,000 (Independent Hospital Pricing Authority, 2015). We used the
238 average cost of uncomplicated thyroidectomies, which provides a conservative economic
239 estimate of the burden of increasing diagnosis. Future economic evaluations would need to
240 take into account additional costs such as diagnosis (e.g. FNA and histopathology
241 examination), complications during the surgical intervention (e.g. ICU admission), hormone
242 replacement therapy, and outpatient consultations. Thus, a deferral of surgery can be
243 expected to lead to significant savings in projected healthcare expenditure of at least AUD\$ 4
244 million per year in the state of NSW. This cost saving over 10 years is weighted heavily
245 towards the later part of the decade and is a very conservative estimate as it does not take into
246 account the treatment factors mentioned previously and of course the emotional burden on
247 patients. Furthermore, given that the DTC incidence rise has been ongoing since the 1980s,
248 our estimate over only the last decade is probably a considerable underestimate of the

249 economic burden as overdetection/thyroidectomy may have increased 4-fold rather than just
250 2-fold. While, the data suggest a clear economic case for surveillance rather than
251 intervention, and accumulated evidence from several studies suggest that this would be a safe
252 approach (Ito et al., 2010, Sugitani et al., 2010, Brito et al., 2014, Ito et al., 2014); the exact
253 process that should be adopted requires further evidence from prospective clinical studies,
254 and funding for such studies must be made a priority.

255 Our findings should be considered in the light of a few limitations. An important one
256 was the inability to conduct sub-group analyses by age group, patient ethnicity, tumour size,
257 and histopathology. However, we were able to stratify the analyses by sex, which is known to
258 be one of the strongest predictors of DTC incidence and thyroidectomy. We also make the
259 assumption based on our previous work that the rising trends are representative of
260 overdiagnosis (Furuya-Kanamori et al., 2016). There have been studies that seem to disagree
261 and for example, from a SEER database analysis by Enewold et al. (2009) amongst White
262 women, the rate of increase for papillary thyroid carcinoma >5cm was similar to that for
263 smaller thyroid cancer. Another study from Spain by Rego-Iraeta et al. (2009) also reported
264 that the rate of rise in thyroid cancer was observed across all tumour sizes. We agree with the
265 latter that the incidence of all sizes are rising but a re-analysis of our previous data
266 (Mankarios et al., 2014) stratified by tumour size and gender clearly demonstrates that the
267 rate of rise decreases with increasing size, though all sizes are increasingly detected (data not
268 shown). We believe that this again is consistent with overdiagnosis. Nevertheless, it is
269 important to distinguish indolent tumours from clinically significant tumours (where delays
270 in diagnosis are important) and this requires guidance from future studies regarding
271 delineation of criteria for patients who need to undergo thyroid nodule biopsy for diagnosis of
272 thyroid cancer (to avoid over-diagnosis of indolent thyroid cancer). Such criteria would likely
273 be prognostic factors that would assist in identification of more advanced thyroid cancers

274 thus avoiding fears that clinicians may delay treatment and increase recurrent/persistent
275 disease within a selected sub-set of thyroid cancer patients with more aggressive disease.

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

282 **Declaration of interest**

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

284

285 **Funding**

286 None

287

288 **Authors' contributions**

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

294 **References**

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

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

299 AUSTRALIAN BUREAU OF STATISTICS. 2008. *NSW Health Department, Admitted*
300 *Patient Data Collection* [Online]. Available:
301 [http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1](http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007)
302 [452007](http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007) [Accessed September 2017].

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

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

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

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

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

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

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

- 323 http://www.statistics.cancerinstitute.org.au/trends/trends_mort_C73_extall_NSW.htm
324 [Accessed September 2017].
- 325 DAVIES, L. & WELCH, H. 2014. Davies and welch draw unfounded conclusions about
326 thyroid cancer from epidemiological data—reply. *JAMA Otolaryngol Head Neck Surg*
327 **140**: 679.
- 328 DAVIES, L. & WELCH, H. G. 2006. Increasing incidence of thyroid cancer in the United
329 States, 1973-2002. *JAMA* **295**: 2164-7.
- 330 DOI, S. A. & WOODHOUSE, N. J. 2000. Ablation of the thyroid remnant and 131I dose in
331 differentiated thyroid cancer. *Clin Endocrinol (Oxf)* **52**: 765-73.
- 332 DOI, S. A. R., WOODHOUSE, N. J., THALIB, L. & ONITILLO, A. 2007. Ablation of the
333 Thyroid Remnant and I-131 Dose in Differentiated Thyroid Cancer: A Meta-Analysis
334 Revisited. *Clin Med Res* **5**: 87-90.
- 335 ENEWOLD, L., ZHU, K., RON, E., MARROGI, A. J., STOJADINOVIC, A., PEOPLES, G.
336 E. & DEVESA, S. S. 2009. Rising thyroid cancer incidence in the United States by
337 demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers*
338 *Prev* **18**: 784-91.
- 339 ENEWOLD, L. R., ZHOU, J., DEVESA, S. S., BERRINGTON DE GONZALEZ, A.,
340 ANDERSON, W. F., ZAHM, S. H., STOJADINOVIC, A., PEOPLES, G. E.,
341 MARROGI, A. J., POTTER, J. F., MCGLYNN, K. A. & ZHU, K. 2011. Thyroid
342 cancer incidence among active duty U.S. military personnel, 1990-2004. *Cancer*
343 *Epidemiol Biomarkers Prev* **20**: 2369-76.
- 344 FURUYA-KANAMORI, L., BELL, K. J., CLARK, J., GLASZIOU, P. & DOI, S. A. 2016.
345 Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A
346 Meta-Analysis. *J Clin Oncol* **34**: 3672-9.
- 347 GOLDSBURY, D. E., ARMSTRONG, K., SIMONELLA, L., ARMSTRONG, B. K. &
348 O'CONNELL, D. L. 2012. Using administrative health data to describe colorectal and
349 lung cancer care in New South Wales, Australia: a validation study. *BMC Health Serv*
350 *Res* **12**: 1472.

- 351 GOLDSBURY, D. E., SMITH, D. P., ARMSTRONG, B. K. & O'CONNELL, D. L. 2011.
352 Using linked routinely collected health data to describe prostate cancer treatment in
353 New South Wales, Australia: a validation study. *BMC Health Services Res* **11**: 253.
- 354 HAGGAR, F. A., PREEN, D. B., PEREIRA, G., HOLMAN, C. D. & EINARSDOTTIR, K.
355 2012. Cancer incidence and mortality trends in Australian adolescents and young
356 adults, 1982-2007. *BMC Cancer* **12**: 151.
- 357 HARTL, D. M. & SCHLUMBERGER, M. 2013. Extent of Thyroidectomy and Incidence of
358 Morbidity: Risk-appropriate Treatment. In: MICCOLI, P., TERRIS, D. J., MINUTO,
359 M. N. & SEYBT, M. W. (eds.) *Thyroid Surgery: Preventing and Managing*
360 *Complications*. Oxford: Wiley-Blackwell.
- 361 HAUGEN, B. R. M., ALEXANDER, E. K., BIBLE, K. C., DOHERTY, G., MANDEL, S. J.,
362 NIKIFOROV, Y. E., PACINI, F., RANDOLPH, G., SAWKA, A.,
363 SCHLUMBERGER, M., SCHUFF, K. G., SHERMAN, S. I., SOSA, J. A.,
364 STEWARD, D., TUTTLE, R. M. M. & WARTOFSKY, L. 2015. 2015 American
365 Thyroid Association management guidelines for adult patients with thyroid nodules
366 and differentiated thyroid cancer. *Thyroid* **26**: 1-133.
- 367 HOANG, J. K., LANGER, J. E., MIDDLETON, W. D., WU, C. C., HAMMERS, L. W.,
368 CRONAN, J. J., TESSLER, F. N., GRANT, E. G. & BERLAND, L. L. 2015.
369 Managing incidental thyroid nodules detected on imaging: white paper of the ACR
370 Incidental Thyroid Findings Committee. *J Am Coll Radiol* **12**: 143-50.
- 371 INDEPENDENT HOSPITAL PRICING AUTHORITY. 2015. *National Hospital Cost Data*
372 *Collection Australian Public Hospitals Cost Report 2012-2013, Round 17* [Online].
373 Available:
374 [https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-](https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-2013_round_17_0.pdf)
375 [2013_round_17_0.pdf](https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-2013_round_17_0.pdf) [Accessed September 2017].
- 376 ITO, Y., MIYAUCHI, A., INOUE, H., FUKUSHIMA, M., KIHARA, M., HIGASHIYAMA,
377 T., TOMODA, C., TAKAMURA, Y., KOBAYASHI, K. & MIYA, A. 2010. An
378 observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J*
379 *Surg* **34**: 28-35.

- 380 ITO, Y., MIYAUCHI, A., KIHARA, M., HIGASHIYAMA, T., KOBAYASHI, K. & MIYA,
381 A. 2014. Patient age is significantly related to the progression of papillary
382 microcarcinoma of the thyroid under observation. *Thyroid* **24**: 27-34.
- 383 LEBOULLEUX, S., TUTTLE, R. M., PACINI, F. & SCHLUMBERGER, M. 2016. Papillary
384 thyroid microcarcinoma: time to shift from surgery to active surveillance? *Lancet*
385 *Diabetes Endocrinol* **4**: 933-42.
- 386 MANKARIOS, D., BAADE, P., YOUL, P., MORTIMER, R. H., ONITILLO, A. A.,
387 RUSSELL, A. & DOI, S. A. 2014. Validation of the QTNM staging system for
388 cancer-specific survival in patients with differentiated thyroid cancer. *Endocrine* **46**:
389 300-8.
- 390 ONITILLO, A. A., ENGEL, J. M., LUNDGREN, C. I., HALL, P., THALIB, L. & DOI, S. A.
391 2009. Simplifying the TNM system for clinical use in differentiated thyroid cancer. *J*
392 *Clin Oncol* **27**: 1872-8.
- 393 PANDEYA, N., MCLEOD, D. S., BALASUBRAMANIAM, K., BAADE, P. D., YOUL, P.
394 H., BAIN, C. J., ALLISON, R. & JORDAN, S. J. 2016. Increasing thyroid cancer
395 incidence in Queensland, Australia 1982-2008 - true increase or overdiagnosis? *Clin*
396 *Endocrinol* **84**: 257-64.
- 397 PELLEGRITI, G., FRASCA, F., REGALBUTO, C., SQUATRITO, S. & VIGNERI, R. 2013.
398 Worldwide increasing incidence of thyroid cancer: Update on epidemiology and risk
399 factors. *J Cancer Epidemiol* **2013**: 965212.
- 400 REGO-IRAETA, A., PEREZ-MENDEZ, L. F., MANTINAN, B. & GARCIA-MAYOR, R.
401 V. 2009. Time trends for thyroid cancer in northwestern Spain: true rise in the
402 incidence of micro and larger forms of papillary thyroid carcinoma. *Thyroid* **19**: 333-
403 40.
- 404 SUGITANI, I., TODA, K., YAMADA, K., YAMAMOTO, N., IKENAGA, M. &
405 FUJIMOTO, Y. 2010. Three distinctly different kinds of papillary thyroid
406 microcarcinoma should be recognized: our treatment strategies and outcomes. *World*
407 *J Surg* **34**: 1222-31.

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

411 WELCH, H. G. & BLACK, W. C. 2010. Overdiagnosis in cancer. *J Natl Cancer Inst* **102**:
412 605-13.

413 **Table Title**

414

415 **Table 1.** Patient's characteristics

416

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

418

419

420

421 **Figure Legend**

422

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

428

429 **Figure 2.** Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC
430 (blue), thyroidectomies (red), and DTC specific mortality (green) over time in males. Gray
431 shaded area represents the excess (potentially avoidable) thyroidectomies performed due to
432 the increase in diagnosis over the last decade and the excess in surgery-related healthcare
433 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

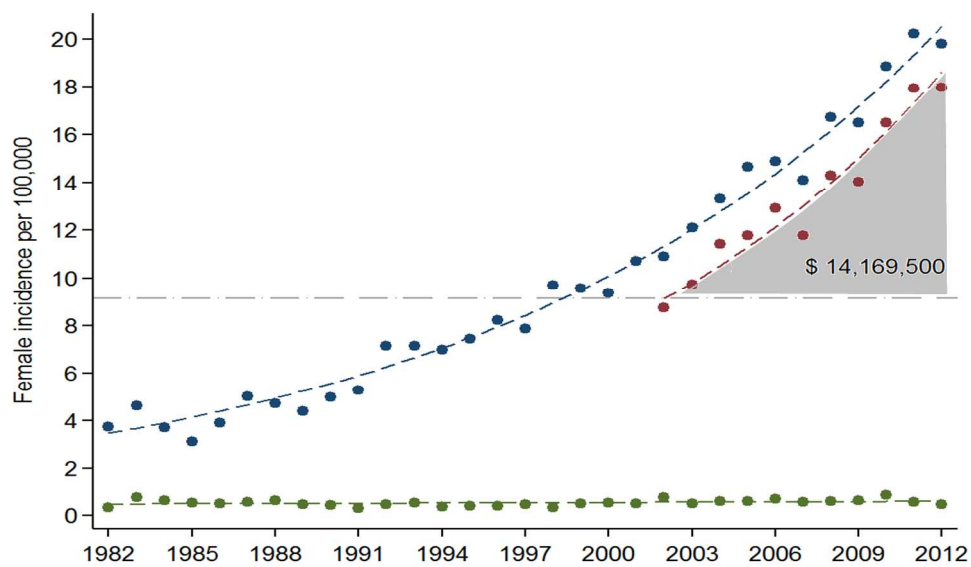


Figure 1. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in females. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over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

1765x1051mm (96 x 96 DPI)

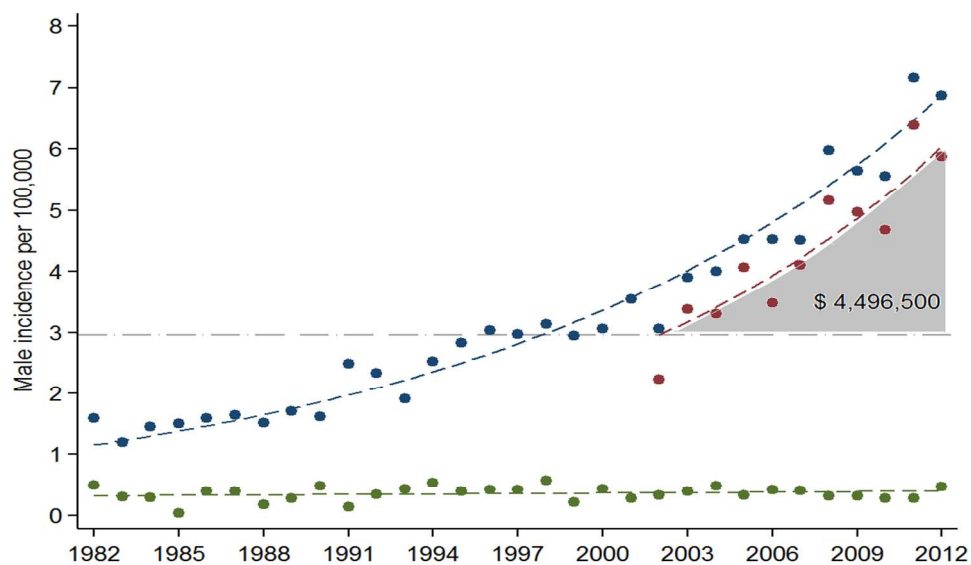


Figure 2. Observed (circles) and modelled (dashed lines) incidence per 100,000 for DTC (blue), thyroidectomies (red), and DTC specific mortality (green) over time in males. Gray shaded area represents the excess (potentially avoidable) thyroidectomies performed due to the increase in diagnosis over the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

1 Original Research

2

3 **Differentiated thyroid cancer: Millions spent with no tangible gain?**

4

5 Running title: Increase in DTC incidence and thyroidectomy

6

7 Luis Furuya-Kanamori *PhD*¹, Professor Art Sedrakyan *PhD*^{2,3}, Adedayo A. Onitilo *PhD*⁴,

8 Nasser Bagheri *PhD*², Professor Paul Glasziou *PhD*⁵, Professor Suhail A.R Doi *PhD*^{6,1*}

9

10

11 ¹ Department of ~~Population~~ Public Medicine ~~Health~~, College of ~~Medicine~~ Health Sciences, Qatar
12 University, Doha, Qatar

13 ² Research School of Population Health, Australian National University, Canberra, ACT,
14 Australia

15 ³ Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, NY,
16 USA

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

18 ⁵ Centre for Research in Evidence Based Practice, Bond University, Gold Coast, QLD,
19 Australia

20 ~~⁶ Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar~~

21

22

23 * Post-publication correspondence to:

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

25 Department of Population Medicine, College of Medicine, Qatar University

26 2713, Al Hala St, Doha, Qatar

27 sardois@gmx.net

28

29

30 Word count: 2574

31 **Abstract**

32 **Background:** The incidence of differentiated thyroid cancer (DTC) has rapidly increased
33 worldwide over the last decades. It is unknown if the increase in diagnosis has been mirrored
34 by an increase in thyroidectomy rates with the concomitant economic impact that this would
35 have on the healthcare system.

36

37 **Methods:** DTC and thyroidectomy incidence as well as DTC specific mortality were
38 modelled using Poisson regression in New South Wales (NSW), Australia per year and by
39 sex. The incidence of 2002 was the point from which the increase in rates were assessed
40 cumulatively over the subsequent decade. The economic burden of potentially avoidable
41 thyroidectomies due to the increase in diagnosis was estimated as the product of the
42 additional thyroidectomy procedures during a decade attributable to rates beyond those
43 reported for 2002 and the national average hospital cost of an uncomplicated thyroidectomy
44 in Australia.

45

46 **Results:** The incidence of both DTC and thyroidectomy doubled in NSW between 2003 and
47 2012, while the DTC specific mortality rate remained unchanged over the same period. Based
48 on the 2002 incidence, the projected increase over 10 years (2003-2012) in thyroidectomy
49 procedures was 2,196. This translates to an extra cost burden of over AUD\$ 18,600,000 in
50 surgery-related healthcare expenditure over one decade in NSW.

51

52 **Conclusions:** Our findings suggest that, if this rise is solely attributable to overdiagnosis, then
53 the rising expenditure serves no additional purpose. Reducing unnecessary detection and a
54 conservative approach to managing DTC are sensible and would lead to millions of dollars in
55 savings and reduced harms to patients.

56

57 Introduction

58 The incidence of thyroid cancer has increased worldwide 3- to 15-fold over the last
59 two decades, but with no significant increase in mortality (Pellegriti et al., 2013, Ahn et al.,
60 2014). The increase in incidence is largely attributable to increased detection of differentiated
61 thyroid cancer ([DTC] – i.e. papillary and follicular cancer) (Burgess and Tucker, 2006,
62 Davies and Welch, 2006, Enewold et al., 2011). Studies have found that the penetrance of
63 thyroid-cancer screening and fine-needle aspiration (FNA) strongly correlate with the
64 observed increase in incidence (Burgess and Tucker, 2006, Ahn et al., 2014). Our recent
65 investigation has also found that the increasing incidence of DTC is not mirrored by the
66 prevalence of incidental DTC in autopsy studies which has remained stable since 1970
67 (Furuya-Kanamori et al., 2016). These findings, especially given the latter, establish the case
68 for the absence of a true population level increase in tumorigenesis and supports the notion
69 that the increasing burden is driven by increasing detection (Davies and Welch, 2006, Welch
70 and Black, 2010, Brito et al., 2014, Furuya-Kanamori et al., 2016).

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

81 | led to a 40% decrease in thyroidectomies within the country in the subsequent year (Ahn and
82 | Welch, 2015).

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

90 **Materials and methods**

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

94

95 ***Data sources and study population***

96 Aggregated data from patients diagnosed with thyroid cancer (Cancer Institute NSW,
97 2016b) and thyroid cancer specific deaths (Cancer Institute NSW, 2016c) in NSW between
98 January 1982 and December 2012 were retrieved from the Cancer Institute NSW. The NSW
99 Cancer Registry (NSWCR) is managed by the Cancer Institute NSW. The NSWCR is a
100 population-based cancer registry that contains records of people with malignant neoplasms in
101 NSW since 1972. Notification of new cancer cases and cancer deaths is legally required in
102 NSW and the NSWCR receives data from public and private hospitals, nursing homes, public
103 and private pathology laboratories, and the Registry of Births, Deaths and Marriage.

104 Data from patients with thyroid gland malignancies (ICD-10-CM C73) that underwent
105 partial (ICD-10-AM 30306-00, 30306-01, 30308-00, 30310-00, 90046-00) or total (ICD-10-
106 AM 30296-00, 30296-01, 90046-01, 90046-02) thyroidectomies between January 2002 and
107 December 2012 in NSW were extracted from the Admitted Patient Data Collection (APDC).
108 Thyroidectomies with indications other than thyroid cancer (i.e. thyrotoxicosis ICD-10-AM
109 30309-00) were excluded from the analysis. To avoid the inclusion of recurrent cases of
110 surgical procedures (e.g. partial thyroidectomy followed by a total thyroidectomy – ICD-10-
111 AM 30297-00, 30297-01, 30297-02) and over estimating the incidence of patients that
112 underwent a thyroidectomy; if a patient had more than one surgical procedure, only the first
113 procedure was included for the analysis. The APDC is administered by the NSW Health
114 Department. The APDC data provides reasonably accurate information on procedures and

115 comorbidities (Goldsbury et al., 2011, Goldsbury et al., 2012). A detailed description of the
116 APDC scope, collection methodology, maintenance, and data accuracy is described
117 elsewhere (Australian Bureau of Statistics, 2008).

118

For Review Only

119 *Statistical analyses*

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

134 Poisson regressions models using robust standard errors and the population as the
135 exposed population at risk were built to model the rates for incident DTC, incident
136 thyroidectomies, and thyroid cancer specific mortality in NSW by including an interaction
137 term for continuous year and sex. The predicted number of cases per year and by sex from the
138 fitted models were used to estimate the incidence of DTC and DTC specific mortality from
139 1982 to 2012 and thyroidectomy procedures from 2002 to 2012 in NSW per 100,000
140 population.

141 The rate observed in 2002 was deemed the baseline from which the increase in the
142 rate of thyroidectomy was computed over the subsequent decade. The increase in
143 thyroidectomy rates was therefore estimated for the period 2003-2012 as the difference from

144 the baseline had it remained at the 2002 levels. To compute the additional number of surgical
145 procedures over the last decade, the modelled difference in rates (from 2002 levels) was
146 multiplied by the population at risk in NSW during each year.

147 The national average hospital cost of uncomplicated thyroidectomy for 2012-2013 in
148 Australia was AUD\$ 8,500 (Independent Hospital Pricing Authority, 2015). The economic
149 burden of potentially avoidable thyroidectomy due to the increase in diagnosis to the
150 Australian healthcare system was estimated as the product of the additional thyroidectomy
151 within the decade after 2002 and the national average hospital cost of an uncomplicated
152 thyroidectomy. We did not estimate the costs of complications or ongoing treatment such as
153 thyroid replacement. All statistical analyses were conducted using Stata® SE, version 14
154 (Stata Corporation; College Station, TX).

155 Results

156 Between 1982 and 2012, 13,131 patients were diagnosed with DTC in NSW and 859
157 had a thyroid cancer specific mortality. The majority of diagnosed patients were females
158 (n=9,877; 75.1%). 6,790 thyroidectomies were recorded among patients with DTC between
159 2002 and 2012 in NSW hospitals. The majority of the thyroidectomy procedures were
160 performed in women (n=5,485; 80.89%) and the median age of the patients was 50 years
161 (IQR 40-62 years) (Table 1).

162 The estimated DTC incidence per 100,000 population increased from 3.4 (females)
163 and 1.2 (males) in 1982 to 20.6 (females) and 6.8 (males) in 2012. The estimated
164 thyroidectomy incidence per 100,000 population increased from 9.1 (females) and 3.0
165 (males) in 2002 to 18.6 (females) and 6.0 (males) in 2012; while the estimated thyroid cancer
166 specific mortality rate demonstrated no change over this period or indeed the prior two
167 decades (Figures 1 and 2 & Supplementary material).

168 During the decade of interest (2003-2012), there was a two-fold increase in both,
169 DTC and thyroidectomies among females and males. Since, the percentage of DTC
170 diagnosed patients getting a thyroidectomy has remained stable, ~~therefore it follows therefore~~
171 that watchful waiting is not happening at a greater rate than previously despite DTC
172 incidence steeply rising (Figures 1 & 2). Based on this increasing incidence, the projected
173 increase in thyroidectomy was 2,196 (1,667 females; 529 males) cases more than would have
174 happened if thyroidectomy rates had remained stable subsequent to 2002. This translates to
175 an increase of AUD\$ 18,666,000 (\$14,169,500 in females; \$4,496,500 in males) in surgery-
176 related healthcare expenditure over one decade in NSW (Figures 1 and 2).

177 **Discussion**

178 DTC incidence has increased to epidemic proportions worldwide over the last few
179 decades. Overdetection has not only increased DTC incidence, but it has also led to a
180 concurrent increase in thyroidectomy procedures with a huge economic burden on the
181 healthcare system (Table 2). Over the last decade, we estimate that the number of potentially
182 avoidable thyroidectomies performed in NSW was 2,196. The increase in thyroidectomy
183 procedures in NSW over this decade actually approximates the total estimated number of new
184 cases of thyroid cancer diagnosed Australia-wide in 2016 (2098 new cases) (Cancer
185 Australia). DTC specific mortality in Australia however has remained essentially unchanged
186 over the last 30 years (Cancer Australia) and among the thyroid cancer specific deaths
187 recorded in 2012 in NSW, half of them occurred in patients aged 80 years or above (Cancer
188 Institute NSW, 2016a). These figures amount to a huge excess in diagnosis and intervention
189 that do not lead to increased survival for patients (Davies and Welch, 2006, Ito et al., 2010,
190 Sugitani et al., 2010, Welch and Black, 2010, Ito et al., 2014, Furuya-Kanamori et al., 2016,
191 Cancer Australia).

192 It should be emphasised that we base our conclusion regarding the lack of tangible
193 clinical gain only on the specific mortality rate having remained unchanged. There is,
194 however, no expectation that intervention may decrease morbidity that does not lead to death.
195 Unfortunately, these interventions themselves have been associated with morbidities. In fact,
196 paradoxically there is likely to be an increase in morbidity related to treatment if patients
197 subject to such (over)diagnosis are given the standard management for thyroid cancer which
198 includes surgical resection and/or radioiodine therapy (Doi and Woodhouse, 2000, Doi et al.,
199 2007, Haugen et al., 2015). Surgical complications may arise and include
200 hypoparathyroidism, a life-threatening condition that requires intensive monitoring and
201 therapy with calcium and vitamin D; laryngeal nerve palsy which will result in voice

202 change; and/or require tracheotomy in cases of bilateral nerve damage. Even when the
203 surgery is complication free, most of the patients will require lifelong surveillance, and
204 thyroid hormone suppression or replacement which may have longer term metabolic
205 implications (Hartl and Schlumberger, 2013).

206 It could be argued that the increased thyroid cancer diagnosis in recent years is
207 associated with stable mortality because of improvement in diagnosis and management over
208 time. However, Davies and Welch have pointed out that this is not likely to be true (Davies
209 and Welch, 2014) because for mortality to remain stable, improvements (in diagnostic
210 techniques and disease management) have to precisely mirror the increase in thyroid
211 incidence. Thus, improvements occurring at a faster or slower rate than changes in incidence
212 rate would certainly alter mortality rates and to assume an exact match between the rising
213 incidence and the improvements over 30 years is highly implausible. In a previous study, we
214 demonstrated that the reservoir of incidental DTC has remained stable since 1970 suggesting
215 that population level of tumorigenesis has remained unchanged (Furuya-Kanamori et al.,
216 2016). Therefore, the most reasonable explanation for the rising thyroid cancer incidence
217 with stable mortality is that subclinical DTC is increasingly being detected due to the
218 improvements in diagnostic techniques, but these newly diagnosed subclinical cases may not
219 progress or will progress so slowly that the patient is more likely to die from other causes.

220 Overdetection of indolent DTC microcarcinomas could lead to unnecessary economic
221 burden, while late diagnosis of clinically significant thyroid cancer could worsen clinical
222 outcome. The current evidence does make the case for the development of strategies to
223 reduce overdetection (the thyroid should not be examined without a specific indication) as
224 well as implementation of a more conservative approach to nodule diagnosis through active
225 surveillance leading on to intervention if thyroid nodules demonstrate progression (i.e. size
226 and/or characteristics) (Leboulleux et al., 2016). At this point, it is not clear which patients

227 are eligible for active surveillance, further studies are required to accurately discriminate
228 patients who need to undergo thyroid nodule biopsy or active surveillance; as well as to
229 recognise prognostic factors that would warrant early intervention among the subset of
230 thyroid cancer patients with more aggressive disease. Currently, nodule size is an important
231 factor in such decision making, along with family history, exposure to radiation, and age of
232 the patient (>45 years) (Onitilo et al., 2009, Mankarios et al., 2014, Haugen et al., 2015,
233 Hoang et al., 2015). Although, differentiation of DTC histopathology (papillary versus
234 follicular) does not seem to play a major role in decision making, FNA cytology may be
235 indicated if there are signs of progression or to differentiate DTC from other types of
236 carcinomas (i.e. medullary and anaplastic) given the different prognosis associated with the
237 latter.

238 In terms of health services expenditure, thyroid gland surgeries in Australia cost on
239 average AUD\$ 8,500; however when there are surgical complications, this amount rapidly
240 increases to over AUD\$ 15,000 (Independent Hospital Pricing Authority, 2015). We used the
241 average cost of uncomplicated thyroidectomies, which provides a conservative economic
242 estimate of the burden of increasing diagnosis. Future economic evaluations would need to
243 take into account additional costs such as diagnosis (e.g. FNA and histopathology
244 examination), complications during the surgical intervention (e.g. ICU admission), hormone
245 replacement therapy, and outpatient consultations. Thus, a deferral of surgery can be
246 expected to lead to significant savings in projected healthcare expenditure of at least AUD\$ 4
247 million per year in the state of NSW. This cost saving over 10 years is weighted heavily
248 towards the later part of the decade and is a very conservative estimate as it does not take into
249 account the treatment factors mentioned previously and of course the emotional burden on
250 patients. Furthermore, given that the DTC incidence rise has been ongoing since the 1980s,
251 our estimate over only the last decade is probably a considerable underestimate of the

252 economic burden as overdetection/thyroidectomy may have increased 4-fold rather than just
253 2-fold. While, the data suggest a clear economic case for surveillance rather than
254 intervention, and accumulated evidence from several studies suggest that this would be a safe
255 approach (Ito et al., 2010, Sugitani et al., 2010, Brito et al., 2014, Ito et al., 2014); the exact
256 process that should be adopted requires further evidence from prospective clinical studies,
257 and funding for such studies must be made a priority.

258 Our findings should be considered in the light of a few limitations. An important one
259 was the inability to conduct sub-group analyses by age group, patient ethnicity, tumour size,
260 and histopathology. However, we were able to stratify the analyses by sex, which is known to
261 be one of the strongest predictors of DTC incidence and thyroidectomy. We also make the
262 assumption based on our previous work that the rising trends are representative of
263 overdiagnosis (Furuya-Kanamori et al., 2016). There have been studies that seem to disagree
264 and for example, from a SEER database analysis by Enewold et al. (2009) amongst White
265 women, the rate of increase for papillary thyroid carcinoma >5cm was similar to that for
266 smaller thyroid cancer. Another study from Spain by Rego-Iraeta et al. (2009) also reported
267 that the rate of rise in thyroid cancer was observed across all tumour sizes. We agree with the
268 latter that the incidence of all sizes are rising but a re-analysis of our previous data
269 (Mankarios et al., 2014) stratified by tumour size and gender clearly demonstrates that the
270 rate of rise decreases with increasing size, though all sizes are increasingly detected (data not
271 shown). We believe that this again is consistent with overdiagnosis. Nevertheless, it is
272 important to distinguish indolent tumours from clinically significant tumours (where delays
273 in diagnosis are important) and this requires guidance from future studies regarding
274 delineation of criteria for patients who need to undergo thyroid nodule biopsy for diagnosis of
275 thyroid cancer (to avoid over-diagnosis of indolent thyroid cancer). Such criteria would likely
276 be prognostic factors that would assist in identification of more advanced thyroid cancers

277 thus avoiding fears that clinicians may delay treatment and increase recurrent/persistent
278 disease within a selected sub-set of thyroid cancer patients with more aggressive disease.

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

285 **Declaration of interest**

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

287

288 **Funding**

289 None

290

291 **Authors' contributions**

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

297 **References**

- 298 AHN, H. S., KIM, H. J. & WELCH, H. G. 2014. Korea's thyroid-cancer "epidemic"-
299 screening and overdiagnosis. *N Engl J Med* **371**: 1765-7.
- 300 AHN, H. S. & WELCH, H. G. 2015. South Korea's thyroid-cancer "Epidemic"- Turning the
301 tide. *N Engl J Med* **373**: 2389-90.
- 302 AUSTRALIAN BUREAU OF STATISTICS. 2008. *NSW Health Department, Admitted*
303 *Patient Data Collection* [Online]. Available:
304 [http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1](http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007)
305 [452007](http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007) [Accessed September 2017].
- 306 BRITO, J. P., DAVIES, L., ZEBALLOS-PALACIOS, C., MORRIS, J. C. & MONTORI, V.
307 M. 2014. Papillary lesions of indolent course: reducing the overdiagnosis of indolent
308 papillary thyroid cancer and unnecessary treatment. *Future Oncol* **10**: 1-4.
- 309 BURGESS, J. R. 2002. Temporal trends for thyroid carcinoma in Australia: an increasing
310 incidence of papillary thyroid carcinoma (1982-1997). *Thyroid* **12**: 141-9.
- 311 BURGESS, J. R. & TUCKER, P. 2006. Incidence trends for papillary thyroid carcinoma and
312 their correlation with thyroid surgery and thyroid fine-needle aspirate cytology.
313 *Thyroid* **16**: 47-53.
- 314 CANCER AUSTRALIA. *Thyroid cancer* [Online]. Available:
315 [https://canceraustralia.gov.au/affected-cancer/cancer-types/thyroid-cancer/thyroid-](https://canceraustralia.gov.au/affected-cancer/cancer-types/thyroid-cancer/thyroid-cancer-statistics)
316 [cancer-statistics](https://canceraustralia.gov.au/affected-cancer/cancer-types/thyroid-cancer/thyroid-cancer-statistics) [Accessed September 2017].
- 317 CANCER INSTITUTE NSW. 2016a. *Thyroid cancer* [Online]. Available:
318 [https://www.cancerinstitute.org.au/understanding-cancer/cancer-in-nsw/thyroid-](https://www.cancerinstitute.org.au/understanding-cancer/cancer-in-nsw/thyroid-cancer)
319 [cancer](https://www.cancerinstitute.org.au/understanding-cancer/cancer-in-nsw/thyroid-cancer) [Accessed September 2017].
- 320 CANCER INSTITUTE NSW. 2016b. *Thyroid cancer - Age Standardised Incidence Rates*
321 [Online]. Available:
322 http://www.statistics.cancerinstitute.org.au/trends/trends_incid_C73_extall_NSW.htm
323 [Accessed September 2017].
- 324 CANCER INSTITUTE NSW. 2016c. *Thyroid cancer - Age Standardised Mortality Rates*
325 [Online]. Available:

- 326 http://www.statistics.cancerinstitute.org.au/trends/trends_mort_C73_extall_NSW.htm
327 [Accessed September 2017].
- 328 DAVIES, L. & WELCH, H. 2014. Davies and welch draw unfounded conclusions about
329 thyroid cancer from epidemiological data—reply. *JAMA Otolaryngol Head Neck Surg*
330 **140**: 679.
- 331 DAVIES, L. & WELCH, H. G. 2006. Increasing incidence of thyroid cancer in the United
332 States, 1973-2002. *JAMA* **295**: 2164-7.
- 333 DOI, S. A. & WOODHOUSE, N. J. 2000. Ablation of the thyroid remnant and 131I dose in
334 differentiated thyroid cancer. *Clin Endocrinol (Oxf)* **52**: 765-73.
- 335 DOI, S. A. R., WOODHOUSE, N. J., THALIB, L. & ONITILLO, A. 2007. Ablation of the
336 Thyroid Remnant and I-131 Dose in Differentiated Thyroid Cancer: A Meta-Analysis
337 Revisited. *Clin Med Res* **5**: 87-90.
- 338 ENEWOLD, L., ZHU, K., RON, E., MARROGI, A. J., STOJADINOVIC, A., PEOPLES, G.
339 E. & DEVESA, S. S. 2009. Rising thyroid cancer incidence in the United States by
340 demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers*
341 *Prev* **18**: 784-91.
- 342 ENEWOLD, L. R., ZHOU, J., DEVESA, S. S., BERRINGTON DE GONZALEZ, A.,
343 ANDERSON, W. F., ZAHM, S. H., STOJADINOVIC, A., PEOPLES, G. E.,
344 MARROGI, A. J., POTTER, J. F., MCGLYNN, K. A. & ZHU, K. 2011. Thyroid
345 cancer incidence among active duty U.S. military personnel, 1990-2004. *Cancer*
346 *Epidemiol Biomarkers Prev* **20**: 2369-76.
- 347 FURUYA-KANAMORI, L., BELL, K. J., CLARK, J., GLASZIOU, P. & DOI, S. A. 2016.
348 Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A
349 Meta-Analysis. *J Clin Oncol* **34**: 3672-9.
- 350 GOLDSBURY, D. E., ARMSTRONG, K., SIMONELLA, L., ARMSTRONG, B. K. &
351 O'CONNELL, D. L. 2012. Using administrative health data to describe colorectal and
352 lung cancer care in New South Wales, Australia: a validation study. *BMC Health Serv*
353 *Res* **12**: 1472.

- 354 GOLDSBURY, D. E., SMITH, D. P., ARMSTRONG, B. K. & O'CONNELL, D. L. 2011.
355 Using linked routinely collected health data to describe prostate cancer treatment in
356 New South Wales, Australia: a validation study. *BMC Health Services Res* **11**: 253.
- 357 HAGGAR, F. A., PREEN, D. B., PEREIRA, G., HOLMAN, C. D. & EINARSDOTTIR, K.
358 2012. Cancer incidence and mortality trends in Australian adolescents and young
359 adults, 1982-2007. *BMC Cancer* **12**: 151.
- 360 HARTL, D. M. & SCHLUMBERGER, M. 2013. Extent of Thyroidectomy and Incidence of
361 Morbidity: Risk-appropriate Treatment. In: MICCOLI, P., TERRIS, D. J., MINUTO,
362 M. N. & SEYBT, M. W. (eds.) *Thyroid Surgery: Preventing and Managing*
363 *Complications*. Oxford: Wiley-Blackwell.
- 364 HAUGEN, B. R. M., ALEXANDER, E. K., BIBLE, K. C., DOHERTY, G., MANDEL, S. J.,
365 NIKIFOROV, Y. E., PACINI, F., RANDOLPH, G., SAWKA, A.,
366 SCHLUMBERGER, M., SCHUFF, K. G., SHERMAN, S. I., SOSA, J. A.,
367 STEWARD, D., TUTTLE, R. M. M. & WARTOFSKY, L. 2015. 2015 American
368 Thyroid Association management guidelines for adult patients with thyroid nodules
369 and differentiated thyroid cancer. *Thyroid* **26**: 1-133.
- 370 HOANG, J. K., LANGER, J. E., MIDDLETON, W. D., WU, C. C., HAMMERS, L. W.,
371 CRONAN, J. J., TESSLER, F. N., GRANT, E. G. & BERLAND, L. L. 2015.
372 Managing incidental thyroid nodules detected on imaging: white paper of the ACR
373 Incidental Thyroid Findings Committee. *J Am Coll Radiol* **12**: 143-50.
- 374 INDEPENDENT HOSPITAL PRICING AUTHORITY. 2015. *National Hospital Cost Data*
375 *Collection Australian Public Hospitals Cost Report 2012-2013, Round 17* [Online].
376 Available:
377 [https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-](https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-2013_round_17_0.pdf)
378 [2013_round_17_0.pdf](https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc_cost_report_2012-2013_round_17_0.pdf) [Accessed September 2017].
- 379 ITO, Y., MIYAUCHI, A., INOUE, H., FUKUSHIMA, M., KIHARA, M., HIGASHIYAMA,
380 T., TOMODA, C., TAKAMURA, Y., KOBAYASHI, K. & MIYA, A. 2010. An
381 observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J*
382 *Surg* **34**: 28-35.

- 383 ITO, Y., MIYAUCHI, A., KIHARA, M., HIGASHIYAMA, T., KOBAYASHI, K. & MIYA,
384 A. 2014. Patient age is significantly related to the progression of papillary
385 microcarcinoma of the thyroid under observation. *Thyroid* **24**: 27-34.
- 386 LEBOULLEUX, S., TUTTLE, R. M., PACINI, F. & SCHLUMBERGER, M. 2016. Papillary
387 thyroid microcarcinoma: time to shift from surgery to active surveillance? *Lancet*
388 *Diabetes Endocrinol* **4**: 933-42.
- 389 MANKARIOS, D., BAADE, P., YOUL, P., MORTIMER, R. H., ONITILLO, A. A.,
390 RUSSELL, A. & DOI, S. A. 2014. Validation of the QTNM staging system for
391 cancer-specific survival in patients with differentiated thyroid cancer. *Endocrine* **46**:
392 300-8.
- 393 ONITILLO, A. A., ENGEL, J. M., LUNDGREN, C. I., HALL, P., THALIB, L. & DOI, S. A.
394 2009. Simplifying the TNM system for clinical use in differentiated thyroid cancer. *J*
395 *Clin Oncol* **27**: 1872-8.
- 396 PANDEYA, N., MCLEOD, D. S., BALASUBRAMANIAM, K., BAADE, P. D., YOUL, P.
397 H., BAIN, C. J., ALLISON, R. & JORDAN, S. J. 2016. Increasing thyroid cancer
398 incidence in Queensland, Australia 1982-2008 - true increase or overdiagnosis? *Clin*
399 *Endocrinol* **84**: 257-64.
- 400 PELLEGRITI, G., FRASCA, F., REGALBUTO, C., SQUATRITO, S. & VIGNERI, R. 2013.
401 Worldwide increasing incidence of thyroid cancer: Update on epidemiology and risk
402 factors. *J Cancer Epidemiol* **2013**: 965212.
- 403 REGO-IRAETA, A., PEREZ-MENDEZ, L. F., MANTINAN, B. & GARCIA-MAYOR, R.
404 V. 2009. Time trends for thyroid cancer in northwestern Spain: true rise in the
405 incidence of micro and larger forms of papillary thyroid carcinoma. *Thyroid* **19**: 333-
406 40.
- 407 SUGITANI, I., TODA, K., YAMADA, K., YAMAMOTO, N., IKENAGA, M. &
408 FUJIMOTO, Y. 2010. Three distinctly different kinds of papillary thyroid
409 microcarcinoma should be recognized: our treatment strategies and outcomes. *World*
410 *J Surg* **34**: 1222-31.

- 411 SUNG, M. W., PARK, B., AN, S. Y., HAH, J. H., JUNG, Y. H. & CHOI, H. G. 2014.
412 Increasing thyroid cancer rate and the extent of thyroid surgery in Korea. *PLoS One* **9**:
413 e113464.
- 414 WELCH, H. G. & BLACK, W. C. 2010. Overdiagnosis in cancer. *J Natl Cancer Inst* **102**:
415 605-13.
- 416

For Review Only

417 **Table Title**

418

419 **Table 1.** Patient's characteristics

420

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

422

423

424

425 **Figure Legend**

426

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

432

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