Title: Increasing thyroid cancer incidence in Queensland, Australia 1982-2008 – true increase or over-diagnosis?

ABSTRACT:

Background: Thyroid cancer incidence has been increasing worldwide. Some suggest greater ascertainment of indolent tumours is the only driver, but others suggest there has been a true increase. Increases in Australia appear to have been among the largest in the world so we investigated incidence trends in the Australian state of Queensland to help understand reasons for the rise.

Methods: Thyroid cancers diagnoses in Queensland 1982-2008 were ascertained from the Queensland Cancer Registry. We calculated age-standardized incidence rates (ASR) and used Poisson regression to estimate annual percentage change (APC) in thyroid cancer incidence by socio-demographic and tumour-related factors.

Results: Thyroid cancer ASR in Queensland increased from 2.2 to 10.6/100,000 between 1982-2008 equating to an APC of 5.5% (95% Confidence Interval (CI) 4.7–6.4) in men and 6.1% (95%CI 5.5–6.6) in women. The rise was evident, and did not significantly differ, across socio-economic and remoteness-of-residence categories. The largest increase seen was in the papillary subtype in women (APC 7.9 %, 95%CI 7.3–8.5). Incidence of localized and more advanced-stage cancers rose over time although the increase was greater for early stage cancers.

Conclusion: There has been a marked increase in thyroid cancer incidence in Queensland. The increase is evident in men and women across all adult age groups, socioeconomic strata and remoteness-of-residence categories as well as in localized and more advanced-stage cancers. Our results suggest 'over-diagnosis' may not entirely explain rising incidence. Contemporary etiological data and individual-level information about diagnostic circumstances are required to further understand reasons for rising thyroid cancer incidence.

INTRODUCTION

Over the last thirty years the incidence of thyroid cancer has been increasing in most regions of the world,[1] but the reason for the rise is not completely clear.

Many attribute rising thyroid cancer incidence purely to the phenomenon of 'over-diagnosis'; that is, tumours that are indolent and would never have caused symptoms or death being diagnosed due to increasing use of more sensitive diagnostic tests. The evidence supporting this contention is compelling. The sharp rise in incidence has been observed predominantly in small (<2 cm) well-differentiated papillary cancers[2-4] without a notable parallel rise in mortality.[2] Furthermore incidental diagnosis is very common;[5] a reservoir of subclinical cancers in autopsy specimens has been documented;[6] there has been a parallel rise in the use of a variety of diagnostic tests;[7, 8] and documented variation in thyroid cancer incidence according to access to healthcare.[9]

However, some data suggest that factors other than over-diagnosis are contributing to rising thyroid cancer incidence. For example, recent United States (US) statistics indicate that thyroid cancer mortality rates have increased over the past 20 years[10] albeit at a much lower rate than the increase in incidence. Furthermore, increases in the incidence of large cancers (>5 cm) and cancers with extra-thyroidal extension and metastases have been reported, suggesting that increased detection may not completely explain the overall increase.[11, 12] In addition, increases in thyroid cancer rates across ethnic groups and geographical regions are not always consistent with levels of health services utilization.[11, 13, 14] It is also not clear that over-diagnosis is the sole explanation for the substantial variation in trends in incidence rates between countries,[1] particularly those with similar health systems and per capita health care spending.[15]

With the increases in thyroid cancer incidence in Australia being among the largest in the world,[1], we have investigated trends in incidence over time in the Australian state of Queensland

by socio-demographic and cancer characteristics to help understand the possible reasons behind the rise.

MATERIALS AND METHODS

Ethical approvals for the study were obtained from The University of Queensland and the Queensland Health Human Research Ethics Committees.

We obtained data from the Australian Bureau of Statistics (ABS), the Royal Brisbane and Woman's Hospital (RBWH) Thyroid Cancer Clinic and the Queensland Cancer Registry (QCR).

The ABS provided census-derived estimates of resident populations in Queensland by year, 5-year age group, sex and area of residence (recorded as Statistical Location Area (SLA)).[16] We used these as denominators for calculating incidence rates. The SLA was also used to derive standard Australian indicators of remoteness of residence (Accessibility/Remoteness Index of Australia (ARIA+)[17]) and socioeconomic status (SES) (Index of Relative Socio-economic Disadvantage (IRSD) [18]) but due to changes over time in the geographic boundaries which define ARIA and IRSD categories these variables were only available after 1995. For analysis we collapsed the standard remoteness categories into Major City, Inner Regional and Outer Regional/Remote/Very Remote. The socio-economic index (IRSD) is derived from census variables including income, education, employment, and motor vehicles per dwelling[19]; higher IRSD scores indicate areas with less socio-economic disadvantage. For analysis, we categorized IRSD scores into three groups based on tertiles of the overall Queensland population distribution of scores.

The RBWH is the only provider of radioactive iodine treatment in Queensland so their Thyroid Cancer Clinic reviews most (~60%) Queenslanders with thyroid cancer. They record information on tumour size, nodal involvement, metastases and overall clinical cancer stage.

The QCR maintains demographic and cancer-specific information about all cases of cancer diagnosed in Queensland since January 1, 1982 (notification of cancer diagnoses, excepting non-melanoma skin cancer, is mandatory in Australia). Cancer stage is *not* routinely collected, but the Registry holds histopathology reports for most cases. Information was extracted from histopathology reports for thyroid cancer cases between 1982 and 2006 to estimate 'clinical stage' based on the International Union for Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) 7th Edition Tumour Node Metastases (TNM) classification system for thyroid cancer.

Linkage of clinic and registry data was undertaken within the QCR and the researchers were provided with de-identified data containing the demographic (sex, age, area of residence based on SLA at diagnosis) and cancer-related variables (site, morphology, clinic-recorded stage, registry-derived stage) for all people registered in Queensland with a thyroid cancer diagnosis (ICD-O code C73.9) between January 1, 1982 and December 31, 2008.

We grouped thyroid cancer subtypes using the morphology codes provided by QCR (ICD-Oncology-3rd edition) into papillary, follicular, anaplastic, medullary, lymphoma, and other subtypes (including insular, poorly differentiated, unspecified subtypes and other less common morphologies). Medullary cancers and lymphomas were included in the overall and subtype-specific incidence rate calculations but were excluded thereafter as these cancers arise from different cell types (parafollicular c-cells and lymphocytes respectively) and studies (including ours) have not shown changes in their incidence over time.[11, 13]

We used stage information from both the RBWH clinic data and the QCR. In general, RBWH staging data (T, N, M) were used when available, otherwise QCR-estimated stage was used. We calculated incidence rates by stage for diagnoses only up until 2006 because QCR estimates were not available after this time and using stage only from those who attended the RBWH between 2007-2008 might bias our estimates of annual percentage change for stage, particularly for more

advanced cancers. Sensitivity analysis was carried out using only the RBWH data to capture trend by stage for the whole period (1982-2008). Stage was grouped into early (clinical stage I and II) and advanced stages (III and IV) so there were sufficient case numbers in each category for calculation of incidence rates.

Statistical methods

Year-, age- and sex-specific rates were calculated using the corresponding number of cases and the denominator Queensland population and then annual age-standardised (Australia 2001) incidence rates (ASR) were calculated. Poisson regression was used to estimate the annual percentage change (APC) in the incidence rate adjusting for various characteristics. Age was grouped in 5 categories (<20, 20-39, 40-59, 60-79 and 80+ years) and time was included as an annual increment in the Poisson model. Interaction effects between time in years since 1982 and other characteristics were used to assess the difference in the APC in incidence rates between the subgroups. Although the gradient in the incidence rate was somewhat lower for earlier years, there was no apparent non-linearity in the incidence trend. Further assessment using Joinpoint analysis[20] also showed no significant differences in the slopes of the trend lines for different periods. Given the large observed differences in the incidence for men and women, we performed sex-stratified analysis in order to explore the possibility of varying trends at different levels of other factors.

RESULTS

Overall 5227 people were ascertained through the QCR as having a new diagnosis of primary thyroid cancer between 1st January 1982 and the 31st December 2008. After excluding people residing outside Queensland at diagnosis, there were a total of 5083 thyroid cancer cases (1295 men, 3788 women). The mean age was 49 years (53 for men, 47 for women).

The incidence pattern differed for men and women according to the age at diagnosis with the peak among women being substantially earlier. Consistent with the population distribution, 62%

of people diagnosed with thyroid cancer lived in major cities (Table 1). Incidence appears slightly higher in the socio-economically advantaged groups with a greater difference among women compared to men.

Papillary cancers were by far the most commonly diagnosed subtype (72.5% of all cases) and, compared with men, a significantly higher proportion of the cancers diagnosed in women were papillary (65% vs 75% cancers in men and women respectively, P<0.001) (Table1). After excluding medullary cancers and lymphomas, 77% of the remaining 4003 cases had clinical stage I/II disease, 15% had stage III/IV disease and 8% had missing stage information. Nine percent of cancers were stage IV at diagnosis with a significantly higher proportion among men (15.8%) than women (7.8%, p<0.01).

Table 1 here

Table 2 shows age-standardized incidence rates across the 27 years by 5-year calendar periods for selected characteristics. The ASR increased consistently in both sexes but was two- to three-fold higher for women compared to men in all periods. The rate of increase appeared greater for the papillary than the follicular subtype particularly from the late 1990s onward. Similarly, the incidence of both early and more advanced stage cancers increased over time although the increase appeared greater in the earlier stage cancers.

Table2 here

We additionally assessed the trend as an annual increment in incidence. The ASR increased from 1.5/100,000 in 1982 to 4.5/100,000 in 2008 for men (Figure 1) equating to an APC of 5.5% (95%CI: 4.7–6.4); and in women the ASR increased from 3.5 to 18.5/100,000 (Figure 1) equating to an APC of 6.1% (95%CI: 5.5–6.6) (Table 3). The APC was slightly higher for women than men but the difference was not statistically significant after age adjustment (P=0.57).

Differences were apparent in the rate of change across age groups, particularly in women (P<0.001) where the greatest rate of increase in incidence was seen among 40-59 year olds (APC=7.3%, 95%

CI: 6.5–8.1), but was much lower (2.4%, 95%CI: -0.04–5.0) in the oldest group (80+ years) (Table3). A significant positive APC was observed across all socioeconomic and area of residence categories. Among men, those living in the most disadvantaged areas and those living in regional/remote areas had the highest rate of increase in incidence. In contrast, women from the least disadvantaged areas had the highest rate of increase. However, the differences in incidence trends across areas were not statistically significant for either sex.

Figure2 here

We observed variations in trends over time according to different cancer characteristics. We found the greatest increase over time occurred for the papillary subtype with an almost 8% increase in the incidence per year in both sexes (Figure 2). Significant increases of 3-4% per year were also observed for the follicular subtype in men and women (Table 3, Figure 2). There were no significant changes in the incidence rates of medullary cancers or lymphomas over time. Although numbers were very small, there was a statistically significant reduction in the incidence of anaplastic cancers among women from 0.20/100,000 in 1982 to 0.12/100,000 in 2007 (no anaplastic cases were recorded in 2008), equating to a 4% decline per year after adjusting for age (Table 3). The incidence of the mixed group of other subtypes also declined in women.

The incidence of both early and advanced thyroid cancers increased significantly over time in both sexes (Figure 3) however the rate of increase was smaller for the advanced than the early stage cancers (men stage I/II APC=7.4%, stage III/IV APC=6.4%; women stage I/II APC=7.3%, stage III/IV APC=4.9%), although this difference was statistically significant only among women (P=0.01).

Figure 3 here

Sensitivity analyses

A higher proportion of stage information was missing for the earlier period compared with the later periods (19% in 1982 vs 4% in 2006) and for men compared with women. To investigate the influence of missing stage data on our results, we randomly assigned missing stage information

in three ways. Firstly we assumed the distribution of stage among those without stage data was similar to the distribution in those with stage data (75% early stage). Then we assumed 60% were early stage cancers (lower than that of observed) and finally that 90% were early stage (higher than that of observed). As expected, the estimate of APC dropped slightly under these assumptions, but the trend remained significant for both stage groups in men and women (data not shown). Under all three assumptions, the observed significant difference in the APC by stage among women remained.

To investigate the possibility that the observed increase over time in more advanced cancers could be due to a recent tendency of surgeons to more often sample level VI nodes (i.e., central compartment nodes via 'prophylactic' neck dissection, therefore potentially biasing the number of clinical stage III cancers upward), we separately analyzed trends in diagnosis of clinical stage IV cancers. Although the estimates were much less stable due to the smaller numbers, an increasing incidence was also observed in this group. Between 1982 and 2006 in men, the incidence of stage IV cancers increased from 0.32 to 0.55/100,000 with an APC 3.2% (95%CI: 0.7 – 5.7) while in women they increased from 0.22 to 0.71/100,000 with an APC of 2.1% (95%CI: 0.2– 4.1). The difference in rate of increase in stage IV cancers between men and women was not statistically significant.

Acknowledging the potential to under-estimate stage when using only histopathology reports, we recalculated changes in incidence rates by stage using only RBWH data. This analysis also showed significant positive APCs in men and women for both early (men 6.6%, 95%CI: 5.2–8.1; women 6.4%, 95%CI: 5.6-7.1) and advanced stage cancers (men 6.4%, 95%CI: 4.4–8.4; women 6.0%, 95%CI 4.2-7.8). The differences in the APCs for early and the more advanced stages were not statistically significant using only the clinic data.

DISCUSSION

Our study showed a marked increase in thyroid cancer incidence in Queensland over time, with this being evident in men and women, across all adult age groups, socioeconomic strata and areas of residence. The incidence of both early and more advanced stage cancers increased over time. The largest annual percentage change in incidence was in papillary cancers although a modest, but significant, increase in the follicular subtype was also observed. The incidence of anaplastic and other less common morphologies significantly decreased over time.

The observed increase in thyroid cancer incidence for Queensland is comparable to that seen in Australia more generally (2.7/100,000 in 1982 to 9.1 in 2008) [21] and is similar to increases reported across many parts of the world.[1] In contrast, the increased rate we have observed is much lower than has recently been reported for South Korea. However, in that country screening asymptomatic people for thyroid cancer is common practice[22] There is no screening program for thyroid cancer in Australia.

Our observation of a three-fold difference in thyroid cancer incidence between men and women is also consistent with other studies,[1][23] as is the finding of a predominance of the papillary subtype[11, 13, 14], suggesting incidence patterns in Queensland are similar to those elsewhere in the developed world.

If increased ascertainment of indolent lesions is solely responsible for the increasing incidence, we might have expected to see an increase almost exclusively in early-stage cancers and mostly among those likely to most frequently access medical services such as women, older people, those from higher socioeconomic areas and those from less remote areas of residence. The increase we observed for early-stage cancers was indeed greater than that for more advanced cancers, significantly so in women, providing support for the assertion that increased ascertainment is driving some of the rise in thyroid cancer incidence over time. However, similar to others[11, 13, 24] we also observed a significant increase in advanced cancers that might be less expected under the scenario of 'over-diagnosis'. We also observed very similar rates of increase in incidence in women and men. Although there were differences in APC across levels of SES and remoteness,

they were not significant and the patterns of difference were not in keeping with expected differences in access to medical services. We did not find a greater increase in the older age groups who more frequently visit medical practitioners, but rather the APC was highest in women in their middle years.

The lack of difference in overall temporal trends between men and women in our study does contrast with some previous studies [13, 25] but is not unique.[24] While it is possible that our study was underpowered to detect small male/female differences, our sex-specific trend estimates are very similar suggesting real differences are unlikely. The higher APC in women aged 40-59 years than women and men of other age groups may reflect the high incidence of some benign thyroid diseases in this group[26] with a resulting greater use of thyroid ultrasound and surgery increasing the chances of diagnosis of asymptomatic thyroid cancers. However, individual level data on circumstances leading to diagnosis is required to confirm this possibility.

Findings in relation to SES and other indicators of healthcare care access have been mixed across studies. Among US studies, several reported differences in rates of change in thyroid cancer incidence based on race, SES or other indicators of healthcare access and suggest that such differences indicate over-diagnosis is the predominant cause of increasing thyroid cancer incidence. [9, 27]'[28] However, others found little or no difference.[11, 13] Although all those studies were undertaken in the US, they were conducted amongst different populations, at different times and used different area-level indicators of healthcare access perhaps explaining some of the inconsistencies. We have also found no differences in APC by area-level SES or remoteness of residence. Again, small numbers may have limited our ability to detect true differences, but health system factors may also be important. All Australians have access to free or subsidised medical treatment (including diagnostic tests and hospital treatment) thus differences in access to healthcare by SES may be less marked here. It is, however, well-documented that Australians living in regional and remote areas have poorer healthcare access [29] and we have found no evidence that

rates of increase are lower in these areas. Again, individual-level data on health care usage may be of more value in assessing this issue.

In keeping with prior work, we have found that the greatest increase in incidence over time occurred for the papillary subtype.[12, 13] As for some others,[11, 30] we also found a smaller but significant increase in the follicular subtype over time. Of note we also observed a decrease in the incidence of other subtypes of cancer and anaplastic cancers, particularly in women. It is possible that changes in how pathologists define histopathological subtypes of thyroid cancer have resulted in some of the changing incidence. However, it is very unlikely that cancers classified in the past as anaplastic cancers would now be called well-differentiated cancers and although there were insufficient numbers for individual analyses of the insular and poorly-differentiated subtypes, the incidence of the group in which these were included also decreased over time. Another possibility is that some well-differentiated cancers may be precursors to anaplastic cancers[31, 32] and the increasing diagnosis and treatment of well-differentiated cancers is preventing the development of this more aggressive subtype.

If over-diagnosis does not account for all the observed increase in thyroid cancer incidence then changing exposure to lifestyle or environmental factors may be driving some of the increase. What these factors may be is not clear; however there are several potential possibilities. Obesity appears to modestly increase the risk of thyroid cancer[33] and the prevalence of obesity has risen substantially in many countries in recent years. Smoking is associated with a reduced risk of thyroid cancer[34] so declining smoking prevalence may also be contributing a contributing factor. Both iodine deficiency and improved iodine nutrition has been suggested potential risk factors for thyroid cancer however iodine levels in Queensland are considered to be sufficient.[35] Finally, while more frequent use of diagnostic imaging may be contributing to increasing ascertainment of indolent thyroid cancers, it is also possible that increasing exposure to radiation from greater use of diagnostic imaging, particularly in children,[36] is contributing to a real rise in the disease. While none of these factors is likely to individually explain the large increase in thyroid cancer, these (and

potentially factors as yet to be identified) may be working in concert with over-diagnosis to increase rates.

Strengths of our study include the use of data from a population-based cancer registry covering all cases diagnosed in Queensland. Having clinical stage information from the RBWH for most of our cases was additional strength of our study. Stage is not routinely collected by most Australian cancer registries so can only be derived by assessing available pathological reports. The stage information from the clinic, in contrast, is based on physical examination, imaging and pathology reports and is likely a more reliable assessment of disease spread. We did not have complete stage information for the years 2007-2008. It is possible that the lack of information for this two-year period resulted in some underestimation of the APC for early stage cancers, however the linear trend in the incidence of both early and more advanced cancers that we observed up until the end of 2006 suggests that an additional two years of data would not have altered our conclusion about the stage-specific APCs. We also had no data prior to 1996 for socioeconomic and remoteness analyses because of changes in the classifications of areas over time. This may have reduced our ability to detect significant differences between groups. However, unless there were major changes in the direction of the time trends outside this period, our conclusions would be unchanged.

In summary, our study shows a significant and substantial temporal increase in the incidence of well-differentiated thyroid cancer in Queensland that is seen across socio-demographic groups and for early and more advanced disease. While increased ascertainment of indolent thyroid lesions over time likely accounts for some of the increase, the patterns we have observed suggest that other factors may be playing a role. In order to mitigate the ever-increasing impact of this disease on individuals and health care systems, contemporary aetiological data as well as individual-level information about circumstances around diagnosis are required to further understand the causes of rising thyroid cancer incidence.

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