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Project Title: The changing face of thyroid cancer in a population-based cohort, 2011-2015.

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Summary (250 words max single spaced):

Objective: Thyroid cancer is the most common malignant endocrine tumor and the incidence continues to increase in North America. Our objective is to determine the trends and factors influencing thyroid cancer incidence and treatment outcomes in Manitoba from 2011-2015.
Methods: The study involved a population-based cohort of 770 new cases of thyroid cancer in Manitoba diagnosed from 2011-2015. ANOVA and chi-square test for categorical data were performed with significance at a p-value < 0.05 and 95% confidence interval.
Results: The age at diagnosis, gender distribution, tumor size and stage did not change significantly. The proportion of papillary thyroid cancers increased significantly, whereas anaplastic forms declines. The ASIR increased from 9.37 in 2010 to 12.11 in 2015 and the 3-year disease-specific survival was on trend at 97.1%.
Conclusion: The incidence of thyroid cancer, particularly the papillary form, continues to rise in Manitoba, while factors, such as age at diagnosis, gender, tumor size and stage do not change. Lastly, survival continues to improve.

Student Signature

Primary Supervisor Signature

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The changing face of thyroid cancer in a population-based cohort, 2011-2015.

Natasha K. Klemm; K. Alok Pathak, Supervisor

Introduction:

Thyroid cancer is the most malignant endocrine tumor and the incidence continues to increase in North America and worldwide.[1-9] In Canada, the incidence has increased at a rate higher than any other cancer in males and females[10], making it the seventh most common cause of cancer. The age standardized incidence rate (ASIR) for males has increased from 1.1 in 1970-1972 to 6.1 in 2012 per 100,000 Canadians,[10] while females have experienced a greater rise from 3.3 to 22.2 during the same period.[10] Similar trends are seen in the United States.[1,2] The lifetime probability of a Canadian female and male developing thyroid cancer is 1/56 and 1/188, respectively, but only 1/1068 females will die from it.[11]

While the increasing incidence of thyroid cancer is alarming, the 5-year survival ratio is 98%—high compared to other malignancies.[6] The different histological types carry different prognoses and survival. Well-differentiated cancers, such as papillary, have high survival ratios compared to undifferentiated types, including anaplastic tumors.[6] Treatment recommendations for thyroid cancer have changed over the past 4 decades resulting in a greater focus on total thyroidectomy and radioactive iodine (RAI).[6] The effects of these changes have been previously studied by the authors in 2306 patients from 1970-2010.[12] This prospective study measures the trends in incidence, clinical presentation, treatment practices and disease outcome of thyroid cancers in Manitoba from 2011-2015 and compares them to the previous study.

Methods

Extending the previous study, 770 new cases of thyroid cancer, occurring in 763 patients, were added to the Manitoba thyroid cancer cohort from January 1, 2011 to December 31, 2015. The new cases were registered with the Manitoba Cancer Registry, a member of the North American Association of Central Cancer Registries, and CancerCare Manitoba. Ethics approval were approved by the University of Manitoba's Research Ethics Board.

The data was collected from electronic and paper records, consisting of 424 cytology reports, 337 pathology reports, 4 autopsies, and 1 radiology report. The ASIR was calculated using the direct method, whereby age-specific incidence of new cases was compared to the population in Manitoba for the given year and then compared to the 2011 standard Canadian population to calculate per 100,000.[13]

Data for each case included demographics, stage, pathology, treatment, recurrence and final disease status as of January 1, 2017. Staging was classified using the American Joint Cancer Committee/Union Internal Contre le Cancer staging (7th edition, 2009), which focuses on predicting survival in patients with cancer; histology coding was performed using the WHO International Classification of Diseases for Oncology (3rd Edition); and signs and symptoms were coded using the International Classification of Diseases (10th edition).

Analysis of variance for group means and the Pearson chi-square test for categorical data were performed, with significance occurring at a p-value <0.05 and 95% confidence intervals. Mean and standard deviation were calculated for normally distributed data, such as age, whereas median was calculated for non-normal distribution data, such as tumor size. The Kaplan-Meier method was used to estimate disease-specific survival. SPSS for Windows version 22.0 was used to record, manage and analyze the data.

Results

During the study period, 770 new cases of thyroid cancer were registered in 763 Manitobans; three patients had two distinct papillary tumors; two had a papillary tumor and a Hürthle tumor; one had a papillary tumor and medullary tumor; and one patient had a Hürthle type tumor and separate follicular tumor on pathology, simultaneously.

The ASIR in 2015 is 12.11 (95% confidence internal [CI] = 9.37-13.11), an increase from 9.37 in 2010.[12] In males, the ASIR increased from 4.94 in 2010[12] to 6.58 (CI = 5.66 – 7.50), while females experienced a rise from 13.75 in 2010[12] to 17.56 (CI= 16.08 – 19.05) in 2015. The most recent Canadian ASIR calculations from 2012 for males and females are 6.8 and 26.3, respectively,[10] demonstrating a lower provincial rate compared to the national statistic. The upward trend continues for papillary thyroid cancer; the ASIR in 1970 was 0.93, 6.64 from 2001-2010[12] and 10.88 from 2011-2015 (95% CI = 10.05-11.70). Previous data revealed a declining incidence for anaplastic cancers with an ASIR of 0.11 in 1970-1980 and 0.05 in 2001-2010.[12] However, our data determined an ASIR of 0.08 (95% CI = 0.03-0.19) from 2011-2015, with nine total cases.

In Manitoba, thyroid cancer occurred in 206 (26.8%) males and 564 (73.2%) females, with a mean age of 50.80 +/- 15.33 years (p = 0.0124, Table I) and a median tumor size of 18 mm (p=0.057 NS, Table I) during the study period. The proportion of thyroid microcarcinomas, (≤ 10 mm) remained non-significant (p=0.770) at 30% compared to the (Table I).[12] Consistent with the previous study, mean age at diagnosis, median tumor size and tumor stage (Table I) has not changed significantly.[12]

Staging remains non-significant (p=0.660, Table I)[12] and the greatest proportion of cases occur in Stage I, 63% (Table I). Lymph node involvement occurred in 186 (24%) cases. Multifocal disease occurred in 306 (40%) and extra-thyroidal extension occurred in 175 (22.7%) cases. Fifteen (1.9%) new cases presented with metastasis at initial diagnosis. Following treatment, complete resection was obtained in 579 (75.1%) cases.

Papillary cancer remains the most common type of thyroid cancer, the majority, 61%, having classic histology; the remaining histology types include 22.4% follicular variant, 1.3% encapsulated papillary, 0.5% tall cell variant, and 0.1% columnar variant (Table I). Follicular cancers have significantly declined from 26% in 1970-1980[11] to 7.2% from 2011-2015. Furthermore, the proportion of anaplastic thyroid cancers has declined from 5.7% to 1.3% (Table I) during the same period, as has medullary cancer from 5.1% to 1.7% (Table I).[12]

There has been a significant rise in the proportion of patients receiving total thyroidectomy, increasing from 28.4% in 1970-1980[12] to 72.4% (p<0.001) in 2010-2015 (Table 1). Post-operative adjuvant radioactive iodine has been provided to more patients, 26.1% in 2011-2015 compared to 10.9% from 1970-1980 (p<0.001),[12] although this is a considerable decrease from 62.1% in 2001-2010 (Table 1).[12]

Of the new cases that received treatment, 78 (10.1%) patients had recurrence, which was evident clinically and radiologically, and not based on exclusive elevations of thyroglobulin; 28 (35.9%) had recurrence in local areas only; 11 (14.1%) had a combination of local and regional sites; 11 (14.1%) in regional sites; 24 (30.8%) had distant recurrences; and four sites were not reported.

During the study period, 21 (2.7%) patients died from thyroid cancer; nine (42.8%) patients had anaplastic cancer, seven (33.3%) had papillary, four (19%) had poorly differentiated subtypes and one (4.8%) had an unspecified thyroid carcinoma. Given that the study period is 5 years,

we calculated the cause-specific survival at 97.1%, using January 1, 2017 as the report period cut-off date (Figure I).

Table I: Clinical characteristics of thyroid cancer by decade of presentation						
	1970-1980	**1981-1990**	**1991-2000**	**2001-2010**	**2011-2015**	**p-value**
Sample Size	331	410	594	971	770	
Mean age years	49.3±18.4	47.5±18.6	48±18.7	49.1±17	50.81±15.34	**0.0124**
Gender ratio (female: male)	2.5:1	2.8:1	3.6:1	3:01	2.74:1	
Median tumor size (mm)	19.9	20	21	20	18	**0.057 (NS)**
Tumor size distribution						
≤ 1 cm	22.6%	28.5%	25.8%	24.9%	32.2%	**0.770 (NS)**
1-2 cm	33.2%	22.7%	24.1%	25.5%	24.5%	
2-4 cm	32.6%	37.0%	33.1%	31.9%	28.0%	
> 4 cm	11.6%	11.8%	17.0%	17.7%	15.3%	
Stage I	62.6%	68.4%	64.0%	62.8%	63.0%	**0.660 (NS)**
Stage II	6.9%	8.3%	10.4%	12.4%	11.6%	
Stage III	9.7%	12.6%	10.4%	12.9%	14.7%	
Stage IV	20.8%	10.7%	15.2%	11.9%	10.1%	
Histology						
Papillary (%)	58.0%	67.8%	77.3%	85.9%	88.1%	**0.0018**
Follicular (%)	26.0%	17.1%	10.4%	5.1%	6.2%	
Hurthle cell (%)	0.9%	5.9%	3.7%	3.7%	2.0%	
Poorly differentiated (%)	2.7%	0.2%	0.5%	0.3%	0.8%	
Medullary (%)	5.1%	5.9%	2.9%	2.2%	1.7%	
Anaplastic (%)	5.7%	2.2%	4.0%	2.1%	1.3%	
Unspecified (%)	1.5%	1.0%	1.2%	0.7%	0.8%	
Total Thyroidectomy	28.4%	38.9%	49.3%	71.2%	72.3%	**<0.001**
Adjuvant radioactive iodine	10.9%	19.3%	29.8%	62.1%	28.2%	**<0.001**

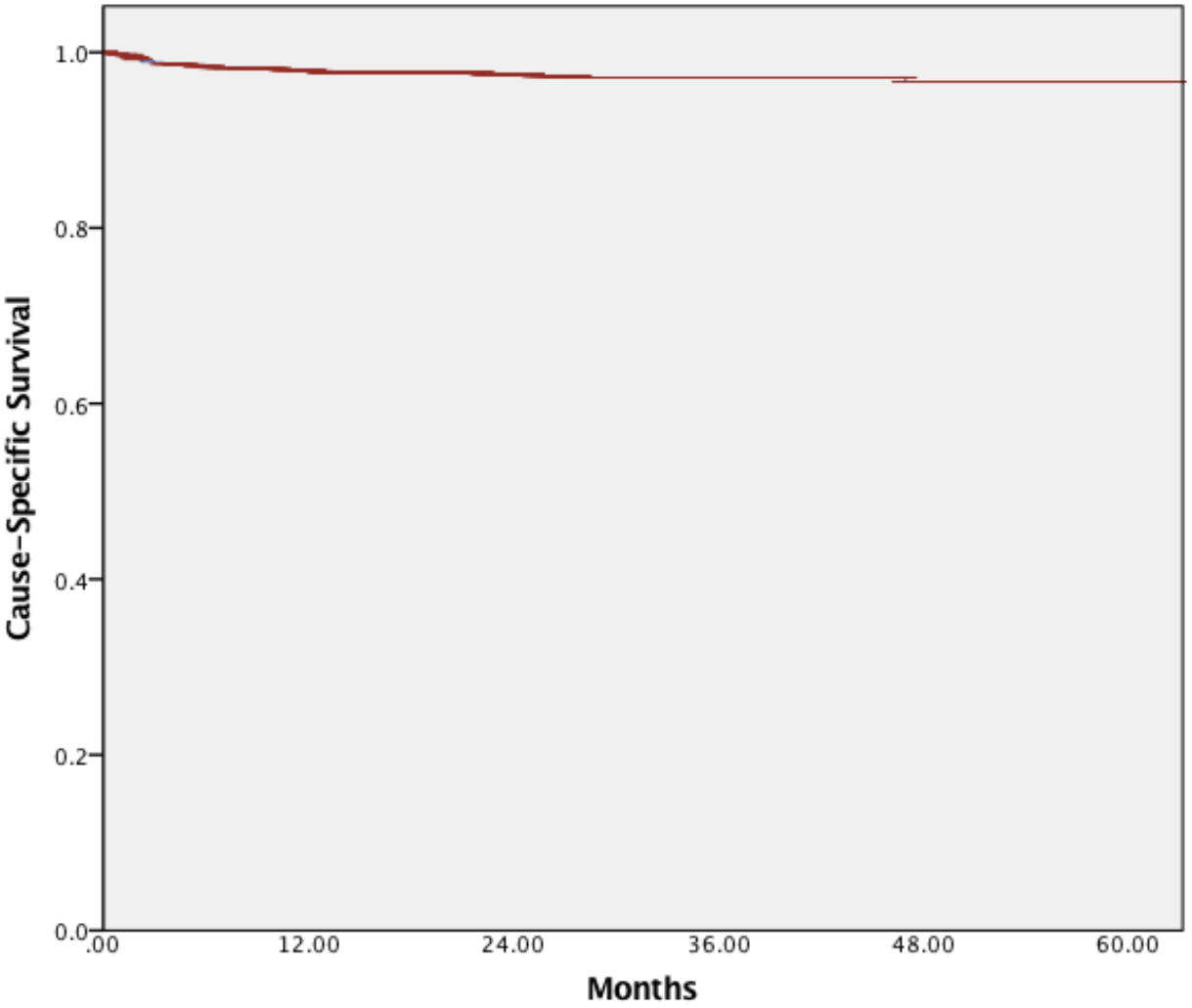

Figure I: Cause-specific survival for thyroid cancer

Discussion

Despite the declining incidence of most cancers, thyroid cancer is one of few malignancies in which the incidence continues to rise and it remains the most malignant of endocrine tumors.[10] Furthermore, it is the most common cancer in 15-20 year-olds and second most common in 30-45 year olds.[11] During these years of life, individuals experience normal biological changes, emotional challenges and future planning, all of which are influenced by cancer.[8] Given that a cohort shares characteristics, such as exposures and standards of medical care, our prospective study on Manitobans contributes to an understanding of the trends and steers further studies on the influences and prognostic factors of thyroid cancer. The low attrition rate (2.7% from 2011-2015) fortifies our analysis of the trends and outcomes.

Previous studies suggest the rise in incidence is due to increased surveillance and overdiagnosis.[1-15] An estimated 50% of new papillary thyroid cancer cases in the United states is due to overdiagnosis[16] since the 1980's introduced the use of ultrasound to diagnose thyroid cancer, replacing reliance on the physical exam. Thus, detection became more accurate.[1,9,15] Likewise, fine needle aspiration replaced nuclear medicine scans and provided greater specificity and sensitivity for thyroid cancer detection.[1,9,15] The rise in detection of incidental thyroid cancers has been ascribed to the increased use of imaging for other health concerns, as well as neck surgeries and subtotal thyroidectomies for non-malignant head and neck

conditions, including goiter.[1,17] Some studies have found that the difference in papillary thyroid cancer incidence among different ethnic groups in the United States is due to detection differences, although this is not a consistent finding.[18] Thyroid cancer incidence is higher in urban areas compared to rural communities across studies, reflecting variations in medical and diagnostic access.[19] Similarly, incidence rates are the highest in North America and Western Europe and lowest in South-Central Asia and Africa where detection is limited by resources.[20] Lastly, previous autopsy studies have determined that up to 35% of individuals have thyroid cancer, which remained undetected and subclinical during one's life.[9]

Understanding the significance of increased surveillance and overdiagnosis is important clinically and economically. The lifetime cost of a patient diagnosed with thyroid cancer without metastasis is $33,463 USD and increases to $58,660 USD if metastasis is present.[21] These costs do not account for the emotional cost and stress related to a cancer diagnosis, treatment recovery, leave from work and life-long medication requirement.[16] Thus, deterring overdiagnosis has a substantial impact on the healthcare system and patient well-being.

Contrary to the theory of overdiagnosis, histology, staging and tumor size describe a different story in Manitoba.[12] With improved diagnostics, it is expected that tumors of all histological types would increase in incidence.[12] Instead, undifferentiated forms have declined, while papillary tumor incidence increases (Table 1). Although our data demonstrates an unexpected increase in ASIR for anaplastic cancers, the authors believe this is a result of the 5-year period compared to the previous data using 10-year increments. In 1988, the classification of follicular cancers changed, and many new cases were classified as follicular variants of papillary cancer.[22] While this may partly explain the increasing incidence of papillary cancer, both follicular, follicular variants and papillary cancers are differentiated forms and the incidence as a whole continues to increase.

With earlier detection, we expect an increase in the proportion of tumors diagnosed at earlier stages.[15] Instead, the staging proportions have remained stable over the past 45 years (Table 1). The authors expect this to change when the new AJCC/TNM staging system comes into effect January 1, 2018. One of the major updates will be raising the cut-off age at diagnosis from 45 years to 55 years, thus down-staging a considerable proportion of new thyroid cancer cases.[23] Furthermore, the updated staging system removes regional lymph node metastases and microscopic extrathyroidal extension from the definition of T3 disease. Presumably, these major changes will increase the proportion of earlier staged disease and decrease the proportion of late staged diseases at the time of diagnosis.[23] This may confound future analyses and support the theory of increased surveillance and overdiagnosis.

It is expected that median tumor size would decrease with increased surveillance.[12] However, tumor size has not changed significantly and detection of large tumors has not declined (Table 1). This agrees with other studies that demonstrate a stable proportion and even increase in large size tumors.[2,14,24,25] Therefore, the increasing incidence cannot be solely explained by overdiagnosis; and multiple influential factors are likely present, including radiation exposure, iodine deficiency, non-malignant thyroid disease and family history.[12]

Ionizing radiation exposure leads to DNA damage, which may result in carcinogenesis, particularly of the lung, breast, leukocytes and thyroid.[26] In the US, an individual's exposure to radiation has doubled in the past 25 years.[20] Many studies have demonstrated that exposure to ionizing radiation for medical and dental diagnostics may partly explain the rise in incidence of thyroid cancer[20]; These diagnostics often use iodinated contrast agents, which readily expose and concentrate in the thyroid gland.[20] Furthermore, thyroid cancer incidence, particularly in children, substantially increased in those exposed to radioactive materials as a result of the Chernobyl disaster in 1986.[26] While the increased incidence is partly explained by a mass-screening project after the disaster, the link between exposure dosage, risk of development and

extent of disease demonstrates a strong association between thyroid cancer and radiation.[26] However, a recent study pointed to a decline in RET/PTC chromosomal rearrangements, which are caused by ionizing radiation and involved in papillary thyroid cancer pathogenesis.[27] The same study pointed to a marked increase in RAS point mutations—a known genetic factor involved in carcinogenesis of the follicular variant type of papillary thyroid cancer—which has followed the rising incidence since 2000.[27] This supports a multi-factorial explanation for the rising incidence of thyroid cancer, including iodine status.[27]

Given that the thyroid gland readily concentrates and utilizes iodine, dietary intake has been linked to thyroid cancer incidence; deficiency is associated with follicular thyroid cancer, whereas papillary thyroid cancer is linked to normal or higher levels of iodine.[20] Low iodine levels cause hyperplasia of thyroid cells and increase uptake of radioactive iodine upon exposure.[26] As a result of the Chernobyl disaster, children with a combination of radiation exposure and iodine deficiency have a two-fold higher risk of thyroid cancer.[26]

The current study builds upon the previous analysis of incidence and outcomes for thyroid cancer.[12] Given that the study period is five years, the cause-specific survival was calculated at 97.1% (Figure 1), agreeing with the 10-year disease-free survival (DSS, 91.8%) reported previously in Manitoba and globally.[12,28] As the study is ongoing, it is the authors' intention to calculate the 10-year DSS for the time period of 2011-2015. This favorable prognosis is influenced by the decline in undifferentiated subtypes.[12] The decline in mortality is additionally associated with a decline in iodine deficiency or excess, improved diets and reduced use of diagnostic radiation in children.[28]

The new 8th edition AJCC/TNM staging system will reclassify tumors smaller than 4 cm as stage I, whereas the 7th edition staged tumors 2-4 cm as stage II.[23] Although this will impact the staging proportions of thyroid cancer, the change was made because the disease-specific survival for these tumor sizes did not differ. In addition, stage III patients in the 8th edition will now be considered high-risk compared to low-risk in the 7th edition and stage IV, by excluding patients with only lateral neck lymph node metastases, includes only patients at highest risk of dying from thyroid cancer.[23] These staging changes may have an impact on treatment options and survival. Moving forward, the authors hope to analyze any change in disease-specific survival as a result of the new guidelines and look to other tools and risk stratification strategies to prevent over diagnosis.

Although the proportion of individuals undergoing total thyroidectomy has increased significantly,[12] the current proportion has not changed from the previous 10 years (71.2% in 2001-2010).[12] This may reflect the modest approach to surgical treatment[30-32] given that thyroidectomy exposes patients to surgical complications, such as hypocalcemia, laryngeal nerve injury and seroma[16] and previous studies have demonstrated a non-significant impact of surgery extent on prognosis.[12] While the use of post-operative radioactive iodine has increased since 1970 ($p<0.001$),[12] the most recent data shows a decline, with no concordant change in survival. This decline may reflect trends towards more conservative use, due to required isolation, side effects, and potential secondary tumor development.[29-34]

While our research builds upon the authors' previous 40-year prospective study, we are limited by the 6-year time period in which the data was collected. As most thyroid cancers have an indolent course, 10-years is more appropriate to determine DSS and ongoing follow up of the cohort is recommended.

In conclusion, the incidence of thyroid cancer in Manitoba is increasing, and this cannot solely be attributed to increased surveillance and over diagnosis. Papillary thyroid cancer is primarily responsible for the increase, as we see other histological forms decreasing in incidence. The implications of increasing are far-reaching clinically and economically. Thus, the study suggests that additional factors contribute to this increase, which we look to future research to identify and address.

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