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# Comprehending thyroid cancer in Sri Lanka: current trends and outstanding questions

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## Abstract

**Introduction:** In Sri Lanka, thyroid cancer (TC) is the second commonest cancer among females and third commonest cancer in both sexes.

**Objectives:** To describe the trend of TC according to sex, age and histology type in Sri Lanka from 2005-2019

**Methods:** Study analysed secondary data from the National Cancer Registry, Sri Lanka (NCR-SL). Age standardized rates (ASR) of TC were extracted for the respective years. Age group specific incidence rates were calculated for each year under consideration. Joinpoint Trend Analysis Software (version 4.9.0.0) was used to analyse trends. Best fit models were reported by annual percentage change (APC) and average annual percentage change (AAPC). P value <0.05 was taken as the level of significance.

**Results:** A total of 23 363 TC cases was analysed from 2005-2019. The ASR among women has increased three-fold from 2005-2019 with an AAPC of 7.5% (95% CI: 4.1, 11.1; p<0.05) and among males, a two-fold rise was seen in ASR with AAPC being 8.0% (95% CI: 5.5, 10.6; p<0.05). Age-specific incidence rates were highest in ≥ 65-year-old males and 25-34-year-old females. However, the highest AAPC was seen in 35-44 age cohort in both sexes. Papillary TC was the main type of differentiated TC in both sexes. AAPC for overall papillary TC in females was 10.54% (95% CI: 4.7, 16.8; p<0.05) and 11.6% (95% CI: 4.6, 18.9; p<0.05) in males. Follicular TC showed a similar pattern with AAPC for females being 13.2% (95% CI: 3.2, 24.4; p<0.05) and 16.0% for males (95% CI: 5.9, 27.1; p<0.05).

**Conclusions & Recommendations:** The incidence of TC in Sri Lanka reveals an increasing trend in both sexes. However, it is uncertain whether it is a true increase or due to better diagnosis and reporting. Therefore, further studies are recommended to explore the reasons for this observed increase.

***Key words**: thyroid cancer, trend, sex, age, histology*

## Introduction

In the world, TC occupies the ninth position among the commonest cancers, accounting for 3% of all malignant tumours in the year 2020. Moreover, it is the most common malignancy of the endocrine glands at any age and sex (1). The incidence of TC has increased globally than any other cancer in recent years, and the increase in incidence is seen in both sexes (2). In the year 2020, globally, one in every 20 cancers diagnosed among women is due to TC and it is three times higher among females compared with males. However, the mortality rates from TC are much lower, with rates of 0.5 per 100 000 in women and 0.3 per 100 000 in men and an estimated 44 000 deaths in both sexes combined (2). In Sri Lanka, the incidence of TC showed an increasing trend from 2001 to 2010 with a greater proportional rise in females (3). Since 2012, it is the third commonest cancer reported in Sri Lanka in both sexes (4).

Histologically, TC is divided into three main subgroups: differentiated, anaplastic and medullary. The majority (>90%) of TC are related to differentiated thyroid carcinoma (DTC) that grow from the thyroid follicle cells. DTC can be further divided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) (5). Even though several non-modifiable (female sex, older age, hereditary, autoimmune) and modifiable (radiation, obesity, low iodine in the diet) risk factors have been described for TC, little is known about the precise aetiology of TC (6).

Cancer surveillance can be defined as a "process of collecting, storing, analysing, interpreting, and disseminating epidemiological data on cancers that occur in a country or a specific geographic area systematically and continuously" (4). In Sri Lanka, cancer incidence data is collected from cancer treatment centres (government sector, private sector and armed services), pathology laboratories and oral and maxillo-facial units, using the 'Cancer Return Form-2' (H-1291). The NCR-SL is an information system designed to collect, manage, analyse, and evaluate data on persons diagnosed with cancer in Sri Lanka. It plays a critical role in cancer surveillance, providing a comprehensive picture of the disease burden and direction to utilize resources for cancer control activities in the country. Aim of the study was to describe and analyse the trend of TC according to sex, age and histology type using cancer surveillance data in Sri Lanka from 2005-2019.

## Methods

The study was conducted using secondary data of TC obtained from the NCR-SL from 2005 to 2019 (4). Classification and coding of TC (C73.9) for NCR-SL is based on the International Classification of Diseases for Oncology (ICD-O) standards provided by the World Health Organization. To describe the trend of TC by sex, ASR per 100 000 during 2005-2019 was extracted. To assess the trend with age, all extracted TC incidence data were categorized into five age groups. Age ≤24 years with TC was grouped and ≥65 years was also grouped because they were relatively small. The rest was stratified into 10-year age groups. For each age category, Age-specific incidence rates were calculated using the mid-year population of the age groups in the respective year. To assess the trend in histological types of TC data was extracted from the NCR-SL from 2010-2019 since the original data sets for some years were not available from 2005-2009. Trend analysis for histology types was limited to DTC and was extracted using its morphology code (PTC: 8050/3, 8052/3, 8260/3, 8340-8344/3, 8347/3; FTC: 8290/3, 8330- 8332/3, 8335/3, 8346/3) (4).

For trend analysis, Joinpoint Trend Analysis Software (version 4.9.0.0) developed by the National Cancer Institute (United States) was used (7). The equal variance choice was assumed, and the network search method (grid search method) was selected to determine the number of joinpoints in the analysis. The results were reported, based on the range, maximum number of joinpoints, APC or AAPC, 95% confidence interval (CI) and the level of significance (8). APC measures trends in cancer incidence over time and is assumed to adjust at a constant percentage of the previous year's rate. To decide when and how often the APC shifts, the joinpoint model employs statistical criteria using joined log-linear segments for cancer incidence rates. The AAPC measures the

average APCs over a period of multiple years (8). P value<0.05 was taken to assess significance of the APC/AAPC models.

## Results

A total of 23 363 TC cases (male=18.1%; female=81.9%) was analysed for the period 2005-2019. From 2010-2019, differentiated carcinoma accounted for 94% (n=17 861) of all TC. Other histology variants accounted only for 6% of the sample. The joinpoint trend analysis of TC by sex, age group and histology types is described in Table 1.

### Thyroid cancer trend by sex

The ASR of TC among women in Sri Lanka has increased from 5.6 per 100 000 in 2005 to 17.3 per 100 000 in 2019, which was a three-fold rise (Figure 1). This is reflected in an AAPC of 7.4% (95% CI: 3.2, 11.8; p<0.05). However, this observed rate of increase was not seen to be consistent throughout the years. The only significant APC was seen from 2011-2015 (20.06%; 95% CI: 7.9, 33.7; p<0.05), whereas in 2005-2011 and 2015-2019, no such significant increase was demonstrated. Among men, the ASR of TC has increased from 1.7 in 2005 to 3.6 in 2019 (Figure 1). Unlike in females, the increasing trend among males has been steady over the years (APC=AAPC=8.7%; 95% CI: 6.2, 11.3; p<0.05).

### Thyroid cancer trend by age group

From 2005-2019, the TC incidence has increased for both sexes for all age groups (Figure 2). The highest age-specific incidence rate of TC among men was reported in ≥65 age cohort and among females in the 25-34 age cohorts. The least number of TC was diagnosed under 24 years of age for both sexes. Among all age groups, the highest AAPC was seen in 35-44 age cohort and was higher in males (12.1%; 95% CI: 8.1, 16.2; p<0.05) compared to females (10.8%; 95% CI: 8.1, 13.6; p<0.05). However, in the 54-64 age cohort and the ≥65-year cohort, the AAPC of the TC incidence was similar in both males and females.

### Thyroid cancer trend by histology type

Between 2010-2019, the incidence of PTC has increased from 1.97 per 100 000 to 4.19 per 100 000 among males and from 7.87 per 100 000 to 13.87 per 100 000 among females. Similarly, FTC has increased from 0.23 per 100 000 to 0.7 per 100 000 among males and 1.67 per 100 000 to 4.74 per 100 000 among females. The joinpoint analysis of trends in histology subtypes revealed an increasing incidence of PTC with AAPC/APC for overall PTCs for both sexes demonstrating a statistically significant increase (male: 11.6%; 95% CI: 4.6, 18.9; p<0.05; female: 10.54%; 95% CI: 4.7, 16.8; p<0.05) (Figure 3). Joinpoint analysis of FTC also demonstrated an increasing incidence in AAPC for both sexes (male: 16%; 95% CI: 5.9, 27.1; p<0.05; female: 13.2%; 95% CI: 3.2, 24.4; p<0.05) (Figure 4).

## Discussion

The current study reveals that TC is more common among females than males. A similar picture is seen globally where TC affects predominantly females (2, 9-10). This is particularly noteworthy because women's oestrogen hormone levels have been shown to be one of the risk factors for thyroid cancer (11). Moreover, women, unlike men, have higher TSH levels during parts of their menstrual cycle, during pregnancy, during treatment with hormone replacement therapy or oral contraceptives, and even during lactation. TSH is a recognized cause for thyroid hyperplasia and thus may play a role in tumorigenesis (12).

According to NCR-SL data, in 2019, the ASR of TC among females was 17.3 and males was 3.6 per 100 000 population. This was much higher than the Southeast Asian estimates for males (2.4/100 000) and females (6.4/100 000) and even higher than the global estimates of males (3.1/100 000) and females (10.1/100 000) for TC (9). Globally, TC diagnosis is well understood to be vulnerable to the problem of overdiagnosis, which is marked by increased identification of smaller tumours with largely differentiated histology. This is seen mainly in

**Table 1: Thyroid cancer trend in Sri Lanka by sex, age and histology subgroup during 2005-2019**

| | Male | | Female | |
|---|---|---|---|---|
| **Variables** | **No.** | **AAPC (95% CI)** | **No.** | **AAPC (95% CI)** |
| **Sex** | 4232 | *8.7 (6.2, 11.3) | 19131 | 7.4* (3.2-11.8) * |
| **Age group** | | | | |
| ≤24 years | 351 | *10.5 (4.5, 16.9) | 1617 | 3.4 (-5.7, 13.4) |
| 25-34 years | 561 | *9.2 (2.6, 16.2) | 4131 | *9.0 (5.8, 12.4) |
| 35-44 years | 904 | *12.1 (8.1, 16.2) | 5094 | *10.8 (8.1, 13.6) |
| 45-54 years | 636 | 4.2 (-8.9, 19.1) | 4098 | *9.7 (7.3, 12.2) |
| 55-64 years | 557 | *6.7 (3.7, 9.8) | 2875 | *6.7 (4.1, 9.5) |
| ≥ 65 years | 537 | *6.2 (4.1, 8.4) | 2108 | *6.3 (4.4, 8.2) |
| **Histology** | | | | |
| **Papillary TC** | | | | |
| ≤24 years | 197 | *7.8 (2.3, 13.6) | 1200 | *13.5 (5.7, 21.9) |
| 25-34 years | 342 | *13.0 (8.0, 18.3) | 2839 | *15.7 (3.4, 29.5) |
| 35-44 years | 504 | *15.0 (10.0, 20.2) | 3826 | *15.4 (9.9, 21.2) |
| 45-54 years | 384 | *10.1 (1.3, 19.7) | 2765 | *15.6 (10.5, 20.9) |
| 55-64 years | 232 | *10.2 (5.1, 15.6) | 1674 | 5.0 (0.1, 10.0) |
| ≥ 65 years | 117 | *12.7 (2.0, 24.5) | 910 | *10.4 (3.3, 18.0) |
| Overall | 1776 | *11.6 (4.6, 18.9) | 13214 | |
| **Follicular TC** | | | | *10.5 (4.7, 16.8) |
| ≤24 years | 69 | 6.4 (-17.5, 37.4) | 310 | *18.5 (8.2, 29.8) |
| 25-34 years | 87 | 15.0 (-5.1, 39.3) | 573 | 11.7 (-0.2, 25.2) |
| 35-44 years | 108 | 15.9 (-4.8, 41.0) | 925 | *15.5 (6.4, 25.3) |
| 45-54 years | 97 | 7.1 (-1.9, 16.8) | 676 | *10.5 (6.2, 15.0) |
| 55-64 years | 89 | 5.2 (-2.6, 13.5) | 576 | *12.8 (7.0, 18.9) |
| ≥ 65 years | 82 | *17.0 (2.2, 34.0) | 429 | *14.8 (4.4, 26.3) |
| Overall | 532 | *16.0 (5.9, 27.1) | 3480 | *13.2 (3.2, 24.4) |

AAPC=average annual percent change

* Indicates that the AAPC is significantly different from zero at alpha=0.005 level

**Figure 1: Trend of thyroid cancer by sex in Sri Lanka, 2005-2019**

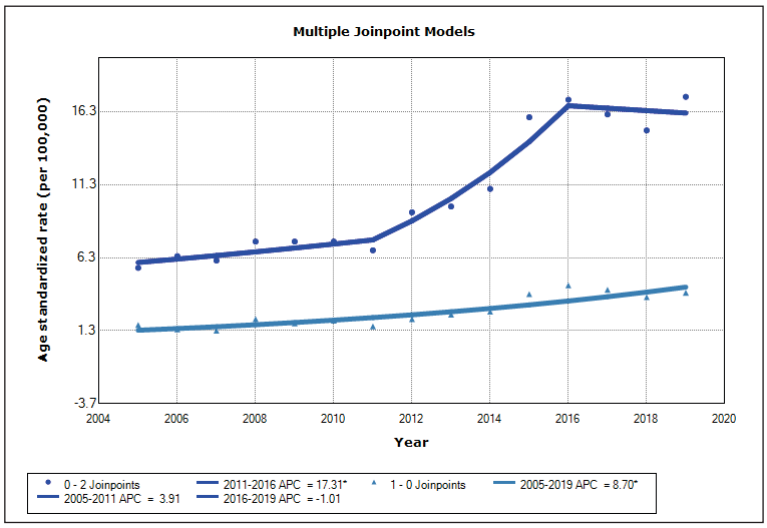



**Figure 2: Trend of thyroid cancer by age at the point of diagnosis in Sri Lanka, 2005-2019**

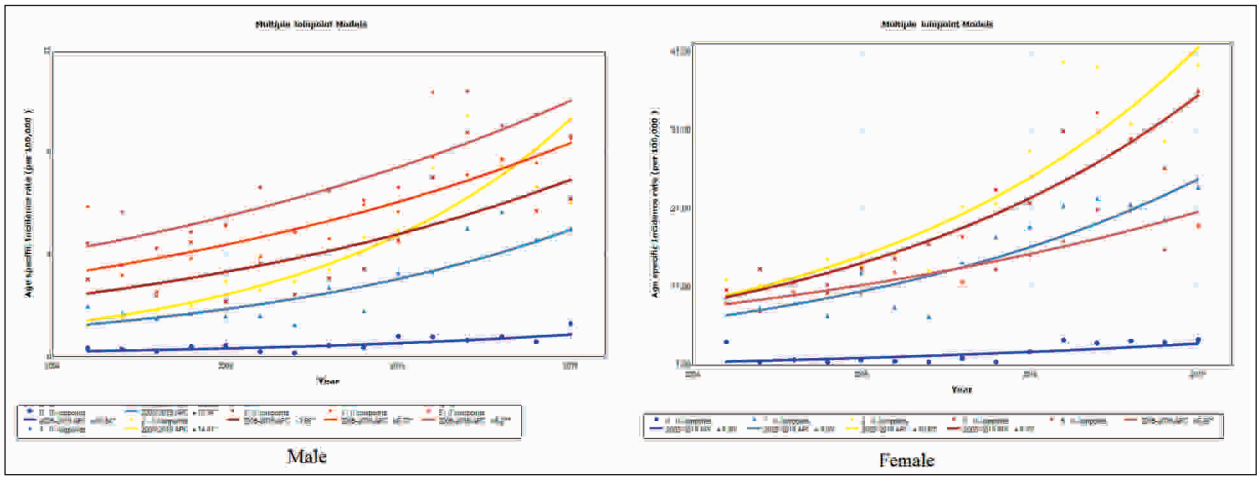



**Figure 3: Trend of papillary thyroid carcinoma in Sri Lanka, 2005-2019**

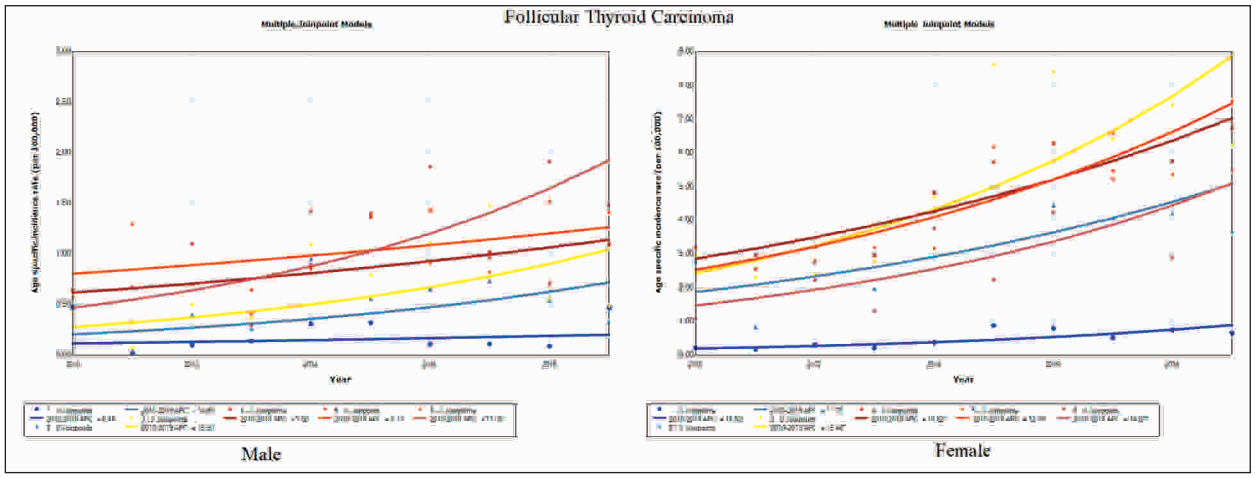
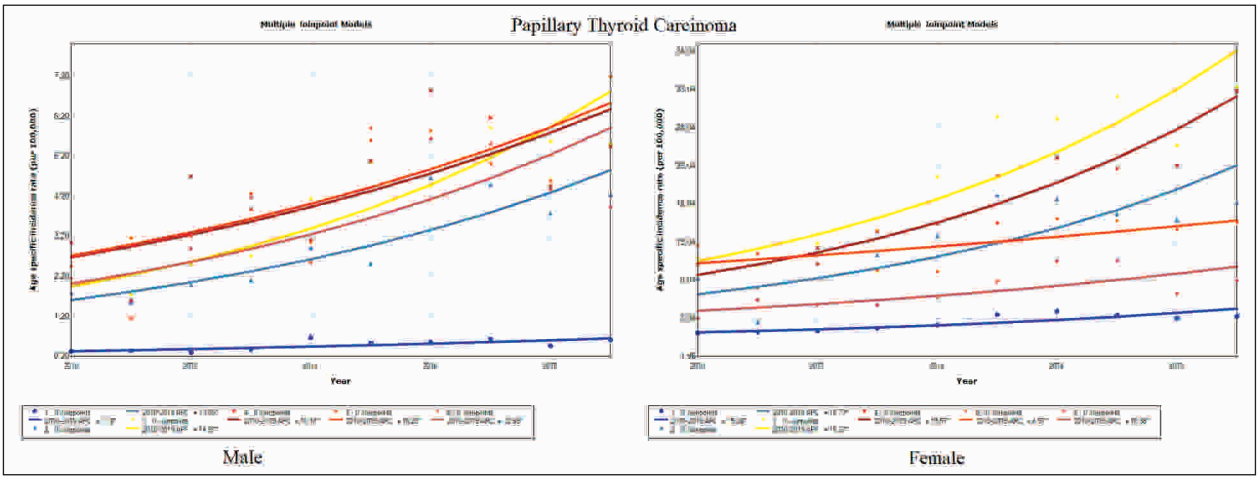


**Figure 4: Trend of follicular thyroid carcinoma in Sri Lanka, 2005-2019**




developed countries and Northern America, Australia, New Zealand, Eastern Asia and Southern Europe, which have the highest incidence rates for TC for both sexes (1). In these countries, TC was over-diagnosed as a result of opportunistic thyroid examinations by national screening programs, or, by private and market-based healthcare systems which enables the overuse of diagnostic facilities by patients and the use of advanced medical examinations by the healthcare providers (10).

Up to 2019, routine examination of the thyroid gland was conducted at well woman clinics (WWC) and healthy lifestyle centres (HLC) in the country. Any abnormality detected was then referred to specialized care. Even though Sri Lanka has no national guidelines on the management of thyroid nodules or goitre, it follows NICE guidelines and conducts ultrasonography and fine-needle aspiration cytology for all patients presenting with thyroid nodules. This may have led to the detection of TC that would not have been otherwise detected or investigated. A similar picture was also reported in the population-based cancer registry in Thiruvananthapuram, Kerala in India where over-diagnosis of TC was suggested for its high thyroid cancer reporting (13). Therefore, the imPACT review report recommended stopping the systematic screening of women in 35- and 45-year-old age cohorts in Sri Lanka (14). As a result, from 2020 thyroid examination has been removed from the routine examination procedures at WWC and HLC.

On the other side, WWC programme Sri Lanka caters for women in only 35 and 45 age cohorts and therefore, unlikely to explain more than a minor proportion of the variation in TC incidence. Moreover, it does not explain the high incidence of TC reported among men. In addition, the coverage of the target population by the HLCs are less than 10% (15). Therefore, it is debatable whether community-level screening contributed to the increase in TC incidence in Sri Lanka. Hence, the incidence of TC patterns should be further studied in years to come to assess the effect of this reform on TC reporting in Sri Lanka.

According to the multiple factor hypothesis of carcinogenesis, the rise in TC may be attributed to increased medical radiation, overweight and obesity, excessive or insufficient iodine intake, as well as other factors that are still unknown (6, 16-17). Ionizing radiation is a factor that should not be overlooked, and the National Strategic Plan for Cancer Prevention and Control 2020-2024 of the NCCP has included ensuring the safety of healthcare workers and patients exposed to radiation and cytotoxic materials as a major strategic area (18). Global studies have demonstrated a causal relationship between high BMI and TC (17, 19). According to the STEPS Survey 2015, almost 29% of adults were overweight or obese, among which 24.6% were male and 34.3% were female (20). Compared to 2006 STEPS Survey data, this demonstrated a 3.9% rise in obesity among women

and a 5% rise in obesity among men (21). Even though more recent national data are not available, it is an important factor worth exploring given the high incidence of TC in Sri Lanka.

From 2005-2019, highest age-specific incidence of TC was seen among the 25-34 age cohort in females and ≥65 age cohort among males. A similar picture was seen in a study in China (11) and in the United Kingdom (22). A possible explanation could be the increased identification in females during routine obstetrical and gynaecological examinations during the reproductive years. Furthermore, studies have shown that women have a far more active health-seeking behaviour than men, which also may have contributed to the said difference (23).

It is generally accepted that poor prognostic outcomes (distant metastasis and disease-specific mortality rates) are higher with FTC than with PTC (24). In the current study, women demonstrated a significantly higher percentage of PTC (63.9% vs. 14.7%) and FTC (18.9% vs. 2.5%) compared to men. A similar picture was seen in a study conducted in the United Kingdom and the previous study conducted in Sri Lanka, which analysed trends of histology subgroups from 2001-2010 (3, 22).

Considering the trend in histological subgroups, PTC and FTC revealed an increasing trend in both sexes. In the overall age cohort, AAPC of PTC revealed a significant increase among both sexes. This is higher than the AAPC for females and males reported in Sri Lanka from 2001-2010 (3). Further, in the overall age cohort, AAPC of FTC among females has increased by 5% (13.2%; 95% CI: 3.2, 24.4; $p<0.05$) from the previous study findings (from 2001-2010) and an exponential increase was also seen in the AAPC of FTC among males from the previous study finding from 2001-2010 (-0.2%; 95% CI: -2.7, 2.5) (3). However, it is unclear if the above increase was due to the improvement in pathology reporting over the years in Sri Lanka or due to an increase in inherent risk factors or the combination of both.

There are a few limitations to the current study. The data of the current study was dependent on NCR-SL reporting. Although the NCCP has made significant efforts to ensure the completeness and accuracy of data, there may be differences in cancer incidence reporting. Moreover, NCR-SL data on TC staging was not complete and mortality data was not available and could not be analysed. However, it would have shed light on the issue of overdiagnosis, since the rise in incidence is primarily limited to the more indolent histological subtype (as PTC) and early tumour stages, without a similar increase in mortality, indicates cancer overdiagnosis (25). Hence, further research is required to determine the true causes for the rapid increase of TC in Sri Lanka. Further, TC incidence must be closely monitored at the district levels to detect geographical variations.

Even though the analysis of the current study was limited to sex, age, and histological subgroups, it analysed the trends of TC for a fifteen-year period using the largest and the most extensive database available covering all cancer treatment centres in the country. Therefore, despite the limitations results derived from the current study is likely to be the most reliable in terms of trends in TC in Sri Lanka.

## Conclusions & Recommendations

This study has shown the incidence of TC in Sri Lanka to be on the rise among both males and females. Although it is uncertain whether this is due to better diagnosis and reporting or due to a true increase, increasing numbers can have detrimental effects to the health care system unless early intervention is not taken. Therefore, further studies are recommended to examine the reasons for the observed increase in TC incidence, NCR-SL should be further strengthened to ensure completeness of cancer data (e.g., staging) and implement hospital-based cancer registry data collection to gather TC survival data to assess mortality, recurrence, and the outcomes of treatment.

### Public Health Implications

- Thyroid cancer is the third commonest cancer among both sexes in Sri Lanka, and the incidence is clearly on the rise. This increase is seen across all age categories and sexes.
- The age standardized incidence rate of thyroid cancer in Sri Lanka is the highest in the Southeast Asian region and is higher than the world average.
- The impact of thyroid cancer is not limited to the patients alone, but the rising numbers are a major public health concern to introduce prevention interventions, early detection and treatment and care.
- Even though multiple factors may have contributed to the current trend, precise causative factors are not yet understood.
- Further studies are recommended to examine the reasons for observed increase in thyroid cancer incidence and hospital-based cancer registry must be implemented to gather thyroid cancer survival data to assess mortality, recurrence, and the outcome of treatment.

## Author Declarations

***Competing interests:*** The authors declare that they have no competing interests.

***Ethics approval and consent to participate:*** The current study analysed anonymous data of TC collected through the NCR-SL of NCCP, Ministry of Health, Sri Lanka. Hence, data for the study were publicly available online and the analysis did not involve a specific person or specimen or contact with patients.

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***Author contributions:*** All authors planned the study; SN and SW extracted the data; SN analysed the data; SW and JV provided comments on the manuscript; MA helped with the graphical presentation of data and the first version of the manuscript; SN wrote the final version of the manuscript. All authors have read and approved the final version of the manuscript.

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