

Rising Thyroid Cancer Incidence in Southern India: An Epidemic of Overdiagnosis?

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Background: Thyroid cancer incidence is rising in high-income countries. This increase in disease burden is attributed to the phenomenon of overdiagnosis.

Objective: We aimed to investigate trends in thyroid cancer rates in India, focusing on the state of Kerala in southern India, which has reported a high incidence of the disease.

Design: Population-based study using data from the National Cancer Registry Program.

Participants: We used data from the Population Based Cancer Registries for Thiruvananthapuram (capital of Kerala state), Delhi, Mumbai, Bangalore, and Chennai. We used data for three reporting periods from 2005 to 2014 (represented as 2006, 2009, and 2012).

Main Outcome Measures: We reported the age-adjusted incidence rate (AARi) and mortality rate (AARm) per 100,000 women and the proportion of thyroid cancers diagnosed in females per 100 cancer cases.

Results: During 2006, the AARi for thyroid cancer in women in Thiruvananthapuram was 6.9 per 100,000, rising to 10 in 2009 and 13.3 in 2012. There was a 93% increase in incidence rates over less than a decade. The AARis in the other four cities were stable. In 2012, Thiruvananthapuram had at least a fourfold higher incidence compared with other regions. Thyroid was the primary site in one of every 10 cancers diagnosed in Thiruvananthapuram, and large numbers of patients were <40 years of age. The AARm remained stable in all regions.

Conclusion: We reported a high burden of thyroid cancer in Kerala, India, which is most likely due to overdiagnosis.

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Freeform/Key Words: thyroid cancer, incidence, overdiagnosis, Kerala, India, thyroid, epidemiology

Thyroid cancer incidence and prevalence rates are rising throughout the world [1]. An analysis of the Surveillance, Epidemiology, and End Results database from the United States showed a tripling of thyroid cancer incidence over 35 years beginning in 1975 [2]. The absolute rates of thyroid cancer in women were four times those seen in men. However, the thyroid cancer-specific mortality rate remained stable over 35 years. Similarly, in Korea, thyroid cancer incidence increased by 15 times from 1993 to 2011 [3]. Such increases in incidence rates have been reported by various countries and regions around the world [4]. Most newly

Abbreviations: AARi, age-adjusted incidence rate; AARm, age-adjusted mortality rate; NCRP, National Cancer Registry Program; PBCR, Population Based Cancer Registry.

diagnosed patients have an indolent type of differentiated thyroid cancer (predominantly papillary histological subtype) and smaller tumors [1, 4].

Thyroid cancer is particularly prone to the phenomenon of overdiagnosis, whereby large numbers of subclinical cases are diagnosed without a positive impact on thyroid cancer-specific mortality [5]. Overdiagnosis results from the widespread prevalence of a subclinical disease state that otherwise would not cause any symptoms combined with an easily accessible diagnostic testing modality. A meta-analysis of 12,834 autopsies reported a prevalence rate of incidental differentiated thyroid cancer of 11.2% in glands that were examined in whole [6]. The meta-analysis also found that prevalence rates have been stable since 1970, suggesting that the increased detection rates were likely due to overdiagnosis and were not a consequence of increasing rates of carcinogenesis. Studies have also noted that the incidence rate of thyroid cancer is higher in regions with greater access to diagnostic tests such as thyroid ultrasonography and needle biopsies [7–9]. Therefore, it is now well understood that rising rates of thyroid cancer (*i.e.*, “epidemic” proportions) are due to overdiagnosis.

Most of the data supporting an epidemic of thyroid cancer come from high-income countries; therefore, this phenomenon is generally considered a problem of the developed world. However, an epidemiologic transition from communicable diseases to chronic noninfectious diseases is rapidly developing in low- and middle-income countries [10]. In the past, infectious diseases overwhelmed the health care infrastructure in these regions; the system has now been overtaken by the burden of noncommunicable diseases such as cancer, diabetes, and heart disease.

The state of Kerala in southern India, home to >34 million people, has health indices comparable to those of developed nations. The health care system in Kerala has undergone the epidemiologic transition much earlier than the rest of the country [11]. Therefore, we hypothesized that a thyroid cancer epidemic may be occurring in the region and aimed to study thyroid cancer diagnosis trends in Kerala.

1. Materials and Methods

A. Study Population

Using data from the Population Based Cancer Registries (PBCRs) compiled by the National Cancer Registry Program (NCRP) of the Government of India, we investigated the burden of thyroid cancer in Thiruvananthapuram, the capital city of Kerala state, and compared it with data from registries in four major cities in India (Delhi, Mumbai, Bangalore, and Chennai) (Fig. 1) [12]. Data reported in each of the PBCRs were collected from multiple hospitals. The data are publicly accessible on the Web site of the Indian Council of Medical Research and are released on a periodic basis [12]. Because the PBCR for Thiruvananthapuram was established in 2006 and reported data collected from January 1, 2005, we used the data reported from that year. The PBCR for Thiruvananthapuram increased its coverage to the district level from 2012 onward; therefore, the number of cases reported to the registry increased in recent years.

B. Reporting Periods

There was variability in the years of reporting for each PBCR: Thiruvananthapuram reported data for 2005 to 2008, 2009 to 2011, and 2012 to 2014; Delhi reported data for 2006 to 2007, 2008 to 2009, and 2012; Mumbai reported data for 2006 to 2008, 2009 to 2010, and 2012; Bangalore reported data for 2006 to 2007, 2008 to 2009, and 2012; and Chennai reported data for 2006 to 2008, 2009, and 2012 to 2013. For ease of research communication, we have used common years to represent the three periodic reports: 2006, 2009, and 2012.

C. Measures of Cancer Incidence

The burden of cancer incidence and mortality is reported in the PBCR reports in two ways: the age-adjusted incidence rate (AAR_i) and age-adjusted mortality rate (AAR_m) per 100,000 females and the relative proportion of thyroid cancer among 100 cancers



Figure 1. Map of India showing the PBCR locations.

diagnosed. Cancer incidence data were obtained from all three reporting periods (2006, 2009, and 2012). Cancer mortality data were obtained only from the first two reporting periods (2006 and 2009), because the recent PBCR report did not provide information on mortality rates. Method of cancer diagnosis was abstracted from the 2012 PBCR report as the proportion of cancers diagnosed through microscopic examination.

We investigated the frequency of thyroid cancer in females because the thyroid cancer epidemic has been observed especially in this population. We also investigated the frequency of breast cancer in females, which is another screen-detected malignancy. We hypothesized that if improved methodology in data collection resulted in spuriously rising cancer incidence rates, it would manifest in increasing rates of breast cancer. We also investigated the frequency of thyroid cancer–specific mortality. Finally, we looked into the proportion of thyroid cancers diagnosed through microscopic examination.

D. Global Rates of Thyroid Cancer

To understand the burden of thyroid cancer in Thiruvananthapuram, we compared data from the 2012 PBCR report with the cancer incidence data for the year 2012 provided by the Globocan Project of the International Agency for Research on Cancer and standardized the incidence rate to the world standard population [13]. Data from cancer registries that provided high-quality national or regional data for 2012 along with data from the 2012 PBCR were used to identify 10 nations or regions with the highest incidence rates of thyroid cancer.

We independently abstracted the data from the PBCR and Globocan reports. No institutional review board approval was necessary because the data are publicly available. Descriptive statistics were used to report the data.

2. Results

A. AARi for Thyroid Cancer

The AARi for thyroid cancer in Thiruvananthapuram during 2006 was 6.9 per 100,000 females, rising to 10 in 2009 and 13.3 in 2012 (Fig. 2). This constitutes a 93% increase in

incidence over 10 years (from 2005 to 2014). This doubling in burden of thyroid cancer diagnosis was not observed in the other four regions, where the incidence rate was stable during the 7 to 8 years of PBCR reporting. The AARi in the four regions ranged from 2 to 4.1. During the last reporting period, Thiruvananthapuram had more than a fourfold higher incidence of thyroid cancer compared with rates in the other four regions.

B. Proportion of Thyroid Cancer Diagnosis

The increase in AARi seen in Thiruvananthapuram was also reflected in the proportion of thyroid cancers diagnosed in the district (Fig. 2). Although thyroid cancers constituted 6.5% of all cancers diagnosed in females in Thiruvananthapuram in 2006, by 2012 the proportion had risen to 10.4%. The proportion of thyroid cancers in the other four regions ranged from 1.6% to 4% during 2012.

C. Breast Cancer Rates

Because the Thiruvananthapuram PBCR reported an increase in the number of cases reported during the study period, we investigated whether breast cancer incidence rates increased as well. As shown in Fig. 3, there was no such increase in incidence or proportion of breast cancers in the five cities during the three reporting periods.

D. AARi of Thyroid Cancer by 5-Year Age Group

On the basis of AARi by 5-year age group, Thiruvananthapuram had a much higher incidence of thyroid cancer in all females <65 years of age compared to the other four regions (Fig. 4). However, the magnitude of the increased incidence was particularly pronounced in women <40 years of age.

E. AARm for Thyroid Cancer

Although the AARi steadily increased in Thiruvananthapuram during the three reporting periods, the AARm remained stable at 0.4 to 0.5 per 100,000 females during the first two reporting periods (Table 1). Stable trends in thyroid cancer-specific mortality were similar in all five cities. Most thyroid cancer diagnoses in the five cities were verified through microscopic examination (Thiruvananthapuram 99%, Delhi 95%, Mumbai 91%, Bangalore 98%, and Chennai 87%).

F. Comparison of Globocan 2012 and PBCR 2012

Finally, using data from Globocan 2012 and PBCR 2012, we identified the 10 regions with the highest incidence of thyroid cancer in 2012. The age-standardized incidence rate adjusted to world standard population for Thiruvananthapuram was 13, which implies that the district is the eighth most affected region in the world (Fig. 5).

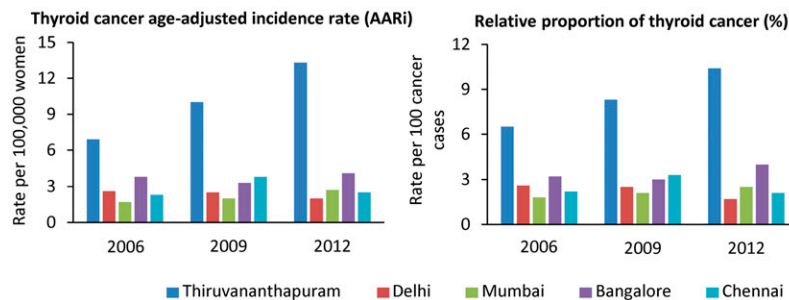


Figure 2. Thyroid cancer rates.

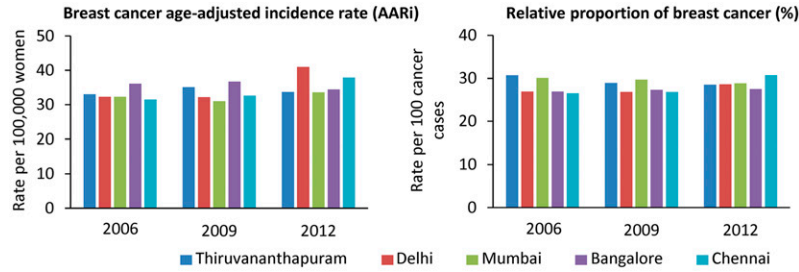


Figure 3. Breast cancer rates.

3. Discussion

We found that the incidence rate of thyroid cancer in Thiruvananthapuram increased by twofold from 2005 to 2014. This increase in diagnoses was not observed in Delhi, Mumbai, Bangalore, or Chennai. The incidence rate of thyroid cancer in Thiruvananthapuram for reporting year 2012 was more than four times higher than the rates in the other four regions. In the Thiruvananthapuram region, thyroid cancer comprised one of every 10 cancers diagnosed in females. In Kerala, women <40 years of age are at high risk for increased diagnosis of thyroid cancer. In addition, we reported that thyroid cancer-specific mortality rates remained stable during the first two reporting periods.

We found a substantial burden of thyroid cancer in the Thiruvananthapuram district compared with the other four regions in India. What could explain the epidemic of thyroid cancer diagnoses in this southern Indian state? Could it be due to overdiagnosis, increased carcinogenesis, or both?

It is well understood that thyroid cancer diagnosis is susceptible to the phenomenon of overdiagnosis, which is characterized by increased detection of smaller tumors that have a predominantly differentiated histology [14]. In a region affected by overdiagnosis, thyroid cancer-specific mortality remains stable despite increasing incidence rates [1–3]. We identified a similar trend of increasing incidence rate and stable mortality rate in Thiruvananthapuram. Not surprisingly, we did not observe a similar trend in the other four regions in India, which validates our hypothesis that the state of Kerala may be susceptible to the problem of thyroid cancer overdiagnosis often seen in high-income countries.

Could the increased burden of thyroid cancers in Thiruvananthapuram be attributed to increased reporting of new cancers to the PBCR, especially considering that the coverage area of the registry increased during the period? If that accounted for the increasing incidence of thyroid cancer, a similar trend would have been observed in breast cancer, which is the leading site of cancer in women. Therefore, the rising incidence of thyroid cancer in Thiruvananthapuram cannot

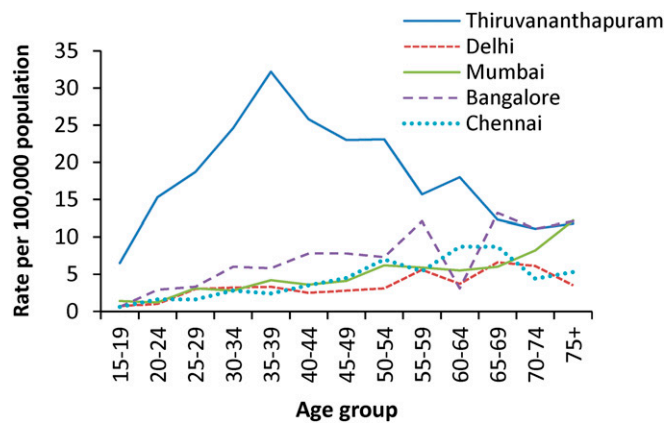


Figure 4. Thyroid cancer AARI by 5-year age groups in PBCR 2012.

Table 1. Thyroid Cancer Age-Adjusted Mortality Rate per 100,000 Women

	Thiruvananthapuram	Delhi	Mumbai	Bangalore	Chennai
2006	0.4	0.1	0.4	0.5	0.3
2009	0.5	0.1	0.4	0.5	0.5

be attributed to an increase in case reporting to the registry. Misdiagnosis is unlikely to explain the increase in incidence because a majority of diagnoses in all the PBCRs (*i.e.*, 87% to 99%) occurred through microscopic examination. The PBCRs do not report if the microscopic examination was conducted through fine-needle aspiration cytology or histopathologic test in a surgical specimen. If there was a difference in rates of microscopic confirmation relative to imaging-based diagnoses, we could have attributed the difference in incidence rates to possible misdiagnosis.

Another reason to attribute increased thyroid cancer rates in the Thiruvananthapuram PBCR to overdiagnosis is the data on incidence rates by 5-year age group. Overdiagnosis affects younger women more than the elderly, and our study found that women <40 years of age constituted a large number of cancers in the Thiruvananthapuram region. Unfortunately, the PBCR did not report the proportions of differentiated thyroid cancer diagnoses during the three reporting periods. However, because differentiated thyroid cancers comprise nearly 90% of all thyroid cancers, we do not think it would be any different in India. In addition, we lack information on the proportion of smaller tumors diagnosed in these regions during the three reporting periods. Regions affected by overdiagnosis have displayed a substantial increase in diagnoses of smaller tumors over time [4, 15].

Although overdiagnosis appears to be a more rational explanation for the increased incidence of thyroid cancer in Kerala compared with rates in other regions of India, an underlying etiology is still plausible for the increased risk for carcinogenesis that is contributing to the thyroid cancer epidemic. However, most of the well-recognized etiologies of thyroid cancer, such as obesity and smoking, family history of thyroid cancer, exposure to environmental ionizing radiation and toxins, or an iodine-rich diet, may not be notably different in the five regions [16–19].

If overdiagnosis is the reason behind the increased burden of thyroid cancer in Kerala, why is it affecting the region? There is a putative association between greater access to health care and increased incidence of thyroid cancer [3, 7, 9, 20]. Unfortunately, to our knowledge, there are no data on the number of thyroid surgeries or the number of thyroid ultrasonography examinations performed in these cities or regions. However, in our experience, all five regions are capital cities of their respective states and are quite comparable regarding access to thyroid ultrasonography and the density of endocrinologists and thyroid surgeons. Kerala state is generally believed to have a

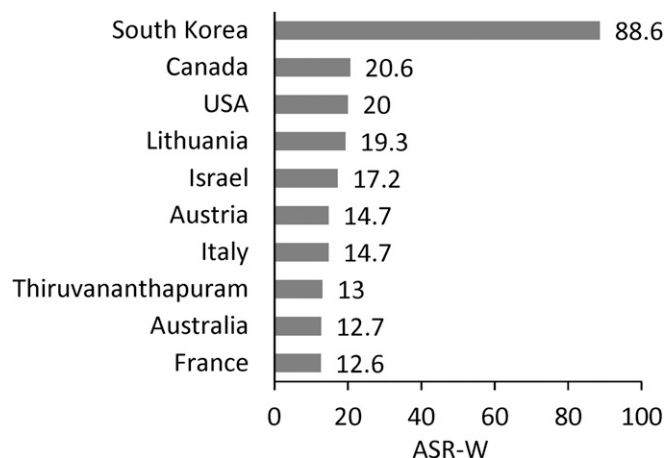


Figure 5. Age-standardized incidence rate adjusted to world standard population (ASR-W; top 10 regions).

higher socioeconomic and educational status than the rest of the country [11]. Higher socioeconomic and educational status in a population may increase thyroid cancer diagnosis rates [8, 20]. A well-conducted case-control study may help unravel this association, which could explain the reason for overdiagnosis of thyroid cancer in Kerala. We also recommend that future PBCR reports include data on tumor size as well as rates of differentiated thyroid cancer diagnosis.

Our study has a few limitations. First, our data are based on reporting from the NCRP of the Government of India. There may be variations in reporting in the PBCRs, although the NCRP has directed considerable effort to ensuring the completeness and accuracy of the data. Second, reporting years vary between PBCRs. Nevertheless, we believe the trends unraveled by our study have internal validity, at least within each PBCR. Third, we do not have mortality data for the third reporting period. However, mortality rates are similar in all five cities, despite a substantially higher incidence rate in Thiruvananthapuram, which suggests an underlying problem of overdiagnosis in the region. According to secular trends in thyroid cancer incidence in the United States over 35 years, mortality rates remained stable despite a rising incidence [2]. Similarly, it is unlikely that a rising trend in mortality rate would be forthcoming in Kerala. Fourth, we do not have data on the proportion of tumors that are small or the proportion of papillary cancers diagnosed. We propose that the PBCR for Thiruvananthapuram obtain and provide such information in upcoming reports because it may help validate the study conclusions. Fifth, research evaluating regional differences in the prevalence of risk factors for thyroid cancer within India are limited. However, we do not believe the prevalence of these risk factors varies significantly between the five regions in our study.

The phenomenon of overdiagnosis seems to be the most plausible explanation for the substantial burden of thyroid cancer in Kerala. It is not without notable personal and societal costs [21]. Because a large proportion of patients diagnosed with thyroid cancer are <40 years of age, this could result in overtreatment, which profoundly increases risks for heart disease, stroke, and osteoporosis [22]. Therefore, if the rise in thyroid cancer is not curtailed, it will lead to major burdens on the health and economic welfare of the people in Kerala. Trends in thyroid cancer incidence must be closely monitored in other regions of India, as well as in other low- and middle-income countries. Strict adherence to thyroid cancer guidelines from various societies may help reduce rates of overdiagnosis and consequently, overtreatment [23, 24].

In conclusion, we report a higher burden of thyroid cancer in the southern Indian state of Kerala and identify overdiagnosis as the most plausible explanation for the rising incidence of thyroid cancers in the region. Unless it is urgently tackled, the diagnosis of indolent, small, differentiated thyroid tumors in young women may continue to rise. Such a trend would result in profound longer-term adverse effects at individual and societal levels.

Acknowledgments

We thank Donna Gilbreath, MA, of the Markey Cancer Center Research Communications Office, who assisted with preparation of the figures in the manuscript.

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Disclosure Summary: The authors have nothing to disclose.

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