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Trend in Thyroid Cancer Incidence in Northern Iran: A Population-based Study (2016–2020)

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ABSTRACT

Background: The incidence of thyroid cancer (TC) is increasing globally. This study examined the incidence of TC in Mazandaran Province, Northern Iran, from 2016 to 2020.

Methods: We conducted a cross-sectional study using data from the Mazandaran cancer registry. Age-standardized incidence rates (ASIRs) and the average annual percentage change (AAPC) with 95% confidence intervals (CI) were calculated using the Joinpoint Regression Program software, version 4.9.0.0.

Results: The number of cases rose by 90.9%, increasing from 253 in 2016 to 483 in 2020. The ASIR increased from 6.43 to 11.14 per 100,000. While the overall trend was not statistically significant (AAPC=14.5%, P=0.08), a significant increase was observed in males (AAPC=19.8%, P<0.05). The incidence rate in women was approximately five times that of men (15.14 vs 3.06 per 100,000, P<0.001) and was more common in urban areas.. Most new cases (over 80%) occurred in the 25–59 age group.

Conclusion: TC incidence has risen substantially in Mazandaran Province, particularly among women and urban residents. These findings highlight the need for further investigation into underlying causes and preventive measures.

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Introduction

Thyroid cancer (TC) is the most common malignant tumor of the endocrine system globally [1]. In 2020, it ranked ninth in incidence among all cancers, with an estimated 586,202 new cases worldwide [2]. It accounted for 0.44% of global cancer mortality (43,646 deaths), resulting in 43,646 deaths and making it the 24th leading cause of cancer-related deaths [3]. The global burden of disease (GBD) Study data from 2017 and 2019 consistently show a rising trend in TC incidence worldwide [2, 3]. However, incidence rates vary significantly by region, with developed countries, such as the USA, Canada, and Australia, reporting rates twice as high as those in developing countries [2]. The worldwide age-standardized incidence rate (ASIR) of TC was 6.6 per 100,000 in 2020, with rates of 3.1 in men and 10.1 in women [3]. Regions, like North and South America, East Asia, Australia, and Southern and Western Europe, are considered high-risk areas, whereas East and West Africa, North and South Africa, and South Central Asia show lower rates [3-5].

In Iran, TC was the 10th most common cancer overall in 2020 (15th in men and 5th in women), with an ASIR of 6.5/100,000 (2.0 in men and 6.7 in women) [6]. It is notably one of the five most common cancers among women in Iran, contributing significantly to the female cancer burden [6]. National epidemiological studies leveraging cancer registry systems in Iran, such as the Iran cancer data system (ICDS) and data collected by the Ministry of Health and Medical Education (MOHME), have reported an increasing trend in TC incidence [7-9]. This increase is generally lower in southern regions and higher in central areas, including the capital Tehran and nearby provinces [7]. The female-to-male ratio for TC in Iran is consistently high, ranging from 2:1 to 5.22:1, reflecting a global pattern of higher incidence in women [8-13]. The median age at diagnosis in Iran tends to be younger than in some Western countries, around 42-45 years, with the highest incidence often observed in middle-aged groups, particularly those under 45 years [8, 9, 12, 14]. National demographic data from the Statistical Center of Iran provide context for these age distributions within the Iranian population structure [9].

Mazandaran Province, located in Northern Iran, shares characteristics with regions where TC incidence trends have been investigated. While past national studies have not consistently identified Mazandaran as a high-risk province for TC, local environmental and lifestyle factors may play a significant role in its regional patterns [7]. For instance, previous research in Iran and neighboring regions has suggested that factors, such as iodine intake or imbalance (Mazandaran was historically part of an endemic goiter area), radiation exposure, and obesity could influence TC incidence [7, 8, 12, 13, 15]. Changes in these factors, alongside improvements in diagnostic techniques and healthcare accessibility, are often implicated in the rising trends observed globally and nationally [8, 14-16].

Understanding these evolving trends at a sub-national level is crucial for effective public health planning and resource allocation. Analyzing cancer incidence trends helps predict future changes and guide disease management strategies [17]. Therefore, this study aimed to investigate the 5-year incidence trends and epidemiological characteristics of TC in Mazandaran Province, Northern Iran, from 2016 to 2020, providing local insights into this growing public health concern.

Materials and Methods

This study employed a cross-sectional design, utilizing data from the Mazandaran population-based cancer registry (MazPBCR) from 2016 to 2020. The registry, a voting member of the IACR since 2019, collects data on new primary cancer cases across the province based on national guidelines. Data were sourced from pathology reports, hospitals, and death registry programs. To identify cases registered only via death certificates, cancer mortality data from the Mazandaran death registry unit were linked to the incidence data.

To ensure data integrity, the registry follows a strict quality control process. Data coding is carried out by an experienced specialist, reviewed by a quality supervisor, and validated through consultations with pathologists and oncologists. Additionally, coding for TC (C73, ICD-O-3) is performed independently by two experts and reviewed by a third [18]. The registry has a formal system to prevent duplicate entries and to address cases with incomplete information by conducting follow-up reviews of patient files.

We calculated crude rates and ASIRs per 100000 population using the 18-group Segi's world standard population. Annual population data for Mazandaran Province were obtained from the Statistics Office of the Deputy of Health.

Trends in the Incidence rates were analyzed using joinpoint regression analysis with the Joinpoint Regression Program software, version 4.9.0.0. Due to the short study

period of five years (2016–2020), which results in a limited number of data points, we decided to restrict the number of allowed joinpoints to zero. This choice was made to prevent overfitting and to maintain the stability of the results. Consequently, the average annual percentage change (AAPC) and its corresponding 95% confidence intervals (CI) represent a descriptive linear trend over the study period rather than a formal test for significant trend changes. All statistical tests were two-sided, and a P<0.05 was considered statistically significant.

Results

Patients' characteristics

Female patients were found to be younger than male patients (41.7±13.1 vs 48.5±16 years, P<0.001), with a female-to-male incidence ratio of 5.22:1. The peak age incidence for females occurred in the 35–45-year age group, accounting for 509 cases (31.7%), whereas in males, the 35-45 and 45-55 year age groups each accounted for 65 new cases (21.2%). Figure 1 shows the age distribution of patients. Among all study cases, 1,129 patients (69%) resided in urban and 506 (31%) in rural areas of Mazandaran Province. In summary, TC in Mazandaran affects women far more often than men, typically during middle age, with most patients residing in urban areas.

Temporal trends in incidence

The highest number of new cancer cases (483) was recorded in 2020 (82 males and 401 females). The ASIR increased from 6.43 per 100000 in 2016 (95% CI, 3.5%, 9.3%) to 11.14 per 100000 in 2020 (95% CI, 6.1%, 16.2%). For females, the ASIR rose from 11.2 to 18.35, while for males, it increased from 1.79 to 4.03 over the study period. Table 1 presents the crude and ASIR values annually. Figure 2 displays the ASIR of TC by gender and residence. This indicates that TC incidence has risen in Mazandaran over the past five years, with women contributing the most to the increase.

Gender-specific trends (Joinpoint analysis)

TC incidence was significantly higher in females than males (15.14 vs 3.06 per 100000, P<0.001). Joinpoint regression showed a significantly increasing incidence in males (AAPC=19.8%, 95% CI, 4.5%, 37.4%), while no significant trend was found in females (AAPC=13.3, 95% CI, –5.%, 35.3%). Figure 3 illustrates the incidence trend by gender. This suggests that although women bear a larger disease burden, the rise in incidence is more pronounced among men.

Urban–rural differences

The ASIR was higher in urban areas than in rural areas (9.24 vs 5.73 per 100000, P>0.05). However, joinpoint regression did not show significant changes in either group (urban AAPC=6.08%, 95% CI, –20%, 40.6%; rural AAPC=8.74%, 95% CI, –18.9%, 45.8%). Figure 4 compares the incidence in urban and rural areas. Overall, both urban and rural populations showed similar temporal patterns, with no significant divergence in trend.

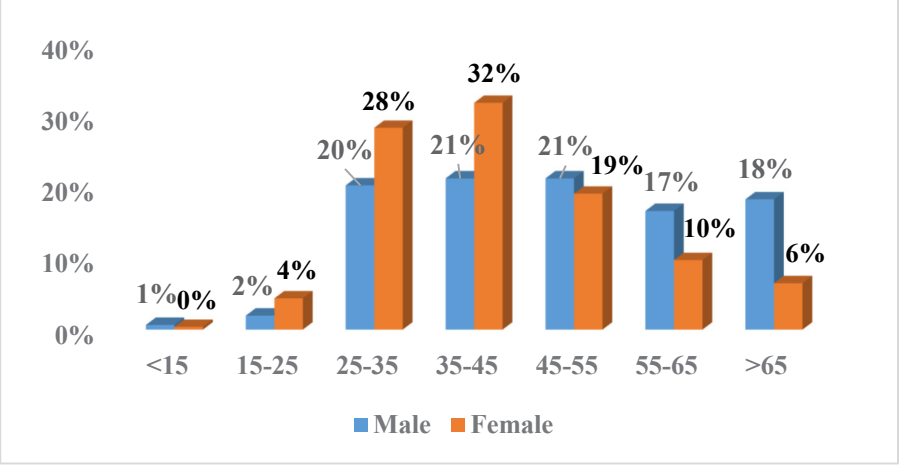

Figure 1. Age distribution of TC incidence by gender in Mazandaran from 2016 to 2020

Table 1. Crude and ASIR values of TC in Mazandaran by gender from 2016 to 2020

Year	Incidence						
	Male			Female			Both Sexes
	New cases	Crude rate (95% CI)	ASIR	New cases	Crude rate (95% CI)	ASIR	ASIR
2016	34	2.06 (1.4, 2.9)	1.79	219	13.72 (11.9, 15.6)	11.2	6.43
2017	50	3 (2.2, 3.9)	2.41	236	14.35 (12.6, 16.3)	11.18	6.77
2018	70	4.16 (3.2, 5.3)	3.51	394	23.77 (21.5, 26.2)	18.56	11
2019	71	4.19 (3.3, 5.3)	3.46	353	21.13 (19.0, 23.4)	16.02	9.71
2020	82	4.8 (3.8, 5.9)	4.03	401	23.81 (21.5, 26.3)	18.35	11.14

Subgroup trends by gender and residence

Regression analysis (Figure 5) showed the highest AAPC in urban men (10.9%, 95% CI, –29.2%, 73.9%), followed by rural men (9.0%, 95% CI, –6.3%, 26.8%) and women (8.5%, 95% CI, –25.1%, 57.1%). The lowest value was seen in urban women (4.6%, 95% CI, –18.5%, 34.2%). None of these trends was statistically significant. Although not statistically significant, these patterns suggest that men—particularly in urban areas—may be driving the upward trend.

Geographic variation

There was substantial geographic variation across Mazandaran. The highest ASIRs were observed in central and eastern regions (5.33 in men and 26.75 in women), while western areas, such as Abbasabad, Tonekabon, and Nowshahr had the lowest rates (0.88 in men and 3.78 in women). Figure 6 presents the spatial distribution. This heterogeneity indicates that local environmental, lifestyle, or healthcare factors may influence TC risk.

Discussion

This population-based study investigated the changes in the incidence of TC in Mazandaran Province from 2016 to 2020. TC is globally on the rise, ranking ninth among all cancers in 2020, and is one of the most common malignancies in Asia and Iran [3, 6]. Our study revealed ASIRs of 3.06 per 100000 for men and 15.14 per 100000 for women, with an overall increasing trend, which aligns with observed global patterns [19].

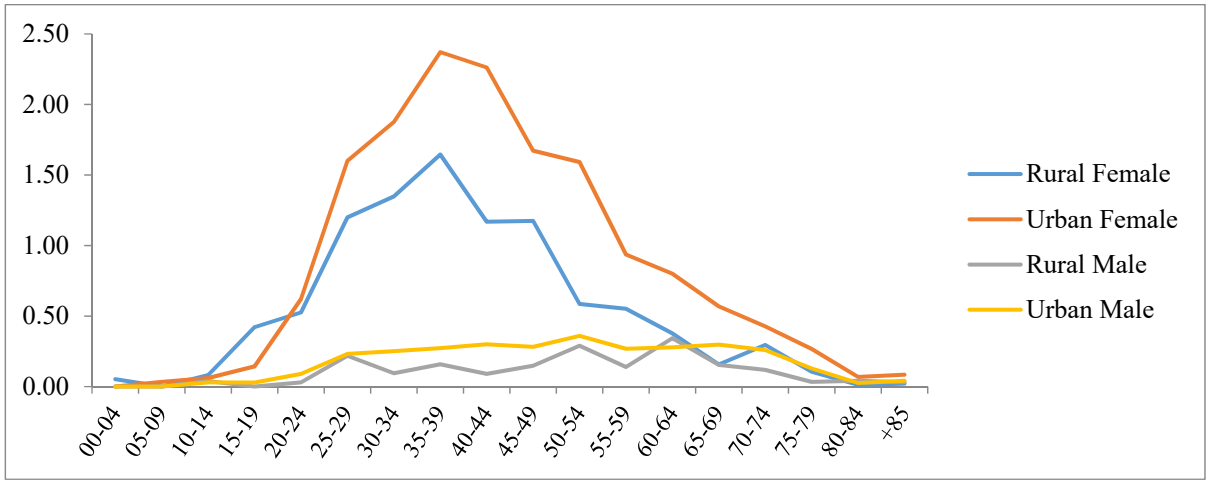

Figure 2. ASIR of TC in Mazandaran by gender and residential area from 2016 to 2020

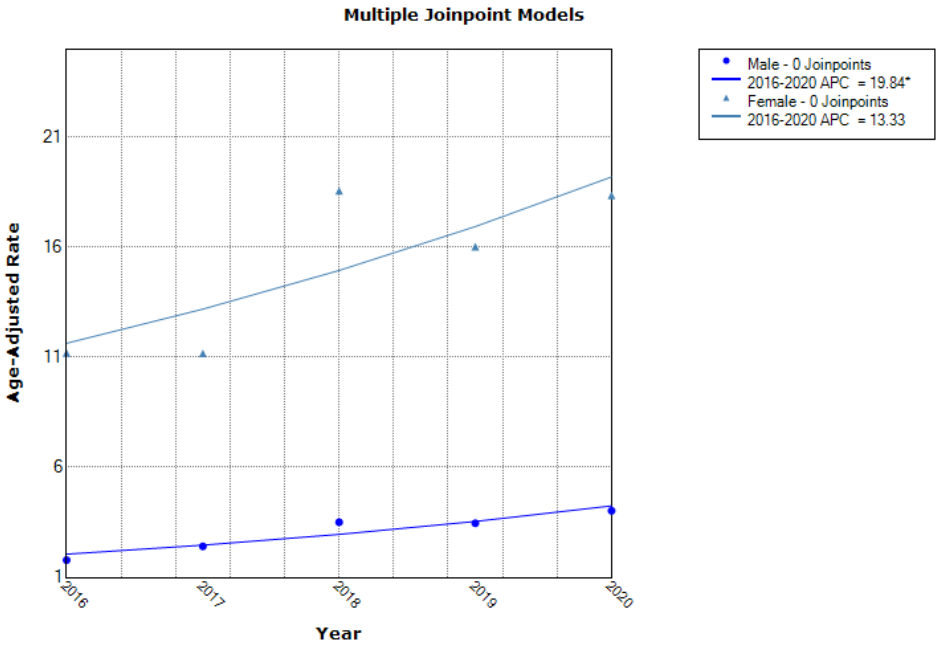

Figure 3. Joinpoint analysis of TC incidence by gender in Mazandaran from 2016 to 2020 (age-standardized rate per 100000 world standard population)

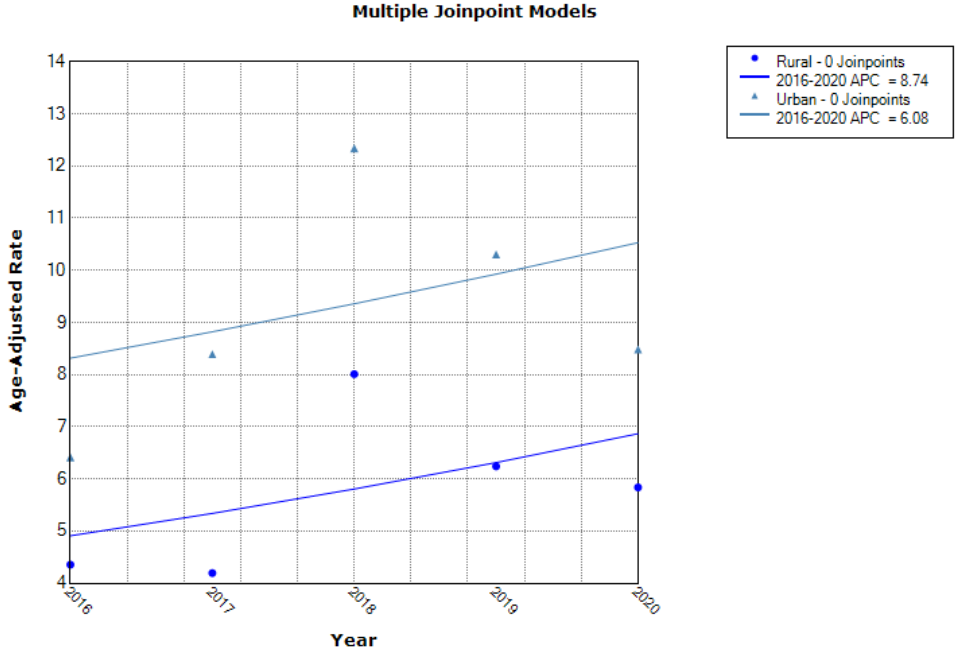

Figure 4. Joinpoint analysis of TC incidence by residential area (urban vs rural) in Mazandaran from 2016 to 2020 (age-standardized rate per 100000 world standard population)

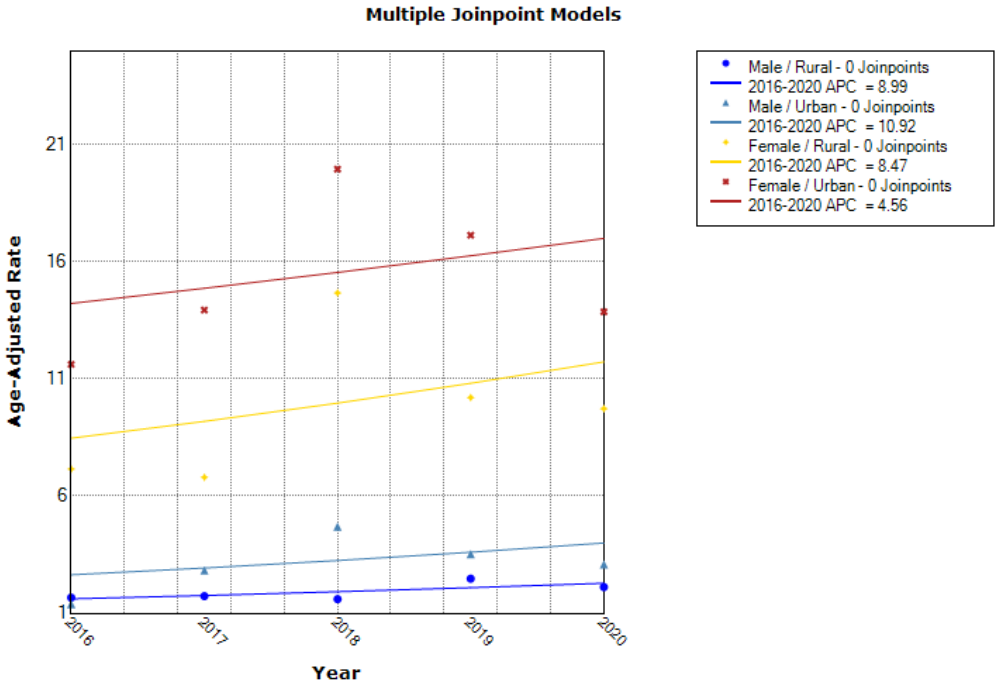

Figure 5. Joinpoint analysis of TC incidence by gender and residential area in Mazandaran from 2016 to 2020 (age-standardized rates per 100000 world standard population)

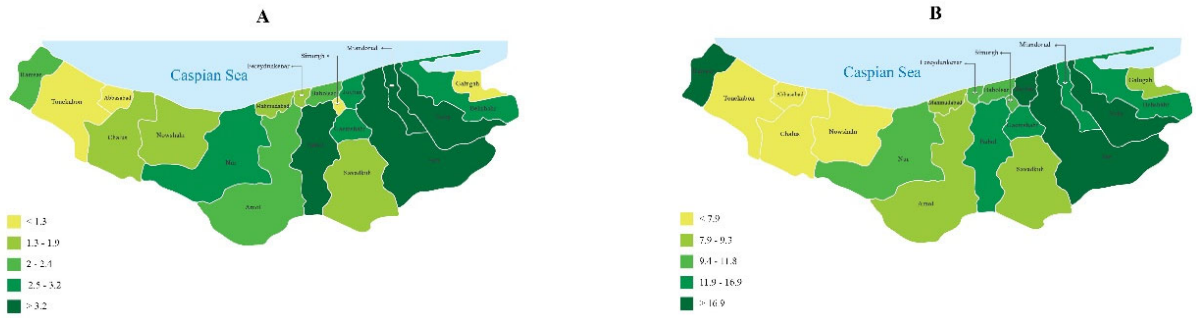

Figure 6. Spatial distribution of TC ASIR in Mazandaran from 2016 to 2020
A) Male, B) Female

It is crucial to acknowledge that the short 5-year study period (2016–2020) inherently limits the statistical reliability of Joinpoint regression analysis. Consequently, the AAPC values derived should be interpreted as descriptive indicators of linear trends over this brief period, rather than definitive assessments of long-term trend changes. This limitation impacts the robustness of formal trend change point detection. The observed increase in TC incidence in Mazandaran is likely a complex interplay of several factors. Firstly, the widespread utilization of more sensitive diagnostic techniques, such as high-resolution thyroid ultrasonography and fine-needle aspiration, has significantly enhanced detection capabilities. This technological advancement can lead to the identification of more subclinical diseases, including small, early-stage tumors that might have remained undetected previously [1, 8, 13, 14, 16, 19]. Secondly, the establishment and ongoing improvement of cancer registration systems play a critical role. The Mazandaran Population-Based Cancer Registry (MazPBCR) became a voting member of the International Association of Cancer Registries (IACR) in 2019, coinciding with

national improvements in registry integration. This enhanced data quality, coverage, and completeness could have contributed to the rise in reported cases. Therefore, the observed increase in incidence in Mazandaran could reflect both a true epidemiological rise and improved detection and reporting due to enhanced registry performance. This study's short timeframe also limits the ability to fully differentiate between these two contributing factors in assessing long-term trends.

Beyond detection, several risk factors have been implicated in the rising incidence of TC globally [16, 19]. These include a high body mass index (BMI), which is recognized as an important attributable risk factor worldwide, particularly in high sociodemographic index (SDI) regions [1, 13, 19, 20]. Other potential factors include a history of benign thyroid diseases, iodine imbalance (both deficiency and excess), radiation exposure, and various genetic and environmental influences [1, 8, 14-16, 19]. Historically, goiter was endemic in Iran due to iodine deficiency, but mass iodide supplementation since 1983 has reduced this prevalence [11, 15]. Improved iodine intake has been associated with an increased incidence of papillary TC [8, 11]. Mazandaran Province, which encompasses areas, like Ramsar that are known for high background radiation [7, 11], might also be influenced by such exposures.

The study also highlights significant gender disparities, with women exhibiting a substantially higher incidence rate than men (15.14 vs 3.06 per 100000). The female-to-male ratio in this study was 5.22:1. This aligns with global data where TC is consistently more prevalent in women [8, 9, 11, 13-15, 19, 21]. For instance, a men-to-women ratio of 1:4.5 was reported in Ho Chi Minh City, Vietnam [16]. In Tehran, Iran, a female-to-male ratio of 3:1 was observed [11], while in Oman, it was 4:1 [13]. This disparity is hypothesized to be linked to hormonal and reproductive factors, with estrogen implicated in thyroid cell proliferation and potential associations with infertility, pregnancy, and menstrual cycles [1, 15, 16, 19]. Women generally utilize healthcare services more frequently due to reproductive and perimenopausal factors, which can lead to additional opportunities for thyroid examination and earlier detection [1, 8, 19].

Regarding age distribution, the mean age of patients in this study was 42.8±13.8 years. This is consistent with other studies, which reported mean ages around 41-48 years for women and men, respectively [9, 12, 13]. TC incidence peaked in middle-aged individuals, specifically between 35–45 years for women and 45–55 years for men, and showed a decrease after the age of 60. This pattern differs from some findings in Golestan Province and central Iran, which reported the highest incidence in those over 70 years of age [7, 15]. The current study confirms that TC is less common in individuals under 14 years of age [7, 8, 12]. The observation that crude incidence rates often exceeded ASIRs in Mazandaran, despite the province having an aging population, can be explained by the younger weighting of the World Health Organization (WHO) world standard population. Since TC incidence typically peaks in middle age rather than among the elderly, the ASIR, which is weighted toward lower-incidence younger age groups in the standard population, can appear lower than the crude rate, even in an aging population.

Urban-rural differences were also notable, with higher ASIRs observed in urban areas (9.24 per 100000) compared to rural areas (5.73 per 100000). This disparity is possibly due to greater access to diagnostic facilities in urban centers, as well as distinct environmental or lifestyle exposures prevalent in urban settings. While urban-rural differences were reported, further in-depth exploration of specific healthcare access points or identified urban risk exposures was beyond the immediate scope of this study [22]. Regional variations within Mazandaran were also evident, with higher ASIRs in central and eastern regions (e.g. Sari, Neka, Ramsar, Babol) and lower rates in western areas (e.g. Abbasabad, Tonekabon, Nowshahr). This aligns with previous Iranian studies showing regional differences, with central provinces, like Isfahan, Yazd, Tehran, and Qazvin identified as high-risk [7]. The heterogeneity across Mazandaran suggests that local environmental, lifestyle, or healthcare factors may differentially influence TC risk.

Conclusion

In conclusion, our findings are consistent with global and national observations of an increasing trend in TC incidence, particularly for papillary subtypes. The interplay of improved diagnostics, advancements in registry performance, and underlying risk factors likely contributes to the patterns observed in Mazandaran.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code: IR.MAZUMS.IMAMHOSPITAL.REC.1401.067).

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Authors contribution's

Conceptualization and study design: Mahmood Moosazadeh; Data collection, statistical analysis, and writing the original draft: Elahe Mahmoodi; Data interpretation: Elahe Mahmoodi, Akbar Hedayatizadeh-Omran, and Mahmood Moosazadeh; Data processing: Reza Alizadeh-Navaei; Review and editing: Akbar Hedayatizadeh-Omran and Reza Alizadeh-Navaei; Final approval: All authors.

Conflict of interest

All the authors declared no conflict of interest.

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