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RESEARCH NOTE

Relationship of modifiable risk factors with the incidence of thyroid cancer: a worldwide study

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Abstract

Background Thyroid cancer is one of the most common cancers of the endocrine system. The incidence of this cancer has increased in many countries. Many cases of thyroid cancer do not have any symptoms. This cancer has different risk factors. Some of them are unchangeable and some can be changed and modified. So, it is necessary to identify these risk factors. Therefore, this global study was conducted for the first time to investigate the correlation between the age-standardized incidence rate of thyroid cancer (ASIR) and some modifiable risk factors worldwide.

Methods The data of this global ecological research has been collected on the official website of health data (https://www.healthdata.org/) for 204 countries and territories from 1990 to 2019. Pearson correlation coefficient was used to evaluate the correlation. Finally, statistical modeling was done using Generalized Additive Model (GAM). Statistical analyzes were performed using R version 4.2.2 software.

Results ASIR of thyroid cancer has a positive and significant correlation with tobacco, Secondhand smoke (SHS), mean BMI, and low physical activity. Multiple GAM showed that gender, alcohol consumption, smoking, SHS, mean BMI, and low physical activity have a statistically significant relationship with the ASIR of thyroid cancer (All Relative Risk > 1).

Conclusion This study showed that the risk of thyroid cancer is higher in women than men. Smoking, alcohol, obesity, and low physical activity may be risk factors for ASIR of thyroid cancer. Also, this study, for the first time globally, hypothesized an association between exposure to secondhand smoke and ASIR of thyroid cancer. To prevent and accurately control thyroid cancer, there is a need to increase awareness about the modifiable risk factors of this cancer.

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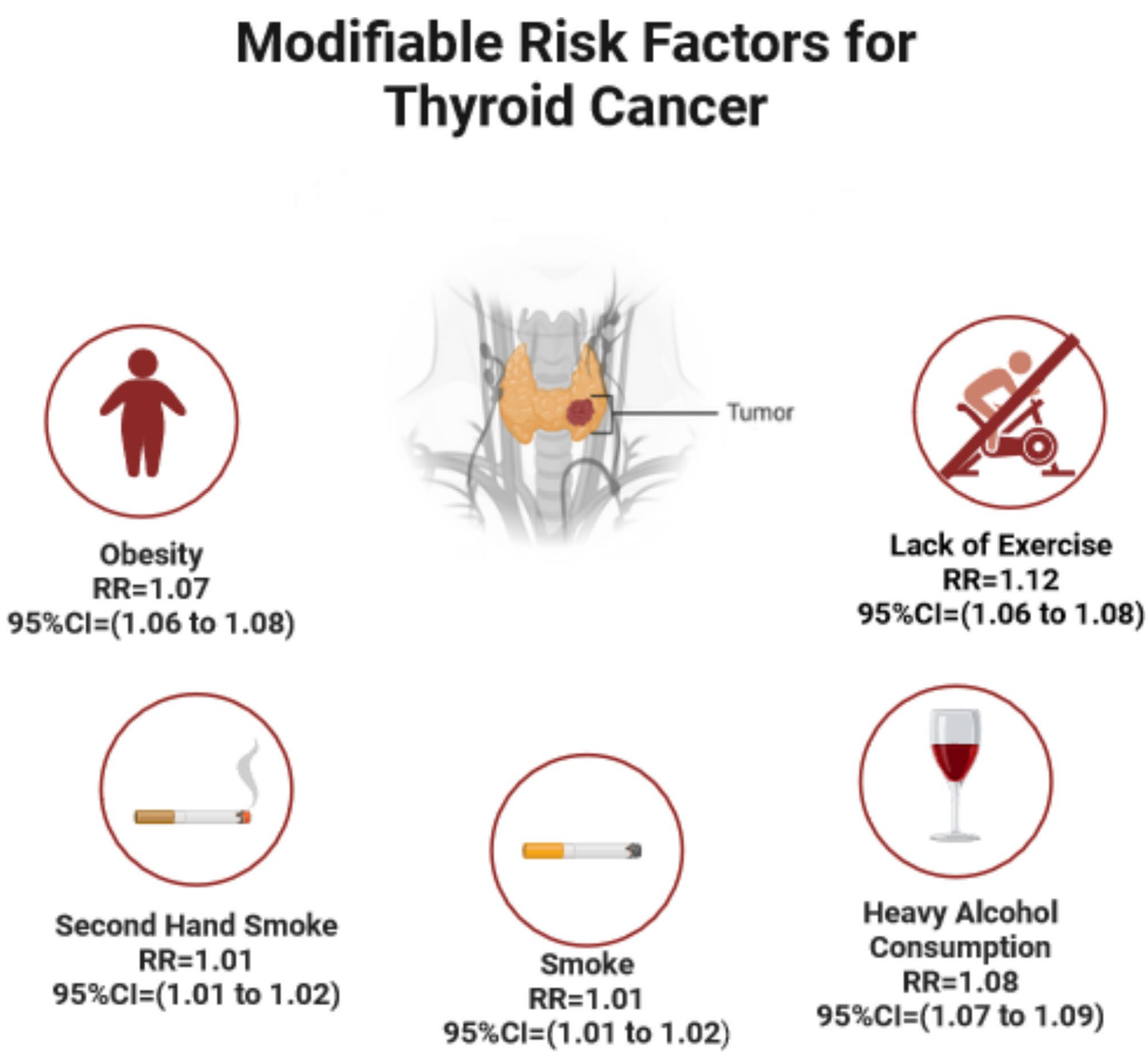
Graphical Abstract



Keywords Thyroid neoplasms, Incidence, Epidemiology, Risk factors, Global

Introduction

Thyroid cancer is clearly the most common endocrine malignancy [1]. It is thought to become the fourth leading type of cancer throughout the world [2]. The incidence of thyroid cancer is increasing in numerous countries, and one of the reasons may be the overdiagnosis due to health screening with ultrasound [3–5]. However, this is not the only reason for the increased incidence of thyroid cancer. Some etiological factors, including obesity, have been shown to affect the increased incidence of thyroid cancer [6, 7]. Other factors such as exposure to radiation and iodine consumption are also considered risk factors for thyroid cancer [3, 8]. Previously, several studies have reported the association between obesity, physical inactivity, smoking, and drinking alcohol with thyroid cancer [9–12]. In the last few decades, the increasing trend of thyroid cancer coincides with the growing trend of obesity. But how they are related is largely unknown [13]. A meta-analysis of prospective cohort studies showed a pooled hazard ratio of 1.53 for thyroid cancer in obese men and women (BMI ≥ 30 kg/m2) [14]. A meta-analysis that included 21 observational studies showed that obesity was associated with an increased risk of papillary thyroid cancer and a decreased risk of medullary cancer [15]. Another meta-analysis found that a 5 kg/m2 increase in BMI was strongly associated with an increased risk of thyroid cancer in men (RR = 1.33) [16]. Physical activity is thought to play a role in mediating cancer risk. In addition, most chronic diseases are attributed to a sedentary lifestyle. Various mechanisms are hypothesized to be involved in the relationship between physical activity and thyroid cancer risk [17], for example, by improving endogenous DNA repair capacity, reducing body fat, reducing insulin resistance, and altering circulating inflammatory factors [18, 19]. Two case-control studies found a slightly reduced risk of thyroid cancer among people who reported recreational physical activity. While the weekly frequency (hours/week) was more related to the risk reduction than the duration (years) [13, 20]. Studies show that smoking may be associated with an increased risk of thyroid cancer [13]. The results of a meta-analysis of five prospective studies showed that smoking reduces the risk of papillary thyroid cancer and possibly follicular thyroid cancer by 30–40% [21]. Smoking can potentially affect thyroid cancer risk by altering thyroid-stimulating hormone, thyroid serum antibodies, and sex steroid hormone levels. Because all studies used self-administered questionnaires, the null correlation may be partially related to selection and recall bias [22, 23]. In addition, tobacco use has been indicated to have several effects on the hypothalamus-pituitary-thyroid axis and the function of the thyroid gland. Adverse mechanisms of smoking exposure include changes in thyroid synthesis, binding, secretion, storage, and clearance, resulting in changes in circulating hormone concentrations. Both active and passive smokers have shown significantly decreased T3 and T4 serum levels and significantly increased TSH serum levels compared to non-smokers, indicating the harmful nature of tobacco smoking on thyroid function [24]. SHS that passive smokers are exposed to, comprised of mainstream smoke (11%) and sidestream smoke (85%) along with other contaminants. Therefore, passive smokers are exposed to a wide range of toxic substances compared to active smokers [25]. Few studies have analyzed obesity, smoking, SHS, and alcohol consumption in one study. Also, a few cohort studies have examined smoking and alcohol consumption with thyroid cancer risk, and their results were inconsistent [26]. Another study showed that the occurrence of thyroid cancer can be influenced by genetic and lifestyle factors. In people of European descent, a healthier lifestyle may reduce the deleterious effects of genetics on thyroid cancer incidence [27].

This study was carried out to determine the correlation between some modifiable risk factors and the global incidence of thyroid cancer in the world between 1990 and 2019. In this study, we examined smoking, SHS exposure, alcohol consumption, tobacco use, mean body mass index (BMI), and low physical activity because they are modifiable and the control of these variables may affect the incidence of thyroid cancer.

Materials and methods

This global and population-based study was conducted to evaluate the correlation between global ASIR of thyroid cancer and some modifiable risk factors. Some modifiable risk factors were consumption of alcohol, tobacco use, cigarette smoking, SHS exposure, mean BMI and low physical activity (Less than 8,000 metabolic equivalent (MET)-minutes per week, with one MET being the energy burned out while sitting quietly) [28]. Data for all countries of the world (204 countries and territories) for all patients between 1990 and 2019 in each year were obtained from the Global Burden of Disease (GBD) (available at https://www.healthdata.org/). The GBD study is the largest and most comprehensive effort to quantify health loss across places and over time, so health systems can be improved and disparities eliminated. More than 11,000 people from more than 160 countries and regions collaborate in reviewing GBD data sources and estimates.

Statistical analysis

In this study, mean and standard deviation were employed to describe quantitative variables. Also, Pearson correlation coefficient was applied to evaluate the correlation between the ASIR of thyroid cancer and some modifiable risk factors. The intensity of correlation was interpreted in accordance with correlation values: $r = 0.8$-1. Very strong correlation, $r = 0.6 - 0.08$ strong correlation, $r = 0.4$–0.6 moderate correlation, $r = 0.2$–0.4 low or weak correlation [29].

Also, because Pearson correlation coefficient is only able to identify linear relationships, the generalized additive model (GAM) was used to identify non-linear relationships between ASIR of thyroid cancer and modifiable risk factors. A GAM is a generalized linear model. This model discovers non-linear and non-uniform relationships between the dependent variable and the independent variables. Therefore, this model maximizes the quality of predicting the dependent variable with more information on the relationships between the data. Using the following formulas, relative risk (RR) and 95% confidence interval (CI) for RR are calculated [30–32].

$$RR = exp\left(\beta\right)$$

$$95\%CI = exp\left(\beta \pm 1.96\ SE\right)$$

Finally, statistical modeling was performed using simple and multiple GAM. Variables that had a p-value smaller than 0.2 in the simple model were included in the multiple model. In this method, ASIR of thyroid cancer was a dependent variable and some modifiable risk factors were independent variables. All reported p-values were two-sided. A p.value of 5% was considered statistically significant. Statistical analyzes were performed using R software and 'mgcv' package, (version 4.2.2) (Supplemental 1).

Results

Table 1 shows descriptive analyzes between ASIR of thyroid cancer and some modifiable risk factors. The highest ASIR of thyroid cancer in 2019 was observed in Monaco (9.50 per 100,000 people). In 2019, countries with the highest consumption of alcohol, tobacco use, cigarette smoking, and SHS were in an order Estonia (27.56), Montenegro (50.52), Armenia (33.37), Greenland (51.12), and Nauru (49.20). The countries of Qatar (56.95), American Soma (33.26), and the United Arab Emirates (18.15) reported the highest BMI, and low physical activity, respectively.

Figure 1 shows that the ASIR of thyroid cancer was significantly positively correlated with tobacco use ($r = 0.33$, P-value ≤ 0.0001), SHS ($r = 0.53$, P-value ≤ 0.0001), mean BMI ($r = 0.39$, P-value ≤ 0.0001), and low physical activity ($r = 0.70$, P-value ≤ 0.0001). However, the correlation between ASIR and cigarette smoking was shown to be significant negative (r=-0.06, P-value ≤ 0.0001). Also, the correlation between ASIR and Alcohol consumption was negative and statistically nonsignificant (r=-0.59, P-value = 0.423).

Multiple GAM also showed that gender, alcohol consumption, cigarette smoking, SHS, mean BMI, and low physical activity were significantly associated with the thyroid cancer incidence. As such, the risk of thyroid cancer is 8.9 times higher in women than in men. Accordingly, one unit increase in exposure to cigarette smoking, alcohol consumption, SHS, BMI index, and physical activity reduction, were shown to increase the risk of thyroid cancer by 1.01, 1.08, 1.01, 1.07, and 1.12 times, respectively (Table 2, Supplemental 1).

Discussion

This global study used a generalized additive model to investigate the relationship between some modifiable risk factors and thyroid cancer incidence. The results showed that the highest incidence rate of thyroid cancer in 2019 was related to the French Republic (7.13 per 100,000). This finding was consistent with the results of the study by Pizzato and his colleagues, which was conducted with the aim of the epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020 [33].

Diagnostic practices in an area, including the amount and type of access to diagnostic methods, regular ultrasound, screenings, and sampling can significantly affect the incidence of thyroid cancer. This is because cancers are diagnosed in the early stages and may lead to an increased incidence rate. While in areas with more limited diagnostic facilities, many cases of cancer may not be diagnosed until advanced stages or not at all. Therefore, the incidence is lower in these areas, although the true rate may be much higher [34, 35]. Screenings in South Korea have led to an increase in the incidence of thyroid cancer, especially among women. Screenings lead to the identification of asymptomatic and benign cases (such as papillary carcinoma) [36].

The results of this study showed a significant positive correlation between tobacco use, SHS, mean BMI, and low physical activity with the ASIR of thyroid cancer. A systematic review study showed that tobacco use changes nearly all functions of the thyroid gland, and currently, studies have pointed out a strong correlation between tobacco use and risk of thyroid diseases. Therefore, the results of this study were consistent with the present study [37]. One study reported that people were exposed to SHS are exposed to a wide variety of toxic substances that can affect their thyroid gland function [25]. Another study showed that Melanesian overweight women were 5 times more likely to develop thyroid cancer than ideal-weight women. These findings were consistent with our study [1]. However, in the present study, a significant weak inverse correlation was found between cigarette smoking and thyroid cancer incidence. T. Rahman and colleagues (2021) concluded that smoking was

Table 1 Summary of ASIR of thyroid cancer and some modifiable risk factors

variables	Mean ± Standard Deviation	P25*	Median	P75**
ASIR of thyroid cancer (per 100,000 people)	2.39 ± 1.93	0.936	1.85	3.39
Consumption of Alcohol (grams)	7.28 ± 6.39	1.95	5.57	11.11
Tobacco (exposure per 100)	24.61 ± 10.77	15.05	25.58	32.57
SHS (exposure per 100)	37.05 ± 12.48	27.30	35.91	45.31
Mean BMI (kg/m^2)	25.23 ± 2.77	23.25	25.38	26.77
Smoking (exposure per 100)	11.45 ± 9.05	2.74	9.76	17.88
Low physical activity (exposure per 100)	3.95 ± 2.94	1.78	2.88	5.38

* 25th percentile, ** 75th percentile

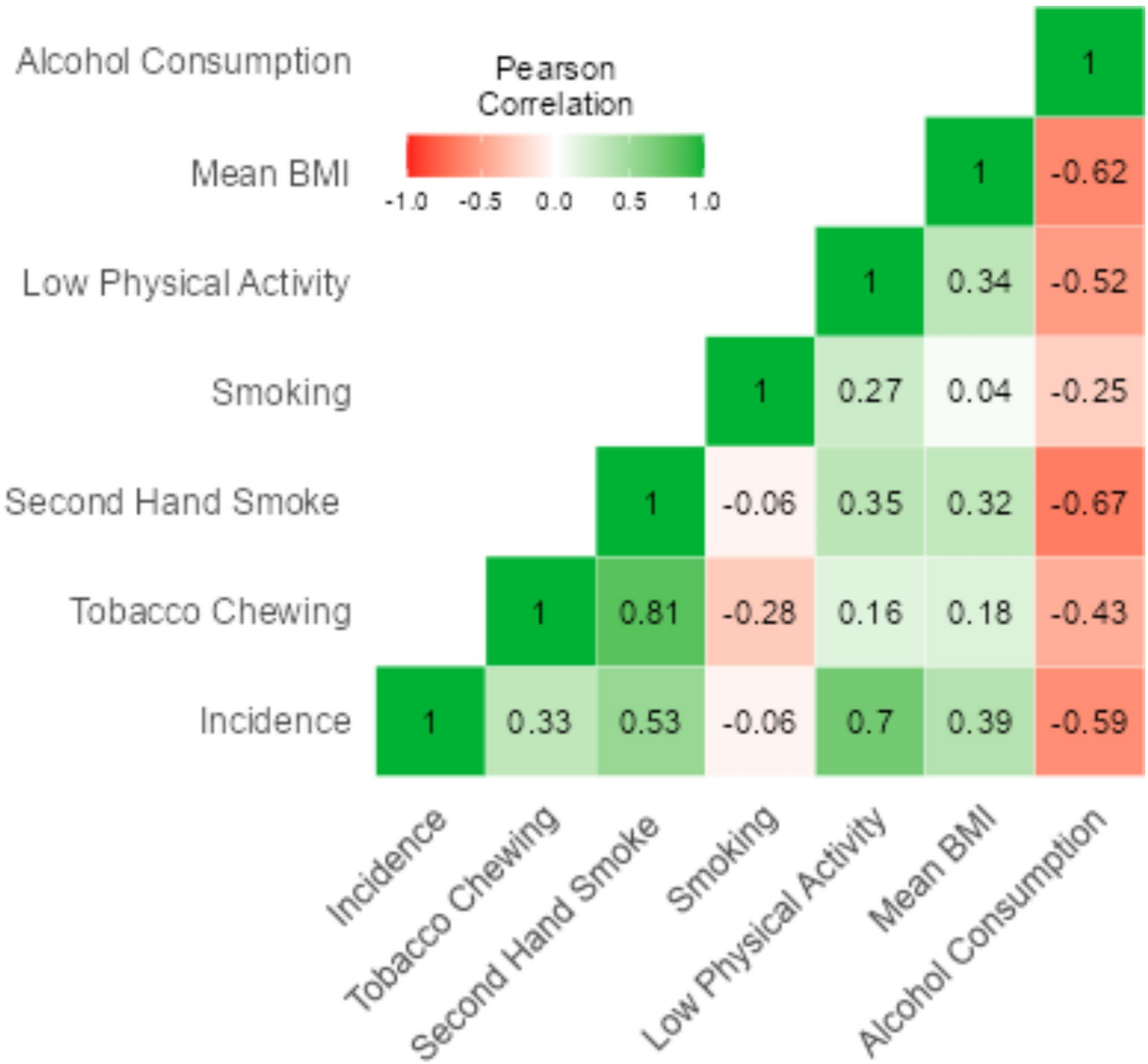


Fig. 1 Correlation between ASIR of thyroid cancer and some modifiable risk factors

Table 2 Association ASIR of thyroid cancer and some modifiable risk factors with multiple GAM

variables		**ASIR of thyroid cancer**			
		Relative Risk	**95%CI**	**Standard Error**	***P*-value**
Gender	**Male**	reference	-	-	-
	Female	8.976	8.267 to 9.745	0.0419	< 0.0001
Smoking		1.017	1.012 to 1.022	0.0024	< 0.0001
Alcohol		1.085	1.079 to 1.091	0.0029	< 0.0001
SHS		1.019	1.017 to 1.022	0.0013	< 0.0001
Mean BMI (kg/m^2)		1.077	1.065 to 1.089	0.0057	< 0.0001
Low physical activity		1.122	1.066 to 1.088	0.0051	< 0.0001

inversely associated with the risk of thyroid cancer [38]. Considering that the Pearson correlation coefficient was performed univariate and the role of other confounding variables were not considered, these findings regarding the relationship between cigarette smoking and risk of thyroid cancer can be ignored. Furthermore, ecological studies are hypothesis-generating design, so the observed relationship is weak and not causal. Therefore, the GAM model was employed to Decrease the impact of confounding variables. The results of this model showed that the incidence of thyroid carcinoma is 8.9 times higher in women than men. A study found that differentiated thyroid cancers are more common in females. This may be due to the influence of sex hormones, although this issue is not sufficiently clear and complete. Estrogens may increase the production of mutagenic molecules in the thyroid cell and contribute to the proliferation and invasion of tumoral cells by regulating the thyrocyte enzymatic machinery and the inflammatory process associated with tumor growth. Nevertheless, the worse prognosis of thyroid cancer associated with the male gender is not well well-understood [39].

In addition, cigarette smoking and SHS have been identified as risk factors for thyroid cancer. These findings are supported by the results of various studies [11]. However, another study reported contradictive results. Thus, studies with a large sample size are required [40]. There is no safe level of exposure to SHS, and even a little exposure can cause immediate damage. The effects of exposure to cigarette smoke on the body are immediate. Exposure to SHS can cause harmful inflammatory effects within the first 60 min of SHS exposure, which can persist for at least three hours following exposure [41]. There is a lot of scientific evidence that SHS can contribute to thyroid dysfunction. Toxic elements in cigarette smoke, such as thiocyanate, may be partly responsible for the disruption of thyroid hormone production. SHS-induced inflammatory stress, i.e., interleukin 1beta (IL-1beta), impairs thyroid function and iodine uptake. Interleukin-6 (IL-6) production is initiated by thyroid epithelial cells which stimulates the expression of molecules exacerbating thyroid autoimmunity. The association between SHS and autoimmune thyroid disease has not been well-documented. Catabolic processes are initiated by elevated inflammatory stress and thyroid hormone secretion in response to SHS exposure. The effect of SHS on thyroid function may rely on a combination of specific biological factors, such as gender and/or the presence of thyroid disease. Exposure to SHS disrupts vital human processes through thyroid disruption [42, 43]. Various studies have shown that cigarette smoke contains many harmful chemicals, including carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and nitrosamines. By smoking, these toxic substances enter the lungs and are absorbed into the bloodstream through the mucous membranes of the respiratory system, so these carcinogenic substances circulate throughout the body and go to the organs, including the thyroid gland. These substances can cause chronic inflammation and genetic mutations (DNA damage) in the cells of the thyroid gland. However, changes in thyroid hormone levels can affect cell growth and proliferation and potentially may lead to cancer [44, 45].

In addition, when humans come in contact with carcinogenic substances such as PAHs, it can lead to increased cellular levels of reactive oxygen species (ROS). Therefore, it can cause oxidative stress and lead to damage to proteins, lipids, and DNA. Oxidative stress can lead to a decrease in cellular repair mechanisms and metabolic homeostasis, potentially leading to tissue damage and cell deformation [46].

Alcohol consumption was also found to be another risk factor associated with thyroid cancer. The risks and harms associated with alcohol intake have been systematically evaluated over the years and are well-documented. The World Health Organization has now published a statement in The Lancet Public Health, "When it comes to alcohol consumption, there is no safe amount that does not affect health" [11, 47].

Also, obesity and lack of physical activity were found as other modifiable risk factors for thyroid cancer in this study. These findings were in compliance with the results of other studies [3, 9, 48, 49]. Obesity can affect thyroid tumorigenesis through different mechanisms [9]. Low levels of physical activity are often associated with weight gain and obesity. Excess body fat can lead to hormonal imbalances and chronic inflammation, which may contribute to the growth of cancer cells in the thyroid gland. Physical activity can affect the hormonal balance in the body. Regular exercise can help regulate insulin levels and reduce insulin resistance. High levels of insulin and insulin resistance are associated with an increased risk of thyroid cancer. Additionally, hormonal changes associated with obesity, such as increased estrogen levels, may also play a role [12, 50].

Obesity can cause chronic inflammation through IL-6, TNF-α, PAI-1, and NF-κB through elevating hyperinsulinemia and leptin and decreasing adiponectin. It may also lead to an elevation in free fatty acids and oxidative stress and DNA damage [51]. A large meta-analysis study on 3,587 patients with thyroid cancer concluded that for every 5 kg/m2 increase in BMI, the risk of thyroid cancer increased 1.33 times (95% CI 1.04–1.70) in men and 1.14 times (95% CI 1.06–1.23) in women [52].

So, weight management, obesity prevention, regular physical activity, and avoiding smoking can help improve overall thyroid health and reduce the incidence of thyroid cancer [53–57].

Strengths and limitations

In this ecological study, the ecological fallacy should not be ignored. The results of the present study were obtained from aggregate data and may not be generalizable to individual people [58]. Also, this ecological study is hypothesis-generating and does not claim a causal relationship between the variables in its results. Therefore, it is suggested to use cohort studies and clinical trials in the future to prove the causal relationship between the variables. In addition, this study only examined some modifiable risk factors associated with thyroid cancer, so it is suggested that future studies examine other risk factors for thyroid cancer that are not present in this study. One of the points that should be considered in the interpretation of the results of this study is that it is necessary to pay attention to the possible differences between the GBD data and other sources. This is because data on cancer incidence rates from different sources may differ due to differences in collection methods, analysis, and geographic conditions.

In interpreting the results, it should be noted that although the p-value is significant due to the large sample size, the relative risk values (no matter how small.) indicate the risk factors. Therefore, pay attention to the clinical importance of this issue.

Conclusions

This global ecological study shows that several modifiable risk factors, such as tobacco use, exposure to secondhand smoke, and low physical activity, may be associated with an increased incidence of thyroid cancer. These findings emphasize that public health measures and lifestyle changes may reduce the risk of thyroid cancer. Considering that many of these risk factors are modifiable, public health measures can help reduce these factors and thus reduce the incidence of thyroid cancer. These results can help public health decision-makers and physicians in the diagnosis and management of thyroid disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-024-07058-2.

Supplementary Material 1

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Author contributions

Z.M. performed the conceptualization, methodology, data review, analysis, and writing of the article. J.H. was responsible for methodology, data analysis, and manuscript review and editing. H.G. performed the conceptualization, methodology, supervision, validation, and review and editing of the manuscript.

Funding

This study was subject to ethical standards and received an ethical approval code at Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1401.053).

Data availability

All raw data used in this study are available at http://www.healthdata.org/. The analyzed data of this study are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

The Ethics Committee approved this study at Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1401.053).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Definition of variables

Tobacco: Tobacco includes tobacco smoking, chewing tobacco use, and secondhand smoke exposure.
Smoking: Smoking is defined as current daily or occasional use of any smoked tobacco product.
Secondhand smoke: This risk factor refers to current exposure to secondhand tobacco smoke at home, at work, or in other public places. Only non-daily smokers are considered to be exposed to secondhand smoke.
Alcohol: We define current drinkers as individuals consuming at least one alcoholic beverage in the past year. Among current drinkers, we estimate the level of exposure based on average grams of pure alcohol consumed per day.
Low physical activity: Low physical activity was measured in total metabolic equivalents (METs) and was defined as average weekly physical activity (at work, home, transport-related, and recreational) of less than 3000–4500 MET minutes per week.
Thyroid cancer: This cause includes death and disability resulting from invasive neoplasms of the thyroid, including ICD-10 codes such as C73.

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