Submitted: 05.09.2023
Accepted: 06.01.2024
Early publication date: 13.03.2024

Endokrynologia Polska
DOI: 10.5603/ep.97258
ISSN 0423–104X, e-ISSN 2299–8306

Modifiable risk factors for thyroid cancer: lifestyle and residence environment

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Abstract

In recent years, there has been a rapid increase in the prevalence of benign and malignant tumours of the thyroid gland worldwide, positioning it as one of the most prevalent neoplasms within the endocrine system. While the pathogenesis of thyroid tumours is still unclear, an increasing number of studies have found that certain lifestyle and residence environments are associated with their occurrence and development. This article endeavours to elucidate the correlation between lifestyle, residential environment, and the increased prevalence of thyroid cancer in recent years. It specifies the frequency of the lifestyle and outlines the scope of the residential environment. It also endeavours to summarise the main mechanistic pathways of various modifiable risk factors that cause thyroid cancer. Factors that prevent thyroid cancer include smoking and alcohol consumption, quality and regular sleep, consumption of cruciferous vegetables and dairy products, and consistent long-term exercise. Conversely, individuals with specific genetic mutations have an elevated risk of thyroid cancer from prolonged and frequent use of mobile phones. In addition, individuals who work in high-pressure jobs, work night shifts, and live near volcanoes or in environments associated with pesticides have an elevated risk of developing thyroid cancer. The impact of living near a nuclear power plant on thyroid cancer remains inconclusive. Raising awareness of modifiable risk factors for thyroid cancer will help to accurately prevent and control thyroid cancer. It will provide a scientific basis for future research on lifestyles and living environments suitable for people at high risk of thyroid cancer.

Key words: *modifiable risk factors; thyroid cancer; lifestyle; residence environment*

Introduction

Thyroid cancer (TC) is currently the most common endocrine cancer [1]. TC is mainly divided into differentiated thyroid cancer (DTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid cancer (ATC), of which DTC accounts for more than 85% [2]. According to several studies, the prevalence of TC has increased significantly in recent decades [3, 4]. Based on the increasing trend in prevalence, TC is projected to become the fourth most common cancer by 2030, surpassing colorectal cancer and following breast, prostate, and lung cancers [5]. The significant rise in TC cases will inevitably lead to a substantial increase in both clinical and economic burden [6]. Several studies have associated behavioural habits [7], such as smoking, alcohol consumption, poor sleep patterns, diet choices, frequent use of mobile phones, sedentary lifestyles, occupation factors, and exercise routines [8–14], with the incidence of TC.

However, there are currently only a few systematic review articles summarising the relationship between lifestyle habits and environmental factors contributing to the rapid increase in TC risk (Fig. 1). There is a lack of exact and unified conclusions on the pathogenesis of TC, and the definitions of various behaviour habits remain unclear. To address these gaps, this paper aims to review the behavioural definitions alongside the pathogenic mechanisms associated with thyroid tumour development. The objective is to identify behavioural targets that can be used for the prevention and control of thyroid tumours, and to provide a basis for accurate and scientific prevention and control of thyroid tumours.

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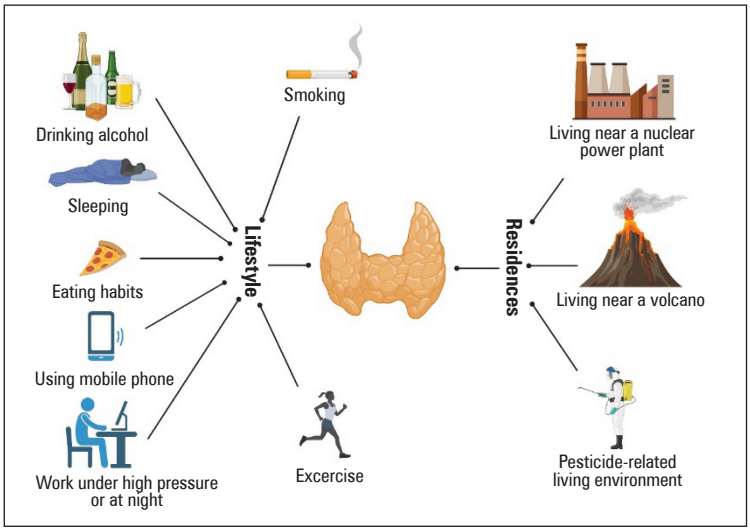

Figure 1. *Lifestyle and residential environment are correlated with the risk of developing thyroid cancer (TC). Lifestyle factors encompass smoking, alcohol consumption, sleep patterns, diet, mobile phone usage, high-stress occupations, night shift work, and physical exercise. Residential factors comprise residing near a nuclear power station, living near a volcano, and residing in an environment associated with pesticide exposure*

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Lifestyle

Smoking

Research suggests that individuals who smoke more than 10 cigarettes per day, smoke for more than 15 years, or have a cumulative smoking dose exceeding 10 cigarettes (cumulative dose = average number of cigarettes per day × number of years of smoking, based on a pack of 20 cigarettes) have a lower risk of developing TC [15]. Contrary to previous belief, a significant number of studies have suggested that smoking may actually be a protective factor against TC [8, 15–18]. This phenomenon could be attributed to the dose-dependent relationship between smoking and thyroid stimulating hormone (TSH) levels. TSH plays a crucial role in regulating the proliferation of TC tissue. Recent research on a large cohort of 5766 white Nordic subjects revealed that smoking is associated with decreased TSH levels and increased levels of free triiodothyronine (FT3) and free tetraiodothyronine (FT4). For every 10-nanograms/ml increase in serum cotinine, TSH levels decreased by 1.4%. Moreover, it was observed that TSH levels gradually increase after smoking cessation or reduction in smoking intensity; however, the duration for which the protective effect of smoking persists after quitting remains unclear [8, 19].

Investigating the impact of smoking on TSH and its potential role in reducing the risk of TC, research has shown that smoking can increase the levels of triiodothyronine (T3) and thyroxine (T4), leading to a "TSH suppression" effect. Ultimately, this suppression may contribute to a reduced incidence of differentiated thyroid cancer subtypes such as papillary and follicular TC [18]. Additionally, studies suggest that smoking alters the metabolism of oestradiol, resulting in an increase in the formation of inactive catechol oestrogen. This is protective because oestrogen has a growth-promoting effect on the thyroid gland [16]. The aryl hydrocarbon receptor (AHR) signalling pathway-mediated antiestrogenic effects induced by cigarette smoke might explain this phenomenon, further reducing TC incidence [20]. Finally, certain researchers propose that elevated sympathetic nerve activity among smokers contributes to increased thyroid hormone levels while subsequently decreasing TSH levels [8]. Therefore, smoking has been shown to be a protective factor for TC, but the underlying mechanisms are still uncertain and may involve multiple mechanisms. Further research is necessary to comprehensively and clearly explain the mechanisms by which smoking affects TC.

Drinking alcohol

Multiple cohort studies and case-control studies have found a negative correlation between alcohol consumption and TC [16, 17]. Persistent light to heavy drinking is associated with a 10% reduction in TC risk (where non-drinkers did not consume alcohol within a week, the average consumption of light drinkers was less than 15 grams/day, the average consumption of moderate drinkers was between 15 grams/day and 30 grams/day, and the average consumption of heavy drinkers was more than 30 grams/day), but there is no clear dose-response relationship [19]. Abstaining from alcohol may increase the likelihood of developing TC. The reduction in TC risk associated with alcohol con-

sumption may be due to the toxic effect of alcohol on the thyroid gland and the decrease in TSH levels caused by alcohol [19].

Regarding the study on TC in people who both drink and smoke, one study found no interaction between smoking and drinking on TC [16]. Another study found that individuals who both smoked and drank were slightly more likely to have TC than those who did not smoke or drink, and that there was an antagonistic effect between smoking and drinking [19]. The inconsistency of these results may be related to the study design type, control of confounding factors in the study, and sample size.

Sleeping

Several studies have linked sleep quality with the incidence of TC, indicating that good sleep quality and a regular sleep schedule can serve as protective factors against TC [21, 22]. When circadian rhythms are disrupted, it can impair sleep quality, which is an independent risk factor for TC [7, 23]. Conversely, a consistent routine and high-quality sleep can lower the risk of TC in older adults [23].

To determine sleep quality, the Pittsburgh Sleep Quality Index questionnaire was used, which assesses sleep disturbances on a 21-point scale. A score above a certain threshold indicates poor sleep quality, while a score below the threshold suggests good sleep quality [24]. The questionnaire covers 7 areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping pills, and daytime dysfunction.

There are currently several mechanisms by which sleep affects the incidence of TC. Firstly, sleep deprivation or poor sleep quality can lead to elevated levels of TSH and T4 [21, 24, 25], which in turn can increase the risk of TC [26]. Secondly, disruption of sleep rhythm can result in dysfunction of the hypothalamic-pituitary-adrenal axis, leading to problems with thyroid function [9]. Moreover, most studies indicate a relationship between the *CLOCK* gene and TC. The worse the sleep quality, the higher the expression level of the *CLOCK* and *BMAL1* genes, and the lower the *CRY2* level, the greater the risk of thyroid malignant tumours [9, 23]. Finally, telomere length can serve as a marker of sleep duration, sleep quality, and sleep disturbance [27]. In a recent Mendelian randomisation study [28], a robust correlation was found between telomere length and the risk of TC, indicating that sleep quality influences telomere length and ultimately affects the risk of developing TC.

Interventions, including pharmacological and non-pharmacological approaches, have proven effective in treating sleep disorders and improving sleep quality [9]. Furthermore, it is necessary to implement and summarise effective sleep training programs in the future to assist individuals or high-risk populations in achieving high-quality sleep and reducing the risk of TC.

Eating habits

Diet plays a crucial role in TC because it influences thyroid hormone secretion (Fig. 2) [29]. Research findings suggest that a higher risk of TC is associated with the consumption of high-sugar foods like starchy foods,

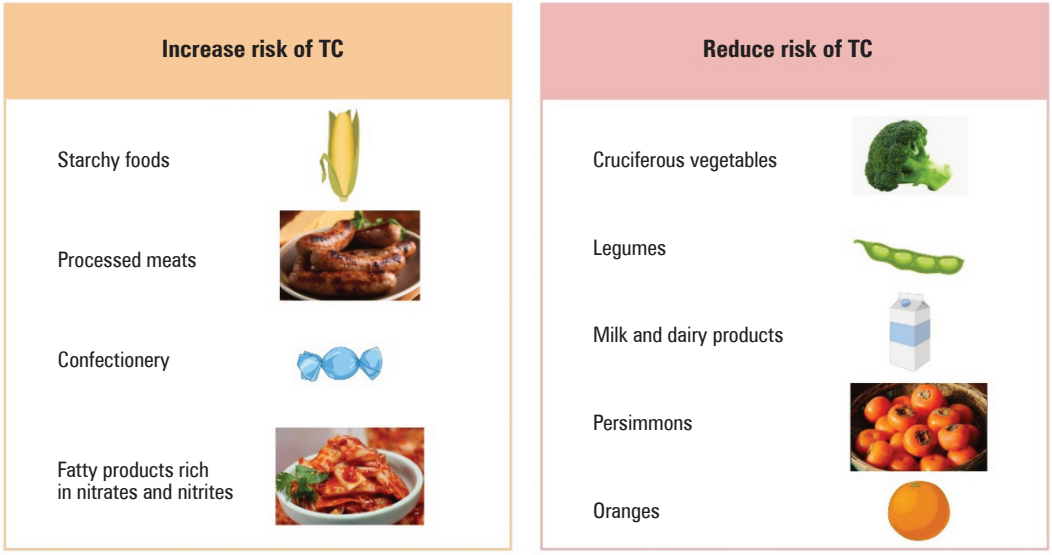

Figure 2. *Diets that increase and decrease the risk of thyroid cancer (TC). Consuming starchy foods, processed meats, confectionery, and fatty products rich in nitrates and nitrites can increase risk of TC. Consuming cruciferous vegetables, legumes, milk, dairy products, persimmons, and oranges can reduce the risk of TC*

Table 1. *Summary of the studies on diet and thyroid cancer (TC)*

Diet	Findings
Starchy foods	In a retrospective study conducted in Catania, Italy, the consumption of starchy foods (such as bread, pasta, pizza, rice, rusks, crackers, breadsticks, potatoes, cereal flakes, and cereals) was found to be a positive correlate of TC [10]
Confectionery	High-sugar foods (biscuits, brioches, croissants, chocolate, and other sweets) have been found to be a positive correlate of TC [10]
Fatty products rich in nitrates and nitrites	Zahra Bahadoran conducted a meta-analysis and found that fatty products rich in nitrates and nitrites are positive correlates of TC [36]. Similarly, a study focusing on women in Shanghai, China [35], confirmed that processed meats and fish rich in nitrites increase the risk of developing TC
Cruciferous vegetables	Cruciferous vegetables have been shown to be a protective factor against TC in numerous studies [10, 29]
Milk and dairy products	Milk and dairy products have been proven to be protective factors against TC in multiple studies [10, 30]
Fruits	A pathological case-control study conducted in Korea found that consuming fruits, particularly persimmons and oranges, is associated with a lower risk of developing TC [31]

refined grains, processed meats, fatty products rich in nitrates and nitrites, and confectionery, particularly in women. In regions with severe iodine deficiency, high iodine intake is protective against TC, particularly in the case of follicular TC. Conversely, positive associations are observed in regions abundant in iodine. In regions with sufficient iodine intake, there is no significant effect [10]. The risk reduction is linked to the intake of cruciferous vegetables, legumes, milk, and dairy products [10, 30]. This risk reduction is also associated with an increase in fruit consumption, especially persimmons and oranges [30, 31]. There has been ongoing controversy regarding the association between coffee consumption and the risk of TC. A recent authoritative meta-analysis found no association between coffee consumption and the risk of developing TC [32]. In the past, many studies yielded inconsistent results regarding the impact of fish on TC. Now, with more research adjusting for confounding factors, it is found that there is not a strong association between fish consumption and TC [10, 30].

Here is a brief introduction to the potential mechanisms linking various foods to TC. Consuming refined grains and foods high in sugar can lead to a rapid increase in blood sugar levels, which in turn can cause hyperinsulinaemia. Insulin is a mitogen that can enhance the biological activity of insulin-like growth factors, which may promote the development of cancer by suppressing apoptosis and stimulating cell proliferation [10]. Iodine deficiency (defined as a median urinary iodine concentration below 100 μg/L [33]) can result in reduced production of thyroid hormones (T3 and T4), potentially leading to excessive production of TSH. This may cause hypertrophy and proliferation of thyroid follicular cells, promoting the development of cancer [34]. Research has found that individuals with a high intake of nitrites (> 1.61 mg/day) have a two-fold increase in the risk of TC compared to those with normal dietary habits [35]. The possible mechanism involves nitrate competing with iodide for binding to the sodium/iodide symporter (NIS), leading to reduced iodide uptake and anti-thyroid effects, followed by the induction of pituitary release of TSH [36].

The indole-3-carbinol (I3C) and its acid catalysed dimer 3,30-diindolylmethane (DIM), present in cruciferous vegetables, exert a significant impact on the quantity, morphology, and structure of TC cells, displaying anti-proliferative effects against these cells [37]. Beans are an excellent source of folate, phytochemicals, sterols, and various substances with putative antioxidant and anti-cancer properties, such as glutathione, tocopherols, and phenolic compounds [10]. Studies have shown that persimmon contains many bioactive agents such as flavonoids, tannins, carotenoids, antioxidant vitamins, and minerals, which may mediate anti-cancer processes. Daily consumption of persimmons in amounts over 15.8 grams is significantly linked to a reduced risk of TC. Oranges are also rich in bioactive compounds, such as flavonoids, vitamin C, carotenoids, limonene, and citric acid. Citrus flavonoids exhibit strong anti-proliferation activity in human cancer cells, which can effectively prevent the incidence of TC [31].

Existing studies have simply elucidated some associations between dietary habits and TC. However, there is still no unified consensus regarding the frequency and quantity of dietary habits. More multi-centre and large-sample prospective studies are needed to clarify the relationship between the frequency and quantity of dietary habits and the risk of TC.

Mobile phone usage

Today's smartphones are not only used for making calls but also for accessing the internet. It has been established since the 1940s that radiation is an independent risk factor for TC, and mobile phones are also a source of radiation [38]. The number of mobile phone users has also increased tremendously. In 2016,

the total number of global mobile phone users reached 7.5 billion, indicating a significant increase in usage [39]. Smartphones are classified as non-ionising electromagnetic field devices, potentially carcinogenic to humans [40]. Due to the antenna being located at the bottom, the thyroid gland in the neck is more susceptible to exposure to radio frequency electromagnetic radiation than the brain [41, 42].

A case-control study conducted in Connecticut showed that certain gene variants may increase the risk of TC in individuals who use cell phones. For example, individuals with *HDAC4 rs1063639*, *DACT2 rs12204529,* or *DACT2 rs3800537* variants are at risk for developing small-tumour TC. Meanwhile, those with *LINC00336 rs396746* gene variant are more likely to develop large TC, while individuals with *PAK6 rs11070256* or *MDM2 rs1695147* gene variants are more prone to developing both large and small TC if they use mobile phones. The risk of TC was found to increase with the frequency and duration of cell phone use. In particular, long-term and frequent users (using mobile phones for more than 2 hours per day and for more than 15 years) showed an increased risk of thyroid microcarcinoma (tumour size ≤ 10 mm) [11, 43].

The pathogenesis of mobile phone use and TC is mainly explained by the carcinogenic mechanism of electromagnetic radiation. Studies have shown that non-ionising radiation can cause oxidative stress by interfering with oxidative repair and damaging cellular components, including DNA, which can eventually lead to cancer. Specifically, electromagnetic radiation can interfere with the production of antioxidants that neutralise free radicals. The body normally produces antioxidants that neutralise free radicals, but interference from electromagnetic radiation leads to an increase in free radicals, causing oxidative damage to cells. This explains why cell phone exposure is associated with an increased risk of cancer [44, 45].

In summary, while certain genetic variants have been identified as increasing the risk of TC with mobile phone use, the underlying mechanisms and interactions between these variants and mobile phone use require further investigation and clarification. Additionally, the case-control study was conducted in 2010 and 2011, and further research is needed to update and expand upon the findings based on current patterns of mobile phone use.

Exercise

Multiple studies have demonstrated that maintaining regular exercise habits can serve as a protective factor against various types of cancer [46]. In one particular cross-sectional study, researchers utilised data from a prospective cohort study in Korea and classified participants' exercise habits into 3 categories: irregular exercise during the week, exercising for less than 150 minutes per week, and exercising for more than 150 minutes per week. The findings indicated that only individuals who exercised for more than 150 minutes per week experienced a protective effect against TC. Further analysis, stratified by age and sex, revealed a significant reduction in TC risk among women and individuals aged 53 years or older who exercised for 150 minutes per week [12]. A recently updated cohort study conducted in Korea utilised the International Physical Activity Questionnaire-Brief Form (IPAQ) to categorise 15,175 participants into low, moderate, and high exercise intensity groups. The results of the Cox proportional hazards regression analysis indicated that as exercise intensity increased, the negative association with TC also increased [47]. These findings, along with another Korean cohort study, suggest that engaging in a weekly high-intensity exercise routine can be beneficial for reducing the risk of TC, particularly in women. Similarly, a case-control study conducted in southern Italy found a similar association and recommended that walking for at least 30 minutes per day could significantly reduce the risk of TC [48].

Consistent exercise habits have been shown to decrease the levels of insulin-like growth factor 1 (IGF1), which plays a crucial role in regulating cell proliferation, differentiation, and apoptosis. This mechanism of action has been confirmed to prevent the progression of cancer [49]. In addition to reducing levels of IGF1, exercise habits also activate the antioxidant pathway by increasing the production of antioxidant enzymes. This process enhances the population's ability to resist oxidative carcinogens in their environment and helps cells avoid damage. However, it is important to note that if the body lacks the necessary nutrients to produce antioxidant enzymes, engaging in intense exercise may result in more harm than good [50]. Regular exercise has been demonstrated to reduce levels of pro-inflammatory factors and increase levels of anti-inflammatory factors [51]. Pro-inflammatory factors have been shown to promote the progression of TC [46]. Additionally, consistent exercise habits decrease the production of leptin and reverse leptin resistance by reducing fat cells, which affects the course of cancer in multiple ways. Leptin is involved in regulating cell proliferation, angiogenesis, cell survival, and cancer progression [52].

To better understand the association between exercise habits and TC, further large-sample studies are necessary to confirm the strength of the relationship after controlling for confounding factors. Additionally, there is a lack of research examining the strength of the association between various exercise programs and TC.

Work under high pressure or at night

A case-control study conducted in Taiwan examined the relationship between work stress and TC prevalence among doctors. The study found that Taiwanese doctors had a significantly higher risk of TC than the general population, which was attributed to their high work stress of 65.6 hours per week and their habits of working night shifts [14]. Heavy work pressure, as a result of long working hours, can contribute to this increased risk. In Japan, labour laws stipulate that no more than 40 hours per week should be worked to prevent individuals from suffering from overwork [53]. Another retrospective study found a significant increase in thyroid nodules among night shift workers, indicating an increased risk of TC [54].

Studies have shown that night shift work can lead to increased secretion of TSH, FT3, and FT4, and increased TSH has been positively associated with TC risk. TSH has also been used as an independent predictor of TC [26, 55]. Similarly, work stress can lead to changes in the body's immune system, which can increase the risk of cancer [56–58]. Specifically, chronic stress can cause dysfunction in the hippocampal cortex and prefrontal lobe by activating the hypothalamic-pituitary-adrenal axis and sympathetic nervous system functions, ultimately leading to the formation of tumours [56]. Work stress not only weakens the body's immune system but also causes inflammation [56]. This inflammation can increase the risk of TC and accelerate the progression of tumours [46].

Previous studies have suggested that work stress or night shift work habits may increase the risk of TC, but the number of current studies is still insufficient. Most of the existing studies are retrospective with a certain recall bias, and more prospective studies are needed to confirm the relationship between work stress or night shift work habits and TC.

Residences

Regarding residence, it mainly involves living near nuclear power plants, living near volcanoes, and living in residential areas with high exposure to pesticides.

Living near a nuclear power plant

Initially, radiation from nuclear power plants is ionising radiation. It is capable of inducing aging and subsequent death of thyroid follicular cells. Cell death stimulates the release of inflammatory cytokines, thereby establishing an inflammatory environment and creating conditions conducive to the initial carcinogenesis of the thyroid [59]. Two ecological studies conducted in Belgium analysed the incidence of TC in the vicinity of 4 nuclear power plants. The distance between the location of residence and nuclear power plants was divided into 4 zones of 0–5 km, 5–10 km, 10–15 km, and 15–20 km. Combining the results from the 4 zones, the relative risk of TC was found to be 1.00 (95% confidence interval [CI]: 0.90; 1.10) for the 0–5 km zone and 0.90 (95% CI: 0.86; 0.94) for the 15–20 km zone [13, 60]. However, the Belgian studies did not consider the influence of environmental factors and individual characteristics such as iodine deficiency, which may have affected the reliability of their results. In contrast, an ecological study of TC rates in people living near 7 French nuclear power plants adjusted for 10 confounding factors, including tobacco, and found that women living within 20 km of a plant had a reduced relative risk of TC [61]. In addition, a recent meta-analysis [62] showed that living within 20 km of a nuclear power plant was associated with a reduced risk of TC incidence [summary odds ratio (OR) = 0.76; 95% confidence interval: 0.59; 0.97]. However, this contradicts the accepted theory that ionising radiation increases the risk of TC. One possible explanation is that there may be differences in the way people are screened at France's 7 nuclear power plants compared to other countries.

More carefully designed trials are needed to determine whether living near a nuclear power plant causes TC.

Living near a volcano

People who live within 20 km of volcanic areas have significantly higher rates of TC than those who live in non-volcanic areas, as numerous studies have demonstrated [63–65]. The primary reason for this is that high exposure to metals in volcanic areas can elevate the risk of various types of cancer [65, 66]. A study that observed cancer incidence in Iceland found that an increase in radon exposure was associated with a rise in TC incidence [66]. In volcanic areas, the concentrations of metals, such as arsenic, boron, cadmium, mercury, manganese, selenium, molybdenum, palladium, uranium, vanadium, and tungsten, are found to be 3 to 50 times higher than those in ordinary non-volcanic residential areas. Arsenic, cadmium, and mercury are recognised as carcinogens among these metals [63]. Eleven of these metals were found to have increased in the body tissues of people living in volcanic areas. Arsenic and mercury, in particular, increased by 16.5% and 25%, respectively, in the thyroid gland. The main explanation for this is that the high metal environment in the volcanic region causes hormonal and genetic changes in the body. Additionally, it should be noted that the increase in these metals was found to be significant in people living in these areas [63, 65].

The current research on heavy metals in volcanic areas is mostly disjointed, as each metal affects

the body in a different way. Moreover, the complexity of the study is increased due to the enhanced antagonism of heavy metals in the body. Therefore, more reliable data are needed to supplement the current conclusions and mechanisms regarding the increased incidence and mechanism of TC caused by increased metal levels in volcanic areas.

Pesticide-related residential environment

The theory that pesticide exposure increases the risk of TC has been around for a long time [67]. In 2003, a study found a significantly increased risk of TC among residents living downwind of pesticide production plants [68]. Additionally, a case-control study conducted in California in 2022 found that exposure to pesticides in residential areas within 500 metres of each other, but not work addresses, could be considered a risk factor for TC. The study revealed that the risk of TC increased with the level of pesticide exposure. Pesticides have been identified to elevate the risk of TC, such as glyphosate, oxyfluorfen, paraquat, naled, and benomyl [69].

Two studies have suggested that pesticides promote TSH elevation [70, 71]. Uncontrolled TSH elevation has been identified as a possible risk factor for the development of TC [72]. The prevalence rate of TC may increase due to pesticide exposure, which can be attributed to the damage caused by reactive oxygen species produced by pesticides to cells in many organs, as well as the abnormal differentiation and proliferation of thyroid cells induced by the chemical components of pesticides [69].

To clarify the relationship between residential pesticide exposure and TC, additional prospective studies are necessary, specifically to investigate the possibility of synergistic effects from various pesticides and their mechanisms of action.

Discussion

TC is the most common endocrine malignancy, which develops through complex interactions between environmental and genetic factors [73]. Moreover, the 10-year survival rate for TC remains above 95%, but there is still a possibility of recurrence and mortality [74]. Therefore, it is necessary to pay attention to modifiable risk factors for TC, including lifestyle and environmental factors. Hence, it is necessary to pay attention to modifiable risk factors for TC, including lifestyle and environmental factors.

This article summarises that smoking, alcohol consumption, good sleep quality, consumption of cruciferous vegetables, non-soy legumes, soybeans, milk, dairy products, raw vegetables, persimmons, and oranges, as well as regular high-intensity exercise, are protective factors for TC. Consumption of refined grains, high-sugar foods, nitrate-rich foods, high-sugar diets, low iodine intake, long-term and frequent use of mobile phones, high metal environment, environments with high levels of pesticide exposure, high-pressure work, and night shift work are considered as risk factors for TC. However, the relationship between the environment near nuclear power plants and the consumption of fish and the risk of TC has not formed a unified conclusion, and more reliable research is needed to draw conclusions.

Through the discussion of the aforementioned lifestyle habits and residential factors, we have identified multiple implicated mechanistic pathways. These include the hypothalamus-pituitary-thyroid axis regulating TSH levels, TC proliferation due to a relative decrease in oestrogen receptor beta (ERbeta), DNA damage induced by oxidative stress, and mechanisms promoting TC occurrence such as IGF1 inhibition of cell death. Next, we will briefly describe these mechanisms and pathways.

TSH is an independent predictor of TC [26, 55], it can promote the proliferation and differentiation of thyroid cells, and play an important promoting role in TC [75]. Therefore, understanding the mechanisms and pathways behind the high or low levels of TSH is extremely important (Fig. 2). Firstly, the hypothalamus secretes thyrotropin-releasing hormone (TRH), regulating the secretion level of TSH. Subsequently, TSH governs the synthesis and release of thyroid hormones (TH). The secretion level of TSH is also subject to negative feedback regulation by TH in the bloodstream [76, 77]. The mechanisms through which TSH stimulates the proliferation of TC cells can be divided into 4 main steps (Fig. 3). The first step involves TSH stimulating the TSH receptor, causing its dissociation from the heterotrimeric G protein and activating the Gαs subunit. The second step involves Gαs-dependent activation of adenylate cyclase (AC), which increases cyclic adenosine monophosphate (cAMP) production. In the third step, cAMP binds and dissociates the regulatory subunits of protein kinase A (PKA), activating PKA. The fourth step involves the activated PKA changing the activity of target proteins (including membrane receptors, signalling molecules, and transcription factors) through phosphorylation, thereby promoting cell growth and differentiation [75]. Finally, it is hoped that there will be more research on the epigenetic events of TSH and other loci to better explain the potential mechanisms of various risk factors for TC.

Oestrogen can act on 2 target sites present in TC cells, namely oestrogen receptor alpha (ERalpha) and ERbeta. An ERalpha agonist can promote TC cell proliferation, while an ERbeta agonist can reduce TC

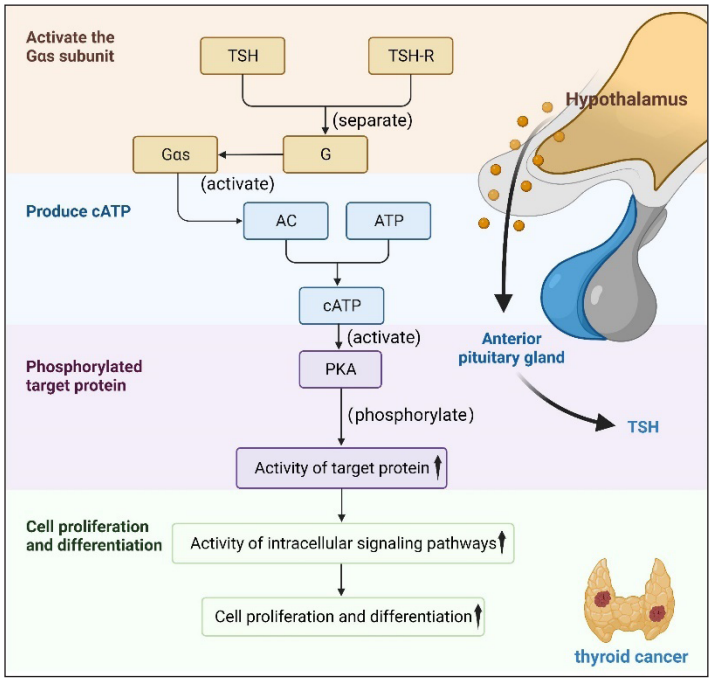

Figure 3. *Mechanism of thyroid-stimulating factor (TSH) promoting cell proliferation and differentiation. TSHR — thyroid-stimulating hormone receptor; G — G protein; Gαs — protein G alpha subunit; AC — adenylate cyclase; ATP — adenosine triphosphate; cAMP — cyclic adenosine monophosphate; PKA — protein kinase A*

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cell proliferation. However, the expression of ERbeta is very low or absent, which is the reason why oestrogen promotes TC cell growth [78].

Oxidative stress reactions are mainly caused by the interaction of reactive oxygen species (ROS) with DNA, resulting in oxidative genetic damage that disrupts genome integrity and leads to mutations. Therefore, oxidative stress may cause DNA damage and initiate tumour development [79].

IGF1 is a mitogen that effectively influences the processes of cell proliferation and differentiation. It also has the ability to inhibit programmed cell death [80]. Many studies have found that IGF1 plays an important role in the development of cancer, including thyroid papillary carcinoma. Its components can serve as potential diagnostic markers and targets for anti-cancer therapy in TC [81], and it has already been recognised as an independent risk factor for TC [82]. Currently, it has been found that IGF1 can promote the proliferation and invasive processes of papillary thyroid carcinoma (PTC) through the STAT3 signalling pathway [83]. More molecular biology experiments and clinical validation are still needed to elucidate the mechanisms of IGF1 in TC.

The mechanisms involved in the previous studies still need to be further explained in more detail, such as which step in the theoretical mechanism these risk factors specifically affect, and how they ultimately influence the outcome. Additionally, some studies may have limitations such as small sample sizes, unknown confounding factors, and lack of sufficient research, which means more reliable studies are needed to confirm the conclusions.

The current research on the specific lifestyle and environmental risk factors for TC is limited. Future research can comprehensively and in-depth explore this field to achieve early clinical precision intervention and reduce the risk of TC. On the other hand, the modifiable risk factors mentioned above are closely related to the general population's lifestyle. Considering the rapid increase in the incidence of TC, early prevention and control, and effective intervention plans for high-risk groups can reduce the social and economic burden.

Conclusions

In conclusion, this article summarises the associations between 7 lifestyle habits: smoking, alcohol consumption, sleeping, diet, exercise, mobile phone usage, and night shifts or high-pressure jobs, and their respective impacts on the risk of TC. Additionally, it explores the associations between residing near nuclear power plants, volcanoes, pesticide-related environments, and TC risk. Compared to the previous review, this paper supplements the definition of some behavioural habits, which can enhance people's understanding of their daily habits. Additionally, this

paper summarises the current mainstream explanations of various behavioural pathogenesis. Finally, the paper provides an outlook on the current research status of these behaviours to serve as a basis for the accurate and scientific prevention and control of TC, increase patient and population awareness of TC, and reduce the burden and pressure on patients and society.

Authors' contributions

S.Y. and W.X. were responsible for writing and reviewing the article, W.L., X.D., C.L., W.C. were responsible for editing the article, and X.L. and L.X. were responsible for reviewing and funding the article.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the Science and Technology Program of Traditional Chinese Medicine of Zhejiang Province(2024ZL1261), the Science and Technology Plan Projects of Liuzhou (2022CAC0229), Doctoral program of Guangxi University of Science and Technology (21Z01) and College Students' Innovative Entrepreneurial Training Plan Program (202110594024).

Acknowledgments

We express our gratitude to the participants and those involved in building the resource.

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