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Ambient air pollution exposure and thyroid cancer incidence in Iran

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ABSTRACT

Introduction: Thyroid cancer is the most common endocrine malignant that is three times more prevalent in women than men. Fine particulate matter ($PM_{2.5}$) has been indicated to affect Thyroid Hormone (TH) homeostasis. We sought to estimate the association between long-term exposure to ambient air pollution and the incidence of thyroid cancer in the Iranian female population.

Materials and methods: We extracted thyroid cancer incidence and ambient air pollution data from Iran from 2000 to 2019 for males and females for all age groups from the Global Burden of Disease (GBD) dataset. We entered the data into Joinpoint to present Annual Percent Change (APC) and Average Annual Percent Change (AAPC) and its confidence intervals. We entered the information into R3.5.0.

Results: Thyroid cancer in females had an upward trend [AAPC=4.9% (4.2-5.6)]. There was a correlation between ambient PM pollution ($p \leq 0.001$, $r=0.84$) and ambient ozone pollution ($p \leq 0.001$, $r=0.94$), and the incidence of thyroid cancer in females. The results of the analysis also showed a significant relationship between thyroid cancer incidence in females and secondhand smoke ($p \leq 0.001$, $r=0.74$).

Conclusion: This study indicated increasing trends in thyroid cancer incidence with exposure to ambient air pollution. Our novel findings provide additional insight into the potential associations between risk factors and thyroid cancer and warrant further investigation, specifically in areas with high levels of air pollution both nationally and internationally. However, causal relationships cannot be fully supported via ecological studies, and this article only focuses on Iran.

Introduction

Air pollution is a major problem in environmental health [1]. Particulate air pollution (PM), especially with fine particulate matter having an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$), is a serious threat to human health in several ways that have been observed in some large areas of the world [2]. In 2015, $PM_{2.5}$ exposure led to 4.2 million deaths [3]. According to previous studies, there is convincing evidence

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on the relationship between increased mortality and long-term exposure to low concentrations of $PM_{2.5}$ (<30 μg/m³) [4–6].

Thyroid Cancer (TC) is the fifth most common malignancy in adult women globally, as well as the second most common cancer in women older than 50 [7]. TC comprises about 1-3% of all human tumors. Over time, the TC mortality has remained low and generally stable or even decreased; it is about 50% of the incidence rate. However, a sharp increase in the related incidence shows that this observed TC epidemic is due to the excessive diagnosis, even in stages that do not cause any clinical symptoms throughout the patient's life [8, 9]. The highest incidence of thyroid cancer can be observed in the age groups with the highest surveillance pressure. Young adult women are more likely to receive an early diagnosis of TC because they have better access to gynecologic and fertility healthcare, thereby having a higher likelihood of undergoing thyroid screening and evaluations [10]. Given the relationship between thyroid disorders and cancers, the genetic or environmental mechanisms underlying the transmission of these complications from mother to fetus have attracted the attention of researchers [11].

Despite the predominant role of diagnosis, identifying the related risk factors and the level of exposure to these risk factors in the community is challenging [12]. Thyroid cancer's global and extensive impact has been well established, while its exact etiology is not fully understood. Exposure to ionizing radiation is the most probable risk factor for thyroid cancer development. Moreover, several epidemiological studies have reported other potential risk factors at the individual (obesity and genetic factors) and environmental levels (iodine supply imbalance, volcanic ash, and occupation) [13]. Previous studies have discussed the potential role of iodine deficiency as an important risk factor for this cancer. However, the increased incidence of thyroid cancer in some areas with mild iodine deficiency is incompatible with this finding [12]. Previous literature has highlighted the potential role of exposure to environmental pollutants in the incidence of TC [14]. According to the previous studies, persistent organic air pollutants [15–18], cadmium [19], and active or passive cigarette smoking [may affect the thyroid hormone regulation and function in infants and adults. The biological mechanisms underlying this long-term relationship are not fully understood. Some pollutants, such as some VOCs, are classified as definitive or potential carcinogens and are suspected to be involved in the development of thyroid malignancies [14]. Several epidemiological studies have evaluated the relationship between toluene exposure and thyroid cancer development [20, 21].

Factors such as healthcare systems, population size, screening, and investigations, may lead to higher detection of subclinical thyroid tumors in some countries. However, identification of unexpected risk factors can help in illustrating the potential mechanisms. Despite the advances in the treatment of TC, which has led to a significant reduction in its incidence, prevention is still considered a priority, especially due to its role in reducing medical costs. Given the endocrine system's susceptibility to some environmental factors as unexpected risk factors, especially air pollution, the present ecological study was conducted to investigate the relationship between exposure to Ambient Air Pollution (AAP) and the incidence of thyroid cancer in the Iranian female population during 2000-2019.

Materials and methods

Data collection

Data on the incidence of thyroid cancer in the Iranian female population in all the age groups during 2000-2019 were collected. Moreover, data regarding tobacco use, smoking, opioid use, and exposure to AAP were collected as well. The exposure to air pollution was classified into two groups of ambient PM pollution, and ambient ozone pollution. Cancer that forms in the thyroid gland (an organ at the base of the throat that makes hormones that help control heart rate,

blood pressure, body temperature, and weight). Four main types of thyroid cancer are papillary, follicular, medullary, and anaplastic thyroid cancer. The four types are based on how the cancer cells look under a microscope [20]. All the data were collected from the health data official website. The mentioned website has covered the hazards and risk factors in 204 countries from 1990 to 2019 based on the Global Burden of Disease (GBD) 2019. In total, 369 causative agents of diseases underwent systematic analysis. The details of the method used in the GBD studies and the main modifications done to this method have been discussed elsewhere [22].

Statistical analysis

Descriptive analysis for TC incidence was conducted using the regression model in the Jointpoint version 4.9.0.0. Moreover, in the present study, we reported the APC, AAPC, and their related confidence intervals in the Iranian female population. Also, the Spearman's correlation in the R (version 3.5.0) was used to investigate the relationships between the incidence of thyroid cancer and the variables of tobacco use, smoking, opioid use, ambient PM pollution, ambient ozone pollution, and total AAP in all the age groups of the Iranian female population. All the statistical analyzes were two-way, and the significance level was considered less than 5%. The correlation strength was interpreted based on the following classification: r=0.8-1, r=0.6-0.8, r=0.4-0.6, and r=0.2-0.4 were considered as very strong, strong, moderate, and weak correlations, respectively [23].

Results and discussion

Research conducted on air and climate pollutants worldwide indicates a relationship between two factors of disease prevalence and mortality rate [24,25]. Recently, environmental factors have been heeded as risk factors for thyroid cancer [13]. The morbidity rate of thyroid cancer has risen by 20% for both men and women between the years 1990 and 2013 worldwide [26]. This study is the first one to examine the relationship

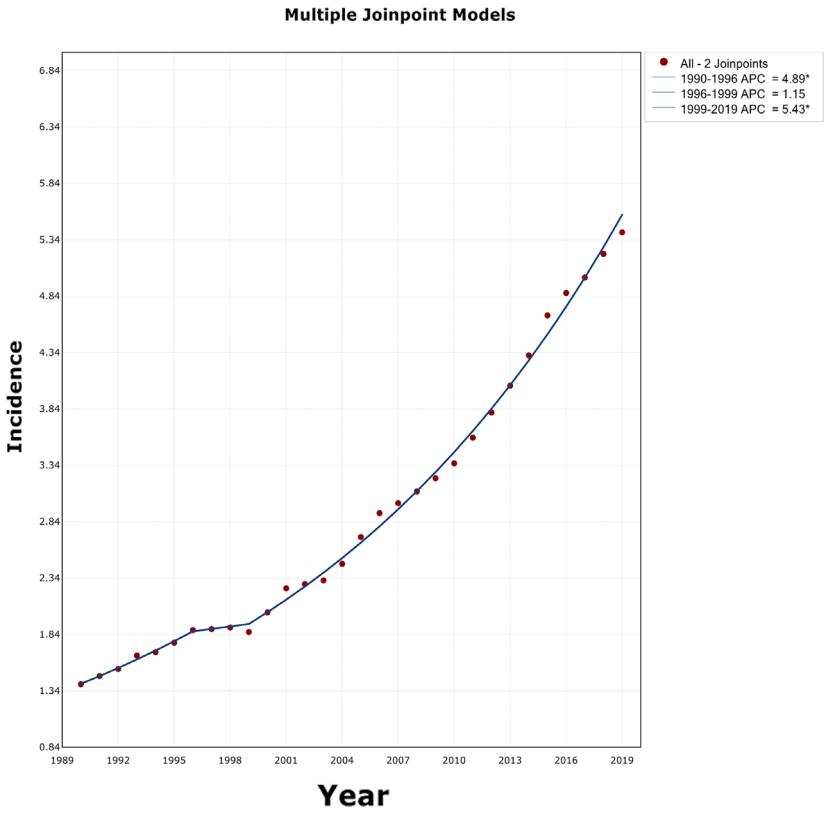

Fig. 1. Thyroid cancer incidence in female, IRAN [AAPC: 4.9% (4.2 to 5.6)]

between exposure to polluted air and the incidence of thyroid cancer.

Descriptive results of thyroid cancer incidence

The descriptive results of thyroid cancer incidence in women of all ages, from 1990 to 2019, have been indicated in Fig. 1. The results show that the incidence rate between the years 1990 and 2019 has increased (shown by a joint point: [AAPC= 4.9, CI: (4.2, 5.6)]). The descriptive results of TC incidence distribution in every 100000 women of all age range separately for every province have been presented in Fig. 2. There were 234 000 incident cases (95% UI 212 000–253 000), 45 600 deaths (41 300–48 800), and 1.23 million (1.11–1·33) DALYs due to thyroid cancer globally in 2019.

Thyroid cancer is known as the most common cancer of endocrine glands with a high progression mostly due to the advanced diagnosis methods identified over the last 50 years [26]. According to Global Cancer Observatory, in 2018, the number of cases newly diagnosed with this condition, and the number of deaths were estimated at 567000 and 41000 respectively across the world, and the incident rate of this ailment in women was three times the number of male cases [7]. This disease is 2 to 4 times more common in women than men and is the second most prevalent tumor within the age range of 0 to 49, and the fifth most common cancer among people aged 50-69. Thyroid cancer is the most common malign cancer among adolescents and youth aged 15-39. The average age of TC diagnosis is lower compared to other cancers. TC rarely occurs in children under 10 [14, 15]. The incidence rate is 1.2 to 2.4 in every 100000 individuals [27]. Thyroid cancer is one of the ten cancers common among women [28]. This ailment has the highest mortality rate among all endocrine cancers [29]. The prevalence of this condition rises with age but ceases to go higher after the age of 50 [30].

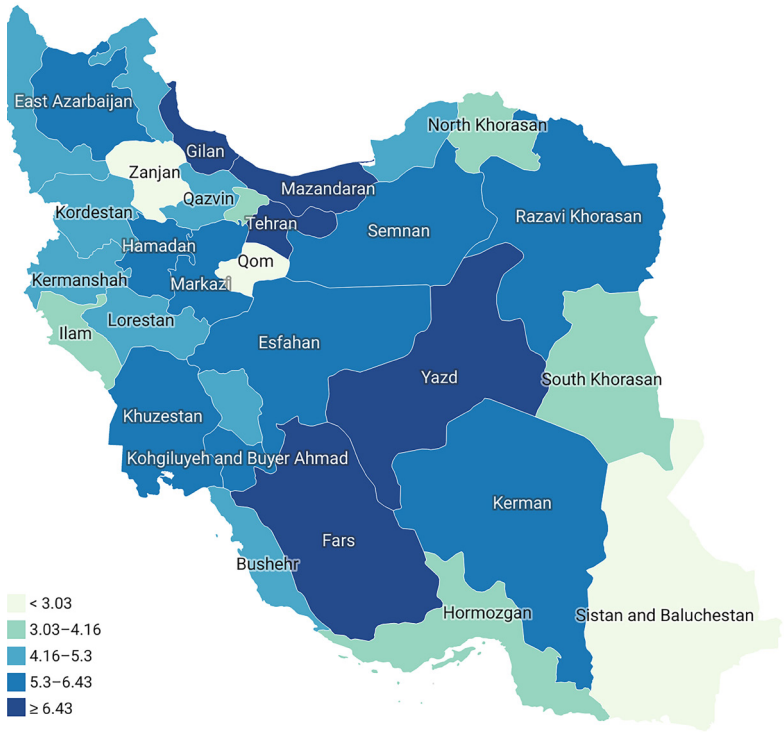

Fig. 2. Incidence of thyroid cancer in provinces of Iran in females of all ages (per 100000).

The relationship between exposure to polluted air and thyroid in women

The correlation between TC and air pollution has been illustrated in Fig. 3. There is a significant correlation between tropospheric ozone level ($p<0.001$, $r=0.95$) as well as atmospheric aerosol particles ($p<0.001$, $r=0.84$) with TC incidence.

Inefficient combustion of solid fuels and tobacco leads to the production of pollutants such as CO, SO_2, and Suspended Particulate Matter (SPM), Black Carbon (BC), and Polycyclic Aromatic Hydrocarbons (PAHs) [31–33]. Toxic metals and PAHs are also kinds of particulate matter [34, 35]. According to the research, cancer signifies the effects of $PM_{2.5}$ on health in more populated areas as PAHs are always present in $PM_{2.5}$ across these areas [36]. concentrations of $PM_{2.5}$ have always been high in China, and the most hazardous elements of $PM_{2.5}$ such as PAHs and heavy metals have been proven to increase the dangerous effects of some common diseases [37, 38]. Some studies inspected the effects of PAHs on health [39–41]. Furthermore, sniffing PM has been identified as a way whereby the metal particles enter the body [42]. Cadmium has been heeded as a risk factor for thyroid cancer [13]. In vitro and in vivo studies present some mechanisms whereby the relationship between exposure to cadmium and thyroid cancer is shown in humans. The number of entomological studies, however, is limited. In these studies, the relationship was only significant in female subjects [43–45]. Prolonged exposure to low levels of cadmium can stimulate cell proliferation and affect the endocrine glands negatively leading to cancer progression. Whereas, high levels of it inhibit cell growth [46].

The research increasingly reports a large number of Endocrine Disrupting Chemicals (EDCs) suspicious of triggering cancer, which initiates new discussions of sniffing EDCs [47]. The studies have shown that exposure to some EDCs changes the functioning of the thyroid, increasing the chances of health issues such as growth disorders, thyroid disorders, and different types of cancer [48, 49]. EDCs are present in indoor [50] and outdoor air [51]. Some of these chemicals are Volatile Organic Compounds (VOC) and semi-volatile organic compounds (SVOC) in the gas phase and also by attaching to particulate matters in the solid phase [52]. Exposure to EDCs might differ due to many factors: personal lifestyle, crop spraying, industrial activities, and waste incineration, the living area (village or town), time of the day (day or night), gases produced by gasoline and diesel fuel combustions, and the type and amount of the pollutants regarding the geographic location [50, 51].

Many types of EDCs are measurable in dust and particulates [53, 54]. EDCs suspicious to trigger thyroid cancer include pesticides, Polychlorinated Biphenyl (PCB) flame retardants, Phthalates, Polyfluoroalkyl Substances (PFAS), and Bisphenol A (PBA). The half-life values of polybrominated diphenyl ethers are estimated from 1 to 12 years in humans [55]. Whereas, the half-lives of polybrominated biphenyls are measured between 8 and 10 years [56]. It has been shown that exposure to flame retardant chemicals changes the functioning of the thyroid [21]. A study on some patients with papillary thyroid cancer indicate that there was a negative relationship between hydroxylated PBDEs and Free Thyroxine (FT4), but their relationship with thyroid-stimulating hormone was positive, and the study shows that OH-PBDEs disrupts the thyroid function of PTC patients [57]. PBBs and PBDEs have similar carcinogenic mechanisms; by forming DNA adducts and disrupting thyroid homeostasis due to similar chemical structures. Hydroxylated PBDEs and PBBs competitively bind to thyroid-related proteins, leading to the displacement of thyroxine (T4), which consequently reduces the half-life of the hormone [58]. Moreover, PBDEs and PBBs also reduce the half-life of thyroid hormone by inducing UDP-glucuronosyltransferase in the liver, resulting in an increase in T4 glucuronidation and the subsequent biliary excretion (25, 26). This disruption in the thyroid hormone mechanism

might induce abnormal cell proliferation [59]. Research shows PBDE quinones bind DNA adducts with potential carcinogenic effects. International Agency for Research on Cancer has categorized PBBs into group A2 (Agents probably carcinogenic to humans) [60]. Radon also plays a role in the pathogenesis of thyroid cancer [61]. Even so, there are only a few studies that have examined the effect of radon on thyroid cancer, some of which attained a negative relationship [13, 62, 63], and some others reported a positive relationship [64]. Although not all studies confirm the positive relationship between exposure to polluted air and thyroid cancer, public health consequences indicate that the potential risk of air pollution is a dangerous environmental factor for thyroid dysfunction and thyroid cancer [38, 65–67].

The relationship between smoking and exposure to secondhand smoke and TC incidence in women

The correlation between TC incidence and smoking, being exposed to secondhand smoke, smoking tobacco, and other narcotics as the disease risk factors have been indicated in Fig. 3. Analytic results of Spearman correlation do not indicate a positive correlation between indoor air pollution and smoking. However, the results indicate a positive significant relationship between TC incidence in Iranian women with exposure to secondhand smoke ($p \leq 0.001$, $r=0.74$), alcohol consumption ($p \leq 0.001$, $r=0.96$) ، tobacco smoking ($p \leq 0.001$, $r=0.81$) ، and using narcotics ($p \leq 0.001$, $r=0.77$). The lack of a significant relationship between smoking and TC incidence was primarily since a low number

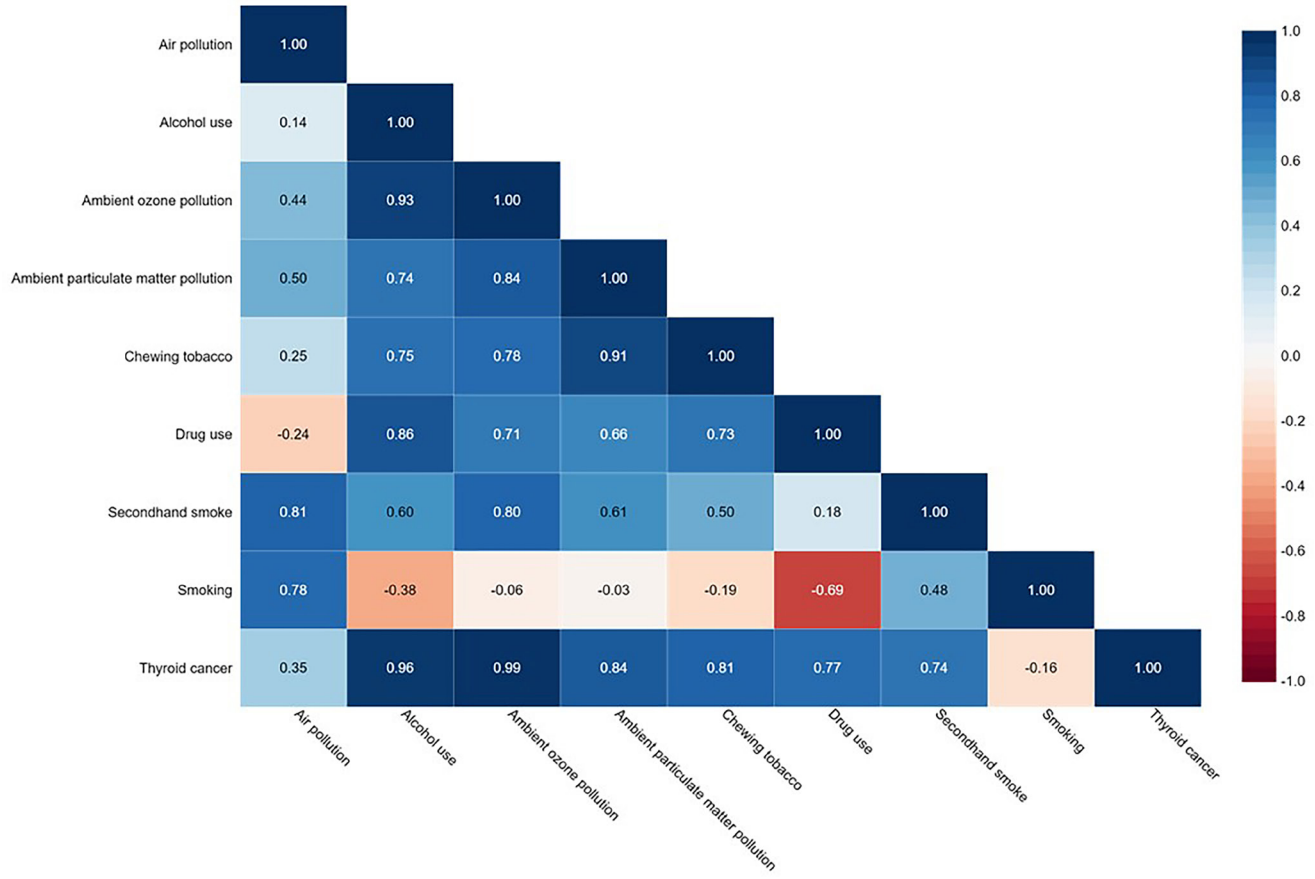

Fig. 3. Correlation between thyroid cancer and environmental factors in females of all ages in Iran

of Iranian women smokers. Therefore, in this study, smoking was not reported as a TC risk factor, although it has always been traditionally considered as a risk factor for TC.

Tobacco smoking as one of the lethal factors related to the increased number of deaths and due to its negative effect on public health has been universally heeded by many health experts. Health care planners are to design and implement proper strategies, reducing cigarette smoking and the harms it causes [68, 69].

The results of this study indicate a significant relationship and positive correlation between smoking and TC incidence, which is consistent with the results of other studies reporting exposure to secondhand smoke as a risk factor of TC. The effects of smoke on the Thyroid were alarming [18]. Cigarette smoke contains 200 toxic chemicals or EDCs and 80 proven or probable carcinogens [70]. In addition, International Agency for Research on Cancer classifies cigarette smoke as a well-known human carcinogen [71]. Secondhand smoke, to which passive smokers have been exposed consists of two forms of mainstream smoke (11%) and sidestream smoke (85%), and some other pollutants [18]. Therefore, passive smokers are exposed to different ranges of toxins compared to active smokers. Several studies indicate that exposure to cigarette smoke has various effects on thyroid function, which is accompanied by a reduction in thyroxine (T4) and triiodothyronine (T3) concentration [72, 73]. Passive and active smoking can interfere with thyroid hormone homeostasis induced by smoke [65]. Exposure to EDCs in an indoor environment in which a cigarette was smoked is probable as these chemicals can be found in the smoke [52].

Strengths, limitations, and recommendations

Despite the rarity of endocrine cancers, they are the most important and potentially treatable cancers [66]. Thyroid cancer accounts for 1% of the cancers and was the third most common cancer among women in 2019 [13]. Exposure to air pollution is universal and widespread. This study scrutinized the emerging trend of thyroid cancer among Iranian women, the relationship between environmental air pollution and TC incidence, and the relationship between exposure to firsthand and secondhand smoke and thyroid cancer (as a risk factor). The previous studies only examined the relationship between exposure to smoke and thyroid disorders. Observing the level of exposure of every person to air pollutants throughout their lives is difficult and costly. An ecologic study was really helpful regarding this issue [67]. In addition, an ecologic study to not pose the limitations normally present in other cross-sectional studies with a limited number of subjects.

The authors are fully aware of the limitations of the methodology used in the study. The results of this study have been attained using only one set of data and might not be true in other cases. The cumulative effects of air pollutants should not be overlooked. It is necessary to keep in mind that levels of air pollutants vary in different days and seasons, therefore, the effects of the temperature on their concentrations and the level of exposure to them must be considered. Although the outdoor pollution can be the same for the residents of one area, the indoor pollution can be different from person to person based on their lifestyle and house ventilation. International studies of disease burden announced that indoor air pollution accounts for more than 3 million deaths worldwide and is the fourth risk factor for types of deaths [74].

Due to the abundance of TC incidence, conducting epidemiologic studies is recommended. It is advisable that future studies have a larger sample volume, and collect information regarding job background, dwelling places, obesity, family history of TC, personal health assessment, and environmental monitoring of air pollution. As the effects of some EDCs (e.g., TCDD, cadmium, and even lead (might last even when the exposure has reduced [75]. It is essential that in future studies as to the risk factors for TC some factors (such as personal information, various approaches of

TC diagnosis, and thyroid disorders, especially for sensitive patients (such as young women)) be taken into account and determine the appropriate extent of using various measures for an early diagnosis of TC. Considering all the other risk factors in total (such as exposure to radiation for medical purposes) can help clarify this relationship more exactly. Also, priority must be given to the reduction of diagnosis harmful effects and omitting unnecessary TC treatment courses, which can lead to low life quality in some patients and unnecessary costs for health care systems while they cannot improve life expectancy.

Conclusion

This paper is the first study that examines the relationship between the extent of TC incidence in women of all ages in Iran and environmental air pollution. The results of the study indicated a positive correlation between exposure to AAP and TC incidence in women in Iran. In addition, exposure to secondhand smoke was shown to be a risk factor for TC. It was an ecologic study conducted only on women in Iran. The findings are incredibly important to public health as exposure to fine PM is widespread, and the possibility of long-term health issues caused by a change in thyroid function by these chemicals is high. Therefore, to create a healthier environment for women, this study suggests that World Health Organization reduce its air pollution limits regarding $PM_{2.5}$ concentration from 25 μg/m^3 (currently the limits in European Union) to 10 μg/m^3 (annual average) [76]. We need to consider the differences in geographical area and sex as the former can cause major differences in the concentration and constitution of $PM_{2.5}$ (usually different in rural and urban areas), and the latter indicates different sensitivity to toxins. Future studies regarding the relationship between exposure to EDCs, present in polluted air, and thyroid cancer, should examine the effects of other intervening factors such as job-related factors, lifestyle, controlled diet regimen, and other potential effects of exposure to EDCs. It is also necessary to conduct some research on vulnerable populations to increase knowledge about the potential dangers of specific pollutants, designing measures, formulating supervision policies, and ultimately general improvement in public health.

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Authors' contributions

All the authors contributed to the design, review, and revision of the study, and approved the final version of the paper.

Competing interests

The authors declare no conflicts of interest.

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Ethical considerations

Ethical considerations (including plagiarism, in¬formed consent, misconduct, data fabrication or-falsification, double publication, and submission) have been completely observed by the authors.

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