ORIGINAL ARTICLE

Occupational Exposure and Thyroid Cancer: Results of a Global Ecological Study (1990-2019) Using a Generalized Additive Model

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Abstract

Background: The thyroid gland cancer is the most common endocrine cancer worldwide. Although many occupational and environmental exposures affect thyroid hormone levels, information about their association with thyroid cancer is limited. Therefore, this global ecological study was conducted from 1990 to 2019 to examine the associations between occupational exposures and thyroid cancer epidemiological markers.

Methods: Data for this global ecological study were extracted from the Global Burden of Disease (GBD) website from 1990 to 2019. The Pearson correlation coefficient was used to correlate occupational exposures, thyroid cancer incidence, and death rates. The final approach was to use the generalized additive model (GAM) for modeling. The data were analyzed using R software version 4.2.2. The significance level of 0.05 was considered.

Results: The average incidence and mortality for thyroid cancer were 2.48 and 0.64 per 100,000 populations, respectively. This generalized additive multiple model of cancer incidence showed that 1 unit of arsenic exposure increased the risk of thyroid cancer incidence and mortality by 6.8 and 1.97, respectively. The risk of developing thyroid cancer increases by 1.18 for each unit of benzene exposure. The modeling was adjusted for the variables of gender, sociodemographic features, and polycyclic aromatic hydrocarbons (PAHs).

Conclusion: The results of this study confirm the world's first modeled hypothesis that there may be a relationship between occupational exposures (benzene, arsenic, and PAHs), and epidemiological indices of thyroid cancer. However, to reach causal conclusions, it is necessary to conduct epidemiological studies at the individual level by controlling confounding variables.

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Introduction

The most common endocrine cancer worldwide is the thyroid gland cancer, which is the ninth most common cancer in women and accounts for about 2.7% of all cancers in women.[1] In 2020, the incidence rate of thyroid cancer was 1.10 per 100,000 women and 1.3 per 100,000 men.[2] The incidence of thyroid cancer has increased more rapidly than other types of cancer in recent decades. Along with thyroid cancer, exposure to metal pollution is increasing worldwide.[3] There are various risk factors for thyroid cancer. One factor that can specifically affect

the thyroid is environmental carcinogens in the industrial lifestyle.[4] Although the results from various studies indicate that many occupational and environmental exposures cause thyroid hormone imbalances, much less information is available about their association with thyroid cancer.[5, 6] A study in China showed that occupational exposure to benzene for 10 years or more in the textile industry can lead to thyroid cancer.[7] A 2021 study in India showed that exposure to arsenic could also cause thyroid hormone disorders.[8] Thyroid Stimulating Hormone (TSH) homeostasis can be affected by a variety of environmental and occupational risk factors and can lead to clinical thyroid hormone disturbances.[9] Toxic elements such as lead, cadmium, and polycyclic aromatic hydrocarbons are considered the chemicals that damage the thyroid. Occupational exposure to lead can disrupt the function of the pituitary-thyroid axis and change the TSH level. Even low levels and general exposure to concentrations of these metals disrupt the thyroid hormone pathway. Exposure to lead causes changes in the serum TSH levels.[6, 9-11]

In addition, chronic exposure to lead causes tissue anatomical changes in the thyroid gland, such as a reduction in the size of thyroid follicles and changes in the follicular cell nuclei.[12] Decreased tetraiodothyronine (T4) production and increased TSH are among the effects of lead on thyroid function.[13] Differences in lead exposure levels and exposure modalities have produced controversial results. An inverse relationship between lead and TSH hormone has been observed in women with hypothyroidism, but this association is absent in men.[13-15] On the other hand, other studies have not reported such a relationship.[16] Additionally, some studies have reported that lead may be one of the risk factors for thyroid cancer.[17] In most studies conducted on men, lead exposure was occupational.[18]

This global ecological study was, therefore, conducted from 1990 to 2019 to examine the associations between occupational exposures and epidemiological markers of thyroid cancer. Furthermore, this work led to the generation of hypotheses using generalized collective modeling for the first time.

Methods

Study Design: A global ecological study

This global ecological and population-based study was designed to assess the association between occupational exposures to benzene, arsenic, cadmium, lead, and PAHs and thyroid cancer incidence and mortality. Global data including 204 countries and regions annually from 1990 to 2019 were obtained from the GBD website (http://www.healthdata.org). In this study, the incidence and mortality rates of thyroid cancer and occupational exposures were extracted for all countries from 1990 to 2019. The data was extracted in an Excel file.

The descriptive analyses included the mean, standard deviation, median, and 25th and 75th percentiles. In addition, Pearson's correlation coefficient was used to determine the correlations between dependent and independent variables. The correlation coefficient between 0.00 and 0.10 is a negligible correlation, between 0.10 and 0.39 is a weak correlation, between 0.40 and 0.69 is a moderate correlation, between 0.70 and 0.89 is a strong correlation, and between 0.9 and 1.0 is a very strong correlation.[19] For the first time in the world, a generalized additive model (GAM) was used for modeling. GAMs are an adaptation that allows us to model non-linear data while maintaining the explanation ability. The generalized additive model was used to estimate the rate ratio (RR) of the effect of occupational exposures on the incidence and mortality of thyroid cancer. This model is an extended form of the generalized linear model (GLM) and has high flexibility. The generalized linear model is only capable of detecting linear relationships between variables, while the generalized additive model maximizes the quality of response prediction by providing more information about the relationships between variables. This model has been used in many studies because it can adjust nonlinear confounding parameters. In this research, first, the simple generalized collective model was implemented. Then, the variables with P-value less than 0.2 were entered into the multiple models. The socio-demographic variables were considered as indicators to determine the socioeconomic status of the countries and as confounding variables. The time unit used in the analysis was years. Using the following formulas, we calculated the relative risk (RR) and 95% confidence interval (CI) for the RR.[20-22]

$RR=\exp(\beta)$

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

Finally, the data were analyzed using R software version 4.2.2. The GAM was fitted by the "mgcv" package. All of the statistical analyses were two-sided. A significance level of 0.05 was considered.

Results

Table 1 shows a descriptive analysis of thyroid cancer incidence and mortality and occupational exposures in the world. The mean incidence and death rates for thyroid cancer were 2.48 and 0.64 per 100,000 people, respectively.

There was a positive and weak correlation between the incidence of thyroid cancer and PAHs ($r=0.1$, $P=0.001$). There was a positive and weak correlation

Table 1: Descriptive statistics of occupational exposures and epidemiological indices

Variables	Mean±Standard Deviation	Percentile 25	Percentile 50	Percentile 75
Incidence rate per 100,000	2.48±2.05	0.98	1.92	3.44
Mortality rate per 100,000	0.64±0.40	0.40	0.54	0.77
Arsenic (µg/m³)	0.38±0.11	0.31	0.38	0.46
Benzene (ppm)	0.93±0.30	0.73	0.91	1.10
PAHs (µg/m³)	0.78±0.41	0.31	0.85	1.12
Cadmium (µg/m³)	0.16±0.08	0.06	0.17	0.22
Lead (µg/m³)	0.40±0.20	0.26	0.49	0.71

between the incidence of thyroid cancer and Benzene (r=0.23, P=0.002). Arsenic (r=0.11, P=0.002) and lead (r=0.1, P=0.001) had a positive and weak correlation. While the correlation of cadmium with the incidence of thyroid cancer had a positive and strong correlation (r=0.52, P=0.001) (Figure 1).

Figure 2 shows the above relationship between mortality from thyroid cancer and occupational exposures. Correlation between benzene (r=0.12, P=0.011), arsenic (r=0.11, P=0.003), cadmium (r=0.14, P=0.021) and polycyclic aromatic hydrocarbons (r=0.14, P=0.031) and mortality.

The generalized collective multiple models for the incidence of this type of cancer showed a 6.8-fold increase in thyroid cancer risk per unit exposure to arsenic. Additionally, 1 unit of benzene exposure increases the risk of thyroid cancer by 1.18. This modeling has been adjusted for variables of gender, sociodemographic index, and PAH. Modeling indicates that 1 unit of arsenic exposure increases the risk of cancer mortality by 1.97, and 1 unit of PAHs exposure increases the risk of cancer mortality by 2.20. This modeling has been adapted for variables such as gender, sociodemographic indices, benzene, and cadmium (Table 2).

Discussion

Heavy metals accumulate more in the thyroid than in other tissues. Thyroid function and homeostatic mechanisms are influenced by metal ions accumulated in the thyroid. Some metal ions are endocrine disruptors (cadmium, lead, arsenic), and some others have been confirmed to be carcinogenic (cadmium, arsenic).[23]

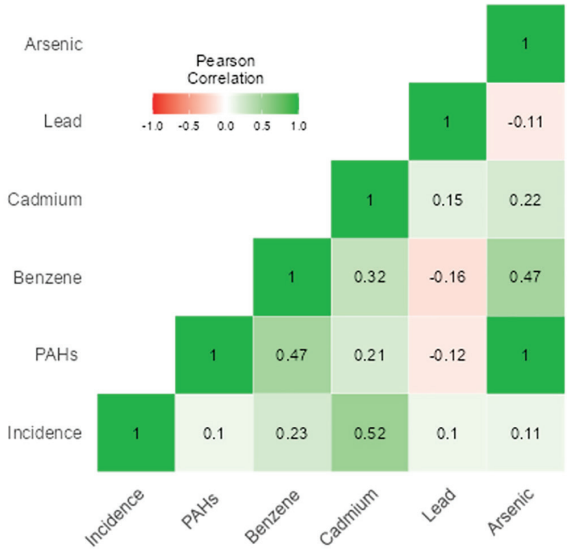

Figure 1: Correlation heatmap between the incidence of thyroid cancer and occupational exposures

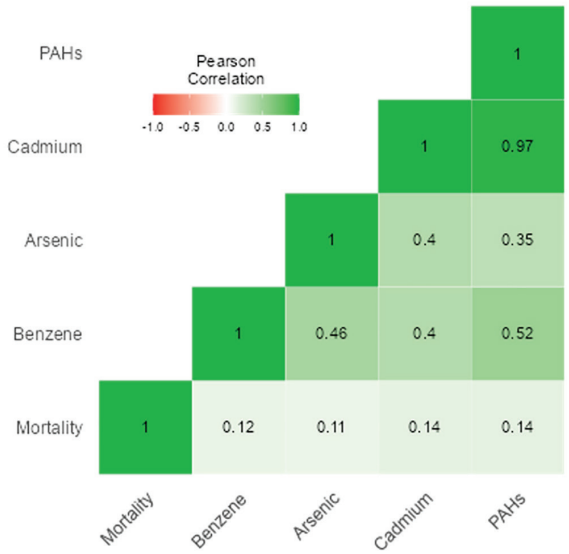

Figure 2: Correlation heatmap between the mortality of thyroid cancer and occupational exposures

Table 2: Statistical modeling for the relationship between occupational exposures and incidence and mortality of thyroid cancer using multiple GAM*

Variables	Incidence of thyroid cancer		
	RR	P value	95% Confidence Interval
Arsenic	6.8	<0.001	4.71-9.98
Benzene	1.18	0.038	1.00-1.38
Mortality of thyroid cancer			
Arsenic	1.97	<0.001	1.77-2.19
PAHs	2.20	<0.001	1.91-2.54

*Adjusted for sex, socio-demographic index, cadmium, and PAHs

Occupational exposure to heavy metals has adverse health effects ranging from poisoning to cancer.[24-26] This global ecological study was conducted to examine the association between occupational exposure to arsenic, benzene, polycyclic aromatic hydrocarbons, cadmium, and lead and the incidence and mortality of thyroid cancer.

The initial results of this study showed that occupational arsenic exposure increased the risk of thyroid cancer 6.8-fold. On the other hand, the risk of death from this cancer is 1.97 times higher. The findings are consistent with those of a meta-analysis study entitled "The Role of Heavy Metals in Thyroid Cancer" conducted in 2022.[23] Another study in 2023 also found that arsenic and cadmium, as endocrine-disrupting chemicals, can cause thyroid cancer.[27] A study by Kitchin et al. is also consistent with the results of this study.[28] Arsenic has a two-sided effect on the thyroid gland. In other words, it disrupts the endocrine glands and has carcinogenic activity. There are three pathways for arsenic carcinogenesis in both experimental (animal) and human models. For example, chromosomal abnormality, oxidative stress, and aberrant growth factor pathways (especially the mitogen-activated protein kinase pathway).[8]

Exposure to cadmium and lead also directly contributes to the development of this type of cancer. Increased industrial activity in the 20th century increased exposure to heavy metals. The most common heavy metals are cadmium and arsenic. Chronic or acute heavy metal poisoning has toxic consequences for the tissues and organs, especially the thyroid gland. Heavy metals impair biological functions such as growth, proliferation, differentiation, damage repair, and apoptosis. It also causes the formation of reactive oxygen species (ROS), suppression of antioxidant defenses, deactivation of enzymes, and oxidative stress.[29, 30] A 2022 case-control study by Jia-Liu et. al was also consistent with the findings of the present study and showed that exposure to lead and arsenic could cause thyroid cancer.[31] Meanwhile, a study by Li and colleagues in China found no relationship between lead and thyroid cancer.[18]

The second finding showed that workplace exposure to benzene increased the risk of cancer by 1.18 times. A study on female textile factory workers in China confirmed that occupational exposure to benzene is associated with an increased incidence of thyroid cancer.[7] Another study found that nurses exposed to cytostatic treatments in the workplace could develop thyroid diseases.[32] Another study found that exposure to benzene in children under the age of 15 caused malignant thyroid disease.[33] These findings are consistent with those of the current study.

The final results of the study showed a 2.20-fold increased risk of death from thyroid cancer with occupational exposure to polycyclic aromatic hydrocarbons. A 2020 study found that exposure to polycyclic aromatic hydrocarbons can cause nodular goiter/papillary thyroid cancer of the thyroid. Furthermore, the study showed that this relationship had a gender effect, being more prevalent in women than in men.[11] Sam De Craemer and his colleagues conducted research that also supports this finding.[34] Exposure to PAHs in industrial settings can increase the risk of certain types of cancer, such as thyroid cancer.[35]

Strengths and Limitations

This study was conducted for the first time using a generalized group model to determine the associations between occupational exposures and epidemiological indices of thyroid cancer. Other studies have been done, but Pearson's correlation coefficient satisfied them.[24, 36] The universality of this study is another strength, as opposed to studies that only explored this subject in one region.[24, 37] The reader should be careful when interpreting the results and not jump to individual conclusions due to the ecological fallacy, which is one of the weaknesses of this study. The ecological nature of the present study does not allow us to interpret the causality of the results, leading to the formation of hypotheses. To establish causality, it is recommended to consult other studies such as retrospective studies and case-control cohort ones.

Conclusion

This study, for the first time, leads to a modeled hypothesis in the world that there may be a relationship between occupational exposures (benzene, arsenic, and PAHs) and epidemiological indicators of thyroid cancer. However, to reach causal conclusions, it is necessary to conduct epidemiological studies at the individual level with the control of confounding variables. The study found that exposure to endocrine-disrupting heavy metals can lead to malignant thyroid disease. However, given the evidence that there is a possible association between exposure to arsenic, cadmium, benzene, and PAHs and thyroid cancer, a larger sample size at the individual level would require more detailed and conclusive information. More comprehensive epidemiological studies should be conducted to accurately control the confounding variables. Overall, the evidence linking exposure to these contaminants to thyroid cancer is complex and may vary with such factors as the level and duration of exposure, individual susceptibility, and carcinogenic mechanisms.

Due to the known health risks of these contaminants, it is important to implement strict regulations and occupational safety measures to minimize exposure in relevant industries and protect public health. Furthermore, continued surveillance and research in this area will lead to a better understanding

of the relationship between these environmental pollutants and thyroid cancer, ultimately leading to more effective preventive measures and possible interventions. Therefore, it is important to continue to comply with existing occupational health and safety regulations and practices to minimize exposure to these hazardous substances and protect the health of workers and the public.

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Authors' Contribution

The authors' contributions are: Z.M. was involved in data collection, data analysis, and manuscript writing and editing; J.H. contributed to project development, data analysis, and editing; H.G. participated in project development, data analysis, manuscript creation, and editing. The submitted manuscript was approved by all authors and met authorship criteria according to the current guidelines of the International Committee of Medical Journal Editors.

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Conflict of Interest

None declared.

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