



Contribution of smoking and occupational chemical exposure to thyroid cancer

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Abstract

Certain occupations with exposure to chemicals have been implicated as potential risk factors for thyroid cancer. This study aimed to examine the association between occupational exposures as well smoking with thyroid cancer risk. In this case-control study, 131 thyroid cancer patients recruited from Minia Oncology Center were matched to 131 healthy controls by age and sex. Job histories were collected via interviews. Multivariate binary logistic regression analyzed associations between employment in specific occupations and industries and thyroid cancer, adjusting for potential confounders like smoking. The majority of the 131 thyroid cancer cases were females (84%). Mean age at diagnosis was 40.9±13.4 years. Papillary carcinoma was the most common histological subtype, accounting for 87% of cases. In multivariate analysis, occupational exposure to chemicals (OR 3.8, 95% CI 1.1-12.9) and current smoking (OR 10.6, 95% CI 1.7-65) were significantly associated with higher thyroid cancer odds. Jobs involving chemical exposures like agriculture and construction had higher thyroid cancer prevalence versus unexposed controls. These findings suggest occupational exposure to chemicals may increase thyroid cancer risk. However, further research is needed to establish a causal relationship between specific job exposures and thyroid cancer. Smoking also showed an independent association with thyroid cancer. Workplace safety measures and smoking cessation should be emphasized to potentially lower thyroid cancer burden.

Keywords: Thyroid cancer, pesticides, smoking, occupational exposure, chemical exposure.

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1. Introduction

Thyroid cancer stands as the most prevalent endocrine malignancy, ranking as the 9th most diagnosed cancer globally, and the fifth most common cancer among women and in the USA [1]. Ionizing radiation is the only acknowledged environmental risk, supported by studies on childhood exposure, atomic bomb survivors, and incidents like Chernobyl. Despite gender and ionizing radiation being recognized risk factors, the increasing rates, especially in females, suggest potential exogenous factors [2].

Starting in the mid-20th century, human population growth and technological advances led to a major increase in industrial, agricultural, and consumer activities. This resulted in an explosion of anthropogenic chemical pollution and spread of xenobiotics that can impact human health [3]. Research has highlighted the potential contribution of

exposure to environmental pollutants, specifically endocrine disruptive chemicals (EDCs), to increased risk of thyroid cancer [4]. The World Health Organization has defined EDCs as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub-) populations” [5]. Pesticides, flame retardants, PCBs (polychlorinated biphenyls), phthalates, PFAS (perfluoroalkyl substances), and BPA (bisphenol A) are suspected EDCs that have been linked to increased risk of thyroid disorders and cancer [4].

There are around 1000 chemicals with endocrine disrupting properties. Major sources of exposure include pesticides, industrial chemicals, plastics, pharmaceuticals, and phytoestrogens. Humans are exposed through ingestion, inhalation, and skin absorption [6]. EDCs can interfere with

the normal signaling pathways of the endocrine system at the cellular and molecular levels, potentially causing disruptions in hormone regulation. This, in turn, can increase the risk of developing cancer in hormone-sensitive organs, such as the breast, prostate, testis, and thyroid [4].

Pesticide exposure, especially persistent organic pollutants (POPs), are known to have thyroid-disrupting properties. Organochlorine pesticides (OCPs), organophosphates (OPs), carbamates and pyrethroids have been implicated. The proposed mechanisms relate to thyroid morphology changes and hormone homeostasis disruption [7]. OCPs resemble thyroid hormones T3 and T4, competitively binding transport proteins. This disrupts thyroid hormone signaling and transport, reducing circulating levels. Thyroid gland disruption and abnormal proliferation may result, promoting tumorigenesis [8]. OPs like diazinon and malathion are among the most widely used insecticides. IARC classifies several organophosphates as possible carcinogens. Due to heavy use and carcinogenic potential, many studies examine links between pesticide exposure and cancers, including thyroid cancer [7].

Textile workers face persistent exposure to a diverse array of chemicals, estimated to be over 2,000, within their work environment. This exposure encompasses substances such as dyes, bleaches, transfer agents, and also includes endotoxin present in cotton dust [9]. The construction industry involves exposure to many carcinogenic agents like polycyclic aromatic hydrocarbons (PAHs), diesel exhaust, silica, asphalt fumes, and solvents. However, the work sites are temporary and change rapidly, making it difficult to estimate exposures and quantify cancer risks using traditional epidemiological methods. While broad epidemiological data provides some indication of risk, the complex and variable nature of construction work makes it insufficient to accurately characterize chemical exposures and cancer hazards for this sector [10].

The aim of this study was to investigate the association between thyroid cancer and occupational with potential high exposure to chemicals. Additionally, the study aimed to explore the relationship between thyroid cancer and smoking status.

2. Materials and methods

2.1 Study Design and Setting

This case-control study was conducted at the Minia Oncology Center in Egypt from April 2022 to March 2022.

2.2 Participants

Cases were 131 patients diagnosed with thyroid cancer at the Minia Oncology Center. Controls were 131 age- and sex-matched individuals recruited from among relatives and companions of patients at the same center.

2.3 Eligibility Criteria

Cases were eligible if they > 18 year and had a histopathological diagnosis of thyroid cancer. Cases with history of prior cancer were excluded. Controls had no current or prior cancer diagnosis.

2.4 Data Collection

Participants completed an interview covering sociodemographic characteristics (e.g., age, sex, education, occupation, household income, and marital status), Participants self-reported smoking history and family

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history. Medical records were reviewed to confirm cancer diagnosis and extract clinical data for cases. Jobs were classified based on potential high exposure to chemicals that have been related to thyroid cancer. High exposure jobs included agricultural workers with pesticides exposure, textile and construction workers. Unexposed jobs were office workers and teachers. Due to small numbers across different exposure categories, jobs were collapsed into a binary variable indicating high versus low potential for exposure to chemicals.

2.5 Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics, version 27. Descriptive statistics for numerical data were expressed as mean \pm standard deviation (SD), while categorical data were presented as frequencies (N) and percentages (%). To compare means between groups, a t-test was employed for numerical variables, while the chi-square test was utilized for categorical variables. Binary logistic regression estimated odds ratios for associations between high chemical exposure jobs and thyroid cancer, adjusting for smoking and demographic variables, smoking and family history. Variables with a univariate p-value less than 0.1 were considered as candidates for entry into the multivariate regression models. Statistical significance was defined as $p < 0.05$. Relative weight analysis (RWA) [11] was conducted to determine the proportional contribution of each risk factor to thyroid cancer status, while accounting for intercorrelations among predictors. This technique transforms the set of predictors into a new set of orthogonal variables, with relative weights for each factor summing to the total R².

2.6 Ethical considerations

The study was performed aligning with the principles outlined in the Declaration of Helsinki. Approval for the research was secured from the Ethics Committee of the Faculty of Medicine at Minia University (Approval No. 87-2021) and the Minia Oncology Center under the General Secretariat of Specialized Medical Centers. Prior to their participation, all individuals involved in the study provided informed consent, emphasizing the commitment to ethical standards and the protection of participants' privacy and confidentiality.

3. Results and Discussions

3.1 Results

A total of 131 thyroid cancer cases and 131 matched controls were included. Table 1 shows the demographic and clinical characteristics of cases and controls. There was a significantly higher proportion of cases with lower educational level ($p=0.023$), positive family history of thyroid cancer ($p=0.002$), exposure to jobs with high risk of chemical contamination ($p=0.012$), and history of smoking ($p=0.041$) compared to controls. The two groups were balanced in terms of age, sex, and residence. As shown in table 2, among participants employed in jobs classified as high risk for chemical exposure, the most common pathology was PTC (93.8%), followed by OCA (6.3%). In the unexposed group, PTC also predominated (86.1%), along with FTC (9.6%). There was no significant association between cancer pathology and potential occupational chemical exposure ($p=0.310$). Regarding

cancer stage, jobs with high chemical exposure had a slightly higher percentage of metastatic presentation (43.8%), compared to the unexposed group (28.7%), but this difference was not statistically significant ($p=0.252$).

In univariate analysis (Table 3), participants ever employed in jobs classified as high chemical exposure had 3.5 times the odds of thyroid cancer compared to those never employed in high exposure jobs (OR= 3.5, 95% CI= 1.2-9.9). In multivariate logistic regression, adjusting for smoking, family history and other confounders, high occupational chemical exposure remained significantly associated with thyroid cancer (OR= 3.8, 95% CI= 1.1-12.9). Current smoking was also an independent risk factor for thyroid cancer (current smoker aOR= 10.6, 95% CI= 1.7-65, $p=0.011$). Additionally, a family history of thyroid cancer was identified as a significant independent risk factor (aOR= 5.9, 95% CI= 1.8-18.6, $p=0.003$). Relative weight analysis was conducted to determine the proportional contribution of each risk factor to the total variance explained in thyroid cancer status. As shown in Table 4, the full model explained 11.4% of the variance in thyroid cancer status. Of the variance explained by all of the variables in our study, jobs with high exposure account for 16.2% of that explained variance. Family history of thyroid cancer had the highest relative weight, explaining 32.3% of the model R². Smoking status had the second highest relative weight at 22.9% (Fig.1).

3.2 Discussion

This is a single-center case-control study of consecutive patients treated for thyroid cancer at Minia Oncology Center. The study explored the risk factors of thyroid cancer specifically focusing on occupational exposure and smoking habits. The study found that occupational exposure to jobs with high chemical contamination risk was independently associated with over 4-fold increased odds of thyroid cancer after adjusting for confounders. This evidence supports the hypothesized link between occupational chemical exposures and thyroid cancer. This association remained significant even after controlling other occupational variables like smoking and family history. The results of the current study showed an association between thyroid cancer and jobs with potential high exposure to chemicals such as those with agricultural exposure to pesticides which comprised a major subset of the occupations examined. This aligns with findings from other epidemiological studies on this topic. For example, analysis of the large Agricultural Health Study (AHS) cohort found higher incidence of thyroid cancer in pesticide-exposed farmers compared to the general population [12]. In a meta-analysis encompassing eight studies on agricultural exposure to pesticides, a significant association with thyroid cancer risk was observed (OR=1.86, 95% CI = 1.04–3.32) [13].

Furthermore, various pesticide ingredients within the AHS cohort have been linked not only to thyroid cancer risk but also to incident self-reported thyroid disease in both applicators and their spouses [14]. However, a recent systematic review on the association between human exposure to pesticides and thyroid cancer revealed mixed

findings, with some pesticides showing a potential risk of thyroid cancer [7].

Egypt is a densely populated, agricultural country that relies heavily on pesticides to control crop pests. With more than 100 million people, most Egyptians live in crowded cities and villages along the fertile Nile River valley and delta. With this limited area and large population, approximately one million metric tons of commercial pesticides are used annually in Egypt [15]. For farmers who work with pesticides, the skin is often the main route of exposure during pesticide splashing or spillage, other routes include oral and respiratory routes [16].

Pesticides pose a cancer risk, affecting both individuals directly applying them and bystanders exposed during the application process. The carcinogenic mechanisms involve both genotoxic and nongenotoxic pathways, with pesticides having diverse chemical structures and exerting various biological actions [13]. Despite the diversity in chemical properties and toxicities among pesticides, they share common mechanisms that can adversely impact human health. These shared mechanisms include oxidative stress, endocrine disruption, mitochondrial dysfunction, immune dysregulation and inflammatory responses [17]. Textile and construction workers made up a small subset and were grouped with other jobs with high chemical exposure limiting the ability to study associations with these occupations independently. A large Chinese cohort study [18] involving 267,400 women in the textile sector found no increased risk of thyroid cancer related to various tasks in the industry, such as cotton handling or weaving. However, when assessing exposure to specific agents, long-term exposure (at least 10 years) to benzene, organic or inorganic gases, and formaldehyde showed a significantly higher risk of thyroid cancer. Lope et al. reported an increased risk of thyroid cancer among men working as construction carpenters/joiners and among women in the prefabricated wooden-building industry [19].

The current study also found smoking and family history to be independent risk factors for thyroid cancer. Cigarette Smoking is widely recognized as a significant risk factor for many types of cancers including colorectal, prostate, lung, stomach, and cervix cancers [20]. In a report published by the International Agency for Research on Cancer, Smoking has been classified as a carcinogenic factor for 12 cancers [21]. However, the relationship between tobacco smoking and thyroid cancer has been inconsistent across previous studies. While some studies have suggested smoking may increase thyroid cancer risk [22], others have found no significant association [23] or even an inverse association between smoking and thyroid cancer. A meta-analysis revealed a reduced risk of thyroid carcinoma among smokers with an odds ratio 0.798; 95% CI=0.681–0.935. [24]. A large cohort study found that current smoking was associated with a significantly decreased risk of incident thyroid cancer in Korean men compared to never smokers [25].

Table 1: Demographic and clinical characteristics of thyroid cancer cases and controls

	Case (n=131)	Control (n=131)	p value
Sex			
Male	21 (16.0%)	21 (16.0%)	...
Female	110 (84.0%)	110 (84.0%)	
Age at diagnosis (years) Mean±SD	40.9±13.4	42.4±11.5	0.364
Partnered marital status			
With partner	115 (87.8%)	110 (84.0%)	
Single / divorced / widowed	16 (12.2%)	21 (16.0%)	0.375
Residence			
Urban	24 (18.3%)	21 (16.0%)	0.623
Rural	107 (81.7%)	110 (84.0%)	
Educational level			
below secondary	89 (67.9%)	71 (54.2%)	0.023*
secondary or above	42 (32.1%)	60 (45.8%)	
Income			
In debt	38 (29.0%)	24 (18.3%)	0.084
Just meet routine expenses	70 (53.4%)	90 (68.7%)	
Meet routine expenses and emergencies	21 (16.0%)	15 (11.5%)	
Able to save money	2 (1.5%)	2 (1.5%)	
Job exposures with high risk of chemical contamination			
No	115 (87.8%)	126 (96.2%)	0.012*
Yes ^a	16 (12.2%)	5 (3.8%)	
Smoking status			
Never smoker	117 (89.3%)	127 (96.9%)	0.041*
Ex-smoker	4 (3.1%)	2 (1.5%)	
Current smoker	10 (7.6%)	2 (1.5%)	
Family history of thyroid cancer			
-ve FH	113 (86.3%)	127 (96.9%)	0.002*
+ve FH	18 (13.7%)	4 (3.1%)	

^a including agricultural workers with pesticides exposure, textile and construction workers.

* p-value considered significant at <0.05

Table 2: Thyroid Cancer Pathology and Stage by Occupational Chemical Exposure Status

	Jobs with high risk of chemical exposure		p value
	No (n=115)	Yes (=16)	
Pathology			
PTC	99 (86.1%)	15 (93.8%)	0.310
FTC	11 (9.6%)	0 (0.0%)	
MTC	3 (2.6%)	0 (0.0%)	
OCA	1 (0.9%)	1 (6.3%)	
PDTC	1 (0.9%)	0 (0.0%)	
Stage			
Localized	82 (71.3%)	9 (56.3%)	0.252
Metastatic	33 (28.7%)	7 (43.8%)	

PTC= papillary thyroid carcinoma, FTC= follicular thyroid carcinoma, OCA= Oncocytic carcinoma; PDTC: poorly differentiated thyroid carcinoma; MTC: Medullary thyroid carcinoma

Table 3: Univariate and multivariate logistic regression analysis for factors associated with thyroid cancer

	Univariate		Multivariate	
	Crude OR (95% CI)	p value	aOR (95% CI)	p value
Sex (female)	1 (0.5-1.9)	1	2.8 (1.1-7.8)	0.044*
Partnered marital status	1.4 (0.7-2.8)	0.376		
Residence (rural)	0.9 (0.4-1.6)	0.623		
Education (below 2ry)	1.8 (1.1-3.0)	0.023*	1.5 (0.9-2.6)	0.134
Financial difficulties	1.8 (1.0-3.3)	0.043*	1.7 (0.9-3.2)	0.087
Jobs with high risk of chemical exposure	3.5 (1.2-9.9)	0.018*	3.8 (1.1-12.9)	0.03*
Smoking status				
Never smoker	1 (ref.)		1 (ref.)	
Ex-smoker	2.2 (0.4-12.1)	0.376	6.6 (0.9-48.1)	0.065
Current smoker	5.4 (1.2-25.3)	0.031*	10.6 (1.7-65)	0.011*
Family history of thyroid cancer	5.1 (1.7-15.4)	0.004*	5.9 (1.8-18.6)	0.003*

Table 4: Results of relative weight analysis of predictors of thyroid cancer

Variable	Raw relative weight	Relative weight as % of R-squared
Sex	0.006	5.2%
Low education level	0.014	12.2%
Financial difficulties	0.013	11.2%
Jobs with high risk of chemical exposure	0.018	16.2%
Smoking status	0.026	22.9%
Family history of thyroid cancer	0.037	32.3%
<i>Model R²=0.114</i>		

Dependent variable = thyroid cancer

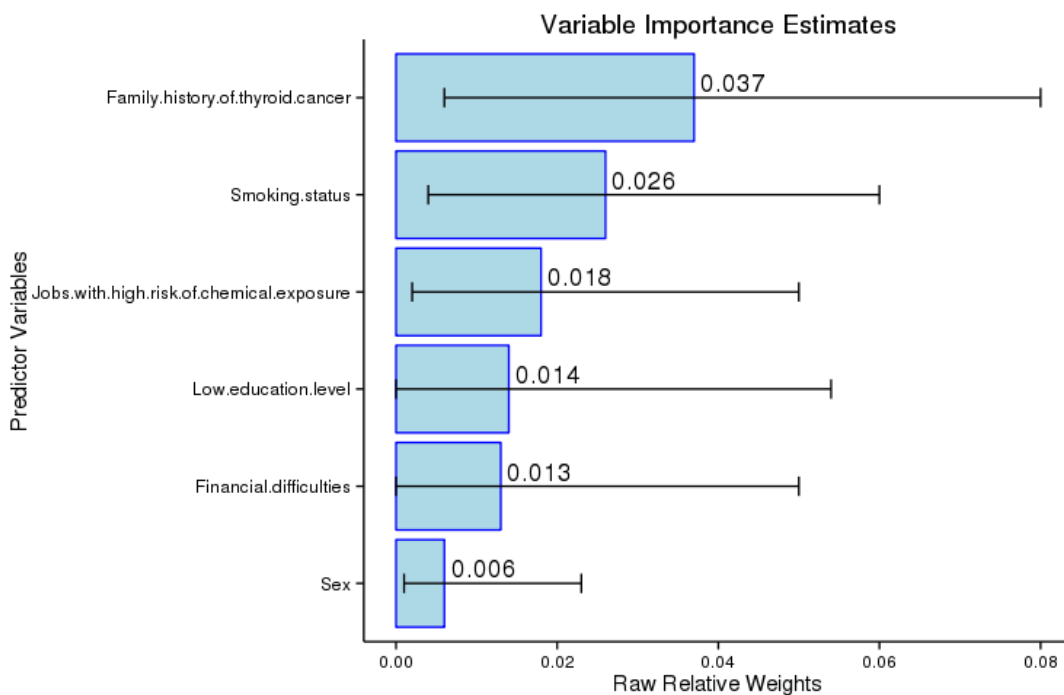


Fig 1: Relative Weight Plot with 95% CI

The researchers propose that the protective effect of smoking on thyroid cancer risk may be linked to several factors. Firstly, they suggest a connection with lower levels of TSH and a lower BM observed among current smokers [26]. In addition, smoking is implicated in influencing the risk of thyroid cancer through altering sex steroid hormone levels [27]. Moreover, it is suggested that smoking may confer a protective effect against autoimmune thyroiditis. The proposed mechanism involves nicotine influencing immune responses, specifically by shifting them from dysfunctional Th1 and Th17 responses—commonly associated with autoimmune diseases—toward a protective Th2 response. This shift in immune responses may potentially decrease the likelihood of developing autoimmune thyroiditis [28]. However, the potential for reverse causality bias highlight that observational studies showing a protective effect of smoking should be interpreted with caution. Patients may have quit smoking close to their thyroid cancer diagnosis or surgery. If recent quitters are misclassified as current smokers, this could artificially make smoking seem protective [29].

The inconsistency in findings across previous research on the association between smoking and thyroid cancer can be attributed to multiple sources of bias including the variability in design and analysis methods, differences in participant characteristics and environmental exposure, lifestyle. A recent study takes a more standardized and robust approach, utilized Mendelian randomization analysis with multiple instrumental variables which provides a powerful and less biased way to explore causal relationships between risk factors and outcomes in observational studies. This study has found no evidence supporting a causative association between cigarette smoking and the development of thyroid carcinoma suggesting that factors beyond smoking play a significant role in thyroid cancer pathogenesis [28].

The present study's findings indicate an elevated risk of developing thyroid cancer associated with a family history of the disease. This aligns with results from a case-control study in Korea, which also identified an increased thyroid cancer risk linked to a family history of the disease [30]. Li and colleagues propose that the heightened thyroid cancer risk among those with a history of the cancer in their first-degree relatives points towards genetic factors playing a role in the disease's development [31].

4. Conclusions

This case-control study found that occupations with potential risk of chemical contamination may increase thyroid cancer risk. However, further research is needed to establish a causal relationship between specific job exposures and thyroid cancer. Smoking and family history also showed an independent association with thyroid cancer. The findings support targeting workplace chemical exposures in primary prevention efforts to reduce the burden of thyroid cancer.

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Competing Interests

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The authors have no relevant financial or non-financial interests to disclose.

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