



# Association Between Papillary Thyroid Cancer and Allergy: A Case-Control Study

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## Abstract

**Background:** Thyroid cancer incidence has dramatically increased in many countries. Several studies have investigated the association between cancer and allergy, and most of them have had equivocal results.

**Objectives:** The aim of this study was to evaluate the association between allergy and papillary thyroid cancer (PTC).

**Methods:** This case-control study was performed among 3 university hospitals of Tehran. Cases (n = 59) were selected among patients with PTC based on final pathology after thyroidectomy. Controls (n = 53) consisted of patients attending the outpatient's clinics of the same hospitals with no symptoms of any cancer. Data about allergic diseases and symptoms were collected by a modified International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire.

**Results:** Logistic regression analysis manifested the reverse association between allergic rhinitis (OR = 0.07, 95% CI: 0.007-0.74) with PTC considering confounding variables (age, body mass index (BMI), and family history of thyroid cancer in first degree relatives). In addition, we found the reverse association between any allergy and PTC in this population (OR = 0.25, 95% CI: 0.1-0.64). Meanwhile, the results in both models revealed a reverse association between BMI (OR < 1, P < 0.05) and PTC. Finally, family history of thyroid cancer had a significant relationship with developing thyroid cancer in our population (OR > 6, P < 0.05).

**Conclusions:** Our data suggest a reverse association between allergy diseases, specifically allergic rhinitis and suffering from thyroid cancer. However, further studies are required to clarify association observed between PTC and allergy considering environmental and host factors.

**Keywords:** Allergy, Case-Control Study, Thyroid Cancer (TC)

## 1. Background

Cancer is a serious problem for health care systems all around the world (1). During the recent decades, thyroid cancer incidence and mortality have dramatically increased in many countries (2, 3).

Papillary thyroid cancer (PTC) is the most prevalent type of thyroid cancer that includes a group of heterogeneous tumors with different biology and prognosis (4, 5). The Tehran Cancer Institute Data System Registry (TCIDSR) has shown that the prevalence of PTC is around 67% of cases with thyroid cancer (6).

In addition, the prevalence of allergic and atopic diseases has significantly increased in western countries, which reached a steady state in the recent years (7). Hopkin et al. showed that 53% of the study population in the United States had an allergic state and 44% had specific im-

munoglobulin E (IgE) in their blood sample, which indicates atopy (8).

Two theories describe the relation between cancer and allergy. The first one emphasizes that allergy is a stimulant for the immune system; so, it can play a protective role against cancer. IgE antibody molecule that attaches to the specific antigens on the tumoral cell surface conducts a relationship between immune system and tumoral cells. This can be a provocative factor for antibody-dependent cellular toxicity and phagocytosis (9). The second theory claims that allergy, as a continuous inflammatory process, causes cancer because of recurrent cell damage and healing (10, 11). There are many debates that whether allergy increases or decreases the risk of cancer. Several studies have investigated the association between cancer and allergy, and most of them have had equivocal results (10-13).

Meanwhile, some researchers concluded that there was insufficient evidence to establish an association between allergy and cancer (14-16).

The usage of Food and Drug Administration (FDA) approved drugs like Rituximab and Trastuzumab for passive immunotherapy in patients with cancer, and the introduction of vaccination against cancer have supported the allergy-cancer relationship (17, 18). A review article manifested passive anaphylaxis or weekly injection of Histamines inhibited tumor growth in a transplant mouse model, pointing towards a possible role of anaphylactic reactions in tumor immunity. They discussed about the IgE antibodies; those are the most abundant class fixed in the cancer tissue and have a natural surveillance function in head and neck cancer malignancies (9).

Since thyroid carcinoma constitute about 76% of all cases of endocrine cancer in Iran and less than one-third of cases are detected (19), the demand for reliable prevention, early diagnosis, and new targeted therapies with IGE antibodies and vaccination strategies in the future is increasing.

Based on the available scientific evidence and the increasing prevalence of thyroid cancer and allergy, our hypothesis was that the allergic disease may be related to thyroid cancer, specifically PTC in Iranian population. A limited number of studies have evaluated the risk of developing thyroid cancer in patients, who had the allergic disease and their results were inconsistent (20-22).

Therefore, the aim of the present study was to evaluate the relationship between allergy and PTC in Iranian population.

## 2. Methods

### 2.1. Patients and Design

This case-control study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. Appropriate informed consent was obtained from all participants.

This investigation was performed among 3 university hospitals of Tehran, Iran and started from 2014 until 2015. Cases were selected among patients with papillary thyroid cancer based on the final pathology after thyroidectomy. Since each hospital usually gives services to a defined geographic area and socioeconomic status population, control group were selected from the same hospital (hospital-based controls). They were patients, who came to the outpatient's orthopedic clinics of the hospital, with no symptom of any cancer. Cases, who received adjuvant treatment or had a history of any other cancer, were excluded from the study.

The trained physician, who was the main investigator, gathered individual information about age, sex, weight, height, marital status, level of education, family history

of thyroid cancer, smoking, and physical activity by the face-to-face interviews. Body mass index (BMI) is defined as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Passive smoker was considered as someone, who is exposed by cigarette smoke by persons other than the intended active smoker. A modified questionnaire developed by the International Study of Asthma and Allergy in Childhood (ISAAC) (23) was translated into Persian and it was used for the evaluation symptoms of allergic diseases.

### 2.2. Sample Size

Based on the results of the pilot study, we predicted that the proportion of allergy in case and control group will be about 10% and 30% in our population. Therefore, we calculated 62 persons will be required in each group to detect a difference in incidence with power of 80% and  $\alpha = 0.05$ , using the Epi Info Web site ([www.cdc.gov/epiinfo/](http://www.cdc.gov/epiinfo/)).

### 2.3. Statistical Analysis

Statistical analysis was performed, using SPSS software (version 18, Chicago, IL, USA). Categorical and continuous variables are expressed as number (%) and mean  $\pm$  standard deviation, respectively. Pearson Chi-square tests, Fisher's Exact test, and independent *t*-test were used to assess differences between baseline demographic and clinical characteristics of study groups. Multivariate logistic regression analysis in a backward manner was used to examine the association between PTC and allergic situations. We adjusted for potential confounder variables such as age (year), BMI ( $\text{kg}/\text{m}^2$ ), and family history of thyroid cancer in the first degree relatives (yes/no). Variables were selected a priori for inclusion in multivariate models on the basis of association with PTC in univariate analysis ( $P < 0.1$ ) or on the basis of an association from the literature, whereas a *P* value of 0.05 was the threshold for a variable to stay in the model. Results were presented as odds ratio (OR) with 95% confidence intervals (CI).

## 3. Results

Final analysis was performed in 59 cases and 53 controls due to excluding incomplete data. Table 1 shows the basic and demographic characteristics of the study sample. There was no significant difference in age, sex, BMI, marital status, educational level, and smoking between two groups (Table 1). The results manifested that family history of thyroid cancer was statistically higher in case group in comparison with control ( $P = 0.01$ ).

Table 2 shows the allergic diseases of both groups. The allergic rhinitis was significantly higher in control group ( $P = 0.005$ ).

The results of the univariate and multivariate logistic regression analysis were presented in Table 3. Since there was a statistically significant difference between two

**Table 1.** Total Characteristics of Case and Control Groups<sup>a</sup>

Variables	Group		P Value <sup>b</sup>
	Case (N = 59)	Control (N = 53)	
Age, y	39.48 ± 12.7	42.98 ± 10.5	0.12
BMI, kg/m <sup>2</sup>	25.52 ± 4.4	24.7 ± 3.8	0.09
Sex			0.61
Male	8 (13.6)	10 (18.9)	
Female	51 (86.4)	43 (81.1)	
Marital status			0.28
Single	6 (10.2)	11 (20.8)	
Married	53 (89.8)	42 (79.2)	
Education level			0.38
Illiterate	14 (23.72)	9 (17)	
Under diploma	29 (49.1)	27 (50.9)	
Graduate	16 (27.1)	17 (32.1)	
Family history of thyroid cancer in the 1st degree relatives	11 (18.6)	2 (3.8)	0.02
Family history of other cancer	10 (16.9)	15 (28.8)	0.17
Smoker	3 (5.1)	6 (12.0)	0.30
Passive smoker	6 (10.2)	7 (14.3)	0.77

Abbreviation: BMI, body mass index.

<sup>a</sup>Values are expressed as mean ± SD or No. (%).

<sup>b</sup>P value refers to student t-test and Chi-square when appropriate.

**Table 2.** The Comparison of Allergic Disorders Between Two Groups<sup>a</sup>

Variables	Case (N = 59)	Control (N = 53)	P Value <sup>b</sup>
Asthma	2 (3.4)	4 (7.5)	0.42
Dermatitis	2 (3.4)	4 (7.5)	0.42
Food allergy	2 (3.4)	3 (5.7)	0.67
Allergic rhinitis	6 (10.2)	17 (30.8)	0.005
Drug allergy	0 (0)	3 (5.7)	0.10
Total allergy	18 (30.5)	26 (49.1)	0.035

<sup>a</sup>Values are expressed as No. (%).

<sup>b</sup>P value refers to Chi-square test and Fisher's Exact test when appropriate.

groups in allergic rhinitis (Table 2), it was entered as a dependent variable in the first model to evaluate the association between this type of allergy with PTC separately in the presence of confounders. The second model shows the result of association between any allergic diseases and PTC. The results in both models manifested the reverse association between allergy rhinitis and total allergy and PTC in this population.

In addition, the results in both models revealed a reverse association between BMI (OR < 1, P < 0.05) with PTC. Family history of thyroid cancer in first degree relatives had a significant relationship with developing thyroid can-

cer in our study sample (OR > 6, P < 0.05) (data were not shown in the Table).

#### 4. Discussion

In this study, we evaluated the association between PTC and allergic disease in Iranian study samples while considering confounding variables. We found a negative association between PTC and allergy. Interestingly, we also discovered a stronger negative association between PTC and allergic rhinitis. Family history of thyroid cancer in first degree relatives significantly increased the risk of PTC as expected.

Similar to the present study, a review article by Turner in 2012 represented the strong inverse association between allergy history and cancer risk (24). Several studies reported the reverse association between allergic rhinitis and the risk of hypothalamus tumors, glioma, Non-Hodgkin lymphoma, pancreatic, cervix, stomach, and breast cancer (25-33). The results of the present study are consistent with the aforementioned studies in other types of cancer. These findings support that human IgE antibody plays an important role in allergic reactions and it is effective in the immune response against tumors (34, 35).

However, two studies reported the positive relationship between thyroid cancer and allergic diseases that contradict with the findings of the present study (21, 22). Mein-

**Table 3.** Univariate and Multivariate Logistic Regression Analysis Results<sup>a</sup>

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
<b>Model 1</b>				
Allergy rhinitis	0.11 (0.01 - 0.95)	0.045	0.07 (0.007 - 0.74)	0.03
<b>Model 2</b>				
Total allergy	0.46 (0.21 - 0.99)	0.046	0.25 (0.1 - 0.64)	0.04

Abbreviation: OR, odds ratio; CI, confidence interval.

<sup>a</sup>Confounding variables in Multivariate analysis include: Age, BMI, and family history of thyroid cancer in the 1st degree relatives.

hold et al. showed that the risk of thyroid cancer will increase in women with a previous history of asthma and their data were based on self-reported medical history in 242 women with thyroid cancer. They also found an elevated risk of thyroid cancer in men with a positive history of asthma (n = 40) that was not statistically significant maybe due to low sample size (21). Another nationwide study reported that allergic rhinitis was statistically increased in only females with thyroid cancer (22). Although in the present study the majority of the study sample were women, we found a negative association between allergic rhinitis and PTC as a most prevalent type of thyroid cancer. Further studies with more sample sizes are needed to evaluate the relationship between Allergy and thyroid cancer in each sex.

These differences in the results of studies about the association between cancer and allergic diseases may be due to some factors. Firstly; it should be noted that the majority of studies examined self-reported allergy history in relation to cancer; however, in the present study, ISAAC questionnaire, as a valuable tool, was used for the diagnosis of allergy. Secondly; in some studies, they used biomarkers like specific IgE or skin tests such as Prick for the diagnosis of allergic states, which are more accurate and this is one of our limitations in this study. Another limitation of the present study was the lack of data about the severity of allergic diseases and it was not possible for us to discuss whether this association between allergy and PTC is related to the severity of the disease or not.

Surprisingly, in this study sample, BMI had a reverse association with PTC. However, a pooled analysis of several studies indicated that the risk of thyroid cancer is greater in obese subjects (36). Another study found that BMI at the time of diagnosis was related to thyroid cancer risk in females (37). Since the present study sample consisted mostly of women, we assume the low BMI (Table 1) in the case group may be dependent on the stage of cancer and its complications. However, we did not record the stage of disease at the time of diagnosis.

One of the host factors involved in the risk of allergy is age and it differs in age categories (38). On the other hand, age is one of the risk factors of cancer and evidence sug-

gested the activity of PTC progression is inversely related to patient's age (39). However, in the present study, the mean age of the two groups was statistically similar and in the final logistic analysis, age had no association with PTC in this study sample.

Since there are many variations of allergens in the different geographic areas (40) and there is not any published data about Middle East countries especially Iran, this investigation could be considered valuable.

#### 4.1. Conclusion

We found the reverse association between allergic states, specifically allergic rhinitis with PTC in our study sample. However, further studies with more sample size considering the different categories such as age, sex, and severity of disease are required to clarify association observed between PTC and allergy. Evaluation of the association of different cancers and allergy in order to setup targeted therapy with IgE antibodies and vaccination strategies in the future in each population is needed.

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#### Footnotes

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