



# The Estimation of Thyroid Cancer Risk based on Type 2 Diabetes Mellitus and ABO Blood Group

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## OBJECTIVE

Multiple potential risk factors have been proposed for the development of thyroid cancer. Type 2 diabetes and ABO blood group had a significant relationship with some cancers. These agents may be related to thyroid cancer. This study investigates the association between thyroid cancer and diabetes and the ABO blood group.

## METHODS

This analytic study was conducted in patients with thyroid cancer (n=87) and the individuals cancer-free (n=929). The odds ratio of thyroid cancer was estimated in diabetic patients after adjusting age and sex. The distribution of the blood groups in both groups was determined and compared with considering confidence interval 95%.

## RESULTS

We observed a significant association between thyroid cancer and type 2 diabetes (odds ratio (OR): 4.42, 95% confidence interval (CI): 2.04-9.57,  $p < 0.001$ ). There was a significantly lower frequency of blood type A in patients with thyroid cancer (25.3%) compared to the control group (34.4%) with a reduced risk of 43% (OR: 0.57; 95% CI: 0.33–0.97,  $p = 0.04$ ). The patients with blood type B had a borderline risk of thyroid cancer (OR: 1.60, 95% CI: 0.96–2.70,  $p = 0.07$ ).

## CONCLUSION

Our findings show the relationship between type 2 diabetes and thyroid cancer. The blood type A can significantly decrease the risk of thyroid cancer, and the blood type B may increase. To confirm these results, further studies should be conducted.

**Keywords:** Blood group; diabetes; thyroid cancer.

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## Introduction

Thyroid cancer (TC) is one of the most common cancers worldwide. The incidence of TC has grown significantly in recent decades. This dramatically rising might be due to early diagnosis by neck ultrasound; of course,

it cannot be justifiable for large size tumors. However, it can be attributed to increasing screening and also potential or unknown risk factors.[1]

Type 2 diabetes (DM) is a major health problem in Iran, as well as in other countries. The prevalence of DM is 11.4% in the Iranian adult population.[2] DM,

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as a potential risk factor, was proposed for some cancers. The significant associations between DM and colon, breast, endometrium, liver, pancreas and bladder cancer have been seen.[3] The ionizing radiation is the only of known risk factor for TC. From the possible risk factors of TC can be mentioned to inadequate or overdose of iodine.[4] The role of DM on TC is remained to be elucidated. In the literature review, the studies with pooled analysis were found a significant relationship between TC and DM, but there was no association in the male patients and Asian population. [5,6] Since the incidence of DM and TC can be depended on the climate condition, ethnicity and lifestyle in the various regions of the world [7,8], our study is a sample of TC and DM in Iran. We have investigated ABO blood group as a potential agent for TC due to the recent reports from the role of blood groups in the development of cancers.[5-7]

## Materials and Methods

This retrospective comparative study was conducted in 2010-2017 Loghman Hakim Hospital. This study was approved by the medical ethics committee of Shahid Beheshti University of medical sciences.

The case group was the patients with thyroid cancer. The medical records of them were extracted from hospital information system from March 21, 2010 to, 2017 based on ICD-10 code (C73). The inclusion criteria for this group included of laboratory data for ABO blood group, diabetes screening and pathological diagnosis of TC. The exclusion criteria were type 1 diabetes, the absence of blood types and fasting plasma glucose or random plasma glucose. The database was 104 patients with TC that two patients had no primary TC, 5 entries were duplicates and 10 patients had no information about studied variables. Of the original data, 87 patients remained for analysis (83.6%). The control group was the individuals' cancer-free that were visited in an outpatients clinic. They were 1045 individuals without cancer history that 929 individuals were selected using the same period and inclusion criteria of the case group. Overall, the selection of the individuals was non-probability sampling and their information was confidentially kept by our colleagues in this study.

## Statistical Analysis

We entered data into SPSS version 18 and compared two groups concerning the demographic variables and the proportion of diabetes and ABO blood group. We compared the proportion of diabetes in studied groups,

two age groups (less than 60 years and 60 years or older) and sex using the  $\chi^2$  test. Univariate and Multivariate unconditional logistic regression were applied to determine the odds ratio of thyroid cancer based on diabetes and ABO blood group. Subgroup analysis was also performed for papillary thyroid cancer (PTC) and non-papillary thyroid cancer (non-PTC). In our analysis, parametric tests were used, if the assumptions of those were set, otherwise the nonparametric tests were applied. The significant level was considered less than 0.05.

## Results

### The Baseline Characteristics

The demographic analysis of the case group and control group is presented in Table 1. The mean age of studied groups was no significant difference ( $p=0.209$ ); 59.8% and 31.3% were female in case group and control group, respectively ( $p<0.001$ ). The proportion of diabetes was significantly higher in the case group than the control group (13.8% vs. 3.9%;  $p<0.001$ ). Of 87 patients with TC, 68 patients (78.2%) had papillary thyroid carcinoma (PTC), and 8 (9.2%), 7 (8.0%), 4 (4.6%) had follicular thyroid carcinoma (FTC), anaplastic thyroid carcinoma (ATC) and medullar thyroid carcinoma (MTC), respectively.

### Association of Diabetes with Thyroid Cancer

There was a statistically significant association between TC and diabetes. The risk of TC in diabetic patients was 3.96, CI 95%:1.98-7.95,  $p<0.001$ . There was a significant association between TC and sex that risk of TC in female was 3-fold male patients (OR: 3.26, CI 95%=2.07-5.11,  $p<0.001$ ). The risk of TC in the age group 60 years and older was 7.28 (CI 95%=3.83-13.84,  $p<0.001$ ) as compared with younger individuals. After adjustment of age and sex (multivariate logistic regression), the risk of TC was 4.42 (CI 95%: 2.04-9.57,  $p<0.001$ ).

### Association of ABO Blood Group with Thyroid Cancer

The most common blood group was blood type O in both groups (34.5% in case and 35.6% in the control group). Blood type A was significantly associated with a lower risk of TC (OR: 0.57, CI 95%: 0.33 -0.97,  $p=0.04$ ). Non-significant increased risk of 60% was detected in the patients with blood type B (Table 2).

### Comparison of PTC and Non-PTC

Table 3 shows that the proportion of diabetes in the patients with PTC was significantly higher than non-PTC

**Table 1** The baseline features of the study groups

Variable	Case group (n=87)	Control group (n=929)	P value
Age (Mean±SD)	44.17±17.05	44.14±8.09	0.209
Age group (n, %)			
<60	70 (80.46)	899 (96.77)	<0.001
≤60	17 (19.54)	30 (3.23)	
Sex (n, %)			
Male	35 (40.2)	638 (68.7)	<0.001
Female	52 (59.8)	291 (31.3)	
Diabetes (n, %)			
Yes	12 (13.8)	36 (3.9)	<0.001
No	75 (86.2)	893 (96.1)	
ABO blood group (n, %)			
Type O	30 (34.5)	328 (35.4)	0.169
Type B	26 (29.9)	203 (21.8)	
Type A	22 (25.3)	320 (34.4)	
Type AB	9 (10.3)	70 (7.6)	
Missing	-	8 (0.8)	
RH+	72 (82.8)	825 (88.8)	0.071
RH-	15 (17.2)	96 (10.4)	
Missing	-	8 (0.8)	

**Table 2** Results of the Univariate and Multivariate logistic regression for risk of thyroid cancer

Variable	OR	95% CI	AOR*	95% CI	P value
Diabetes (Yes)	3.96	1.98–7.95	4.42	2.04–9.57	<0.001
Age (≥60)	7.28	3.82–13.84	9.13	4.51–18.50	<0.001
Sex (Female)	3.26	2.07–5.11	4.29	2.60–6.93	<0.001
Type O vs. others	1.05	0.66–1.67	1.00	0.61–1.62	1.00
Type A vs. others	0.64	0.38–1.05	0.57	0.33–0.97	0.04
Type B vs. others	1.51	0.93–2.45	1.60	0.96–2.70	0.07
Type AB vs. others	1.40	0.67–2.92	1.43	0.65–3.15	0.37
RH+ vs. RH-	0.56	0.30–1.01	0.58	0.31–1.07	0.08

OR: Crude Odds Ratio; AOR\*: Adjusted Odds Ratio was estimated the by model of Multivariate unconditional logistic regression; P value: less than 0.05 is significant

patients (OR: 4.28; CI 95%: 2.02- 9.05; p=0.001). The risk of PTC was higher in patients less than 60 years (p=0.038). The blood type O (33.8%) and B (42.1%) were the most abundant type in patients with PTC and non-PTC, respectively (Table 3). There was no significant relationship between PTC and ABO blood group (p=0.436).

For the validity of the inferences, we randomly selected 175 control individuals from all control group (two control each case) and compared and analyzed with the case group. Its statistical results were similar to the primary analysis and showed the significant relationship between diabetes and TC after adjusting other variables that findings were mentioned in a Supplementary Table 1.

## Discussion

Our study was a retrospective study about the association TC with the potential risk factors, including diabetes and the ABO blood group. We used the control group with high sample that were selected with the same period and geographical areas of the case group. To control confounding variables of sex and age, we used multivariate unconditional logistic regression.

We found type 2 diabetes as an independent risk factor for TC. This relationship was statistical significance in female patients. Our findings were consistent with Hemminki et al.'s and Tulinins et al.' study.[8,9] Chodiac et al. and Aschebrook et al. have found no this relationship.[10,11] Yohwan et al. conducted a pooled

**Table 3** Association between risk factors and thyroid cancer types

Variables (n, %)	PTC (n=68)	FTC (n=8)	ATC (n=7)	MTC (n=4)	p-value	PTC/Non-PTC OR (CI 95%)
Sex						
Female (Referenced)	44 (64.7)	5 (62.5)	2 (28.6)	1 (25.0)	0.081	2.52 (0.89-7.11)
Male	24 (35.3)	3 (37.5)	5 (71.4)	3 (75.0)		
Age group						
<60 years	58 (85.3)	7 (87.5)	3 (42.9)	2 (50.0)	0.038	3.38 (1.07-10.67)
≥60 years (Referenced)	10 (14.7)	1 (12.5)	4 (57.1)	2 (50.0)		
Diabetes (Yes)	10 (14.7)	1 (12.5)	1 (14.2)	0 (0.0)	0.001	4.27 (2.02-9.04)
Blood type O	23 (33.8)	3 (37.5)	4 (57.1)	0 (0.0)	0.807	0.876 (0.30-2.53)
Blood type A	19 (27.9)	1 (12.5)	2 (28.6)	0 (0.0)	0.289	2.06 (0.54-7.91)
Blood type B	18 (26.5)	3 (37.5)	1 (14.3)	4 (100.0)	0.193	0.49 (0.17-1.43)
Blood type AB	8 (11.8)	1 (12.5)	0 (0.0)	0 (0.0)	0.424	2.40 (0.28-20.49)
RH+	57 (83.8)	7 (87.5)	5 (71.4)	3 (75.0)	0.620	1.38 (0.38-4.96)
RH- (Referenced)	11 (16.2)	1 (12.5)	2 (28.6)	1 (25.0)		

PTC: Papillary thyroid cancer; FTC: Follicular thyroid carcinoma; ATC: Anaplastic thyroid carcinoma; MTC: Medullar thyroid carcinoma; P value: Less than 0.05 is significant

**Supplementary Table 1** Results of the Univariate and Multivariate logistic regression for risk of thyroid cancer

Variable	Case (n,%)	Control (n,%)	AOR*	95% CI	P value
Diabetes (Yes)	12 (13.8)	6 (3.4)	4.47	1.46-13.62	0.008
Age (≥60)	17 (19.5)	8 (4.6)	9.11	3.31-25.13	<0.001
Sex (Female)	52 (59.8)	60 (34.3)	3.96	2.13-7.35	<0.001
Type O vs. others	30 (34.5)	59 (34.7)	0.42	0.13-1.39	0.15
Type A vs. others	22 (25.3)	60 (35.3)	0.23	0.06-0.79	0.02
Type B vs. others	26 (29.9)	44 (25.9)	0.51	0.15-1.75	0.28
Type AB vs. others	9 (10.3)	7 (4.1)	1.94	0.57-6.59	0.28
RH+ vs. RH-	72 (82.8)	155 (91.2)	0.63	0.26-1.50	0.30

OR: Crude Odds Ratio; AOR\*: Adjusted Odds Ratio was estimated by the model of Multivariate unconditional logistic regression; P value: less than 0.05 is significant

analysis in 2014 and found a significant relative risk between TC and DM; that analysis was significantly found in female patients.[12] Li et al., in 2017, tried to use cohort studies for analysis, and they reached to significant risk with lower heterogeneity than the Yohwan study.[13] Both pooled studies were found on significant relative risk in male patients in similar to our study. Those were not reached a definite conclusion about the Asian population due to a few primary studies (only three articles) from Asian countries.

What is for certain that the occurrence of non-communicable diseases, such as diabetes and cancers, can be different in worldwide because of various ethnicity, environmental factors and lifestyle. Thus, we think this study can be a sample of the Middle Eastern countries.

The incidence of thyroid cancer is related to multiple factors, including modified and unmodified factors. Diabetes type 2 is a known risk factor for some cardio-

vascular diseases and cerebrovascular diseases; also it can be a potential risk factor for cancers. The mechanism of carcinogenic of diabetes is not clear on thyroid cancer. The proposed theories consisted of thyroid cell proliferation, and decreased apoptosis may be due to insulin resistance, higher body mass index (BMI), the long-term elevation of TSH, or use of insulin-enhancing drugs.[1] Some studies have also observed a high risk of thyroid nodules in diabetic patients [4,14,15] that those can be a point for thyroid cancer. In a variety of thyroid cancers, such as papillary thyroid cancer and anaplastic thyroid cancer, diabetes is mentioned as a risk factor.[16,17] Based on our findings, it is necessary to be considered thyroid cancer in diabetic patients, especially female patients.

For the addition of diabetes, we studied the role of the ABO blood group on TC. Some evidence was recently proposed about the relationship of blood groups

with some diseases like cancers. For example, it can be noticed to the association of stomach and pancreas cancer with blood group A.[18,19] The blood group O was found a poor prognostic factor in the patients with laryngeal cancer and also reported it a protective factor in the patients with nasopharyngeal carcinoma.[20,21] However, according to the reports, we paid attention to this issue and reached interesting findings. Our findings were similar to Gong et al. study and a significant negative relationship between TC and blood type A [7], that the patients with blood type A, after adjusting age, sex and diabetes have a 43% reduced risk of TC. Also, we found an increased risk of 60% in the patients with blood type B. Statistically, the risk of blood type B was not significant but had a narrow and borderline confidence interval. Some studies were showed a significant relationship between TC and blood type B.[5-7] Thus, our finding was non-negligible and may be due to the small sample size of the case group.

### Limitations

The findings obtained in this study are limited to the small size of case group and incomplete data of medical records, such as body mass index, duration of diabetes, type of diabetes medications and thyroid stimulation hormone level. However, this study recommended prospective research with measured mentioned confounders.

### Conclusion

Our study suggests that thyroid cancer may be associated with diabetes and the ABO blood group. Diabetes as a modified risk factor can be considered a starting point for screening cancer in diabetic patients, especially female patients.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors declare that there is no conflict of interest for the publication of this study.

**Ethics Committee Approval:** This study was approved by the medical ethics committee of Shahid Beheshti University of medical sciences.

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