

Association of diabetes mellitus with thyroid cancer risk

A meta-analysis of cohort studies

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Abstract

Background: Diabetes mellitus (DM) is inconsistently associated with thyroid cancer risk. The purpose of this study was to summarize findings from cohort studies regarding the strength of the association of DM with subsequent thyroid cancer risk.

Methods: Electronic searches were performed in PubMed, EmBase, and the Cochrane Library to identify studies from inception to July 2016. Cohort studies reporting risk estimates with 95% confidence intervals (CIs) of thyroid cancer in DM and non-DM patients were included. A random-effects meta-analysis was performed to the risk of thyroid cancer in DM compared with non-DM participants.

Results: Sixteen cohort studies were included, with a total of 10,725,884 individuals. These studies reported a total of 8032 cases of thyroid cancer. Overall, DM was associated with an increased risk of thyroid cancer (relative risk [RR], 1.20; 95% CI, 1.09–1.33; $P < .001$). Further, there was no significant difference was found between DM and non-DM for the risk of thyroid cancer in men (RR, 1.14; 95% CI, 1.00–1.30; $P = .057$), while a significant correlation was found in a pooled analysis in women (RR, 1.11; 95% CI, 1.06–1.17; $P < .001$). Finally, subgroup analyses suggested that country and mean age might correlate with the relationship between DM and the risk of thyroid cancer.

Conclusion: This study suggested that patients with DM have significantly increased risk of thyroid cancer compared nondiabetics. This positive association was prominent in women, and not significant in men. Further large-scale studies are required to verify the nature of the association, which should be evaluated in specific subpopulations.

Abbreviations: BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, OR = odds ratio, RR = relative risk, SIR = standard incidence ratio.

Keywords: diabetes mellitus, meta-analysis, thyroid cancer

1. Introduction

Thyroid cancer is the most common malignancy of the endocrine system worldwide in women.^[1] The most frequent types include papillary, follicular, and differentiated thyroid carcinomas.^[2] The American Cancer Society reported an incidence of thyroid cancer of 1 per 10,000 in the USA, a rate rising faster than those of any other cancers.^[3] Previous meta-analyses have illustrated the impact of multiple factors on thyroid cancer risk,^[4–9] while the impact of diabetes on subsequent thyroid cancer is less studied with limited and inconclusive findings.

Diabetes mellitus (DM) is considered a major global public health concern, and likely to be among the 5 leading disease burden contributors by 2030.^[10] Recently, associations of DM with the risk of cancer at different sites were evaluated using a meta-analytic approach.^[11–18] In addition, Yeo et al^[19] suggested that DM is associated with higher thyroid cancer risk compared with that of individuals without DM, although substantial heterogeneity existed. Furthermore, these relationships in women were statistically significant, whereas no significant impact was observed in men. However, previous meta-analyses did not further stratify analyses based on various baseline characteristics which might significantly impact the relationship between DM and thyroid cancer risk.

Several cohort studies indicated that participants with DM may have increased thyroid cancer risk,^[20–22] whereas other trials showed no association of DM with thyroid cancer risk.^[23–25] Clarifying the association of DM and thyroid cancer risk among participants with different baseline characteristics is particularly important, as this has not been definitively determined. This study attempted a large-scale examination of available cohort studies to determine the relationship between DM and thyroid cancer risk.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-

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Analysis Statement issued in 2009 (PRISMA Checklist).^[26] Ethics approval was not necessary for this study, as only deidentified pooled data from individual studies were analyzed. Any cohort study that evaluated the association of DM with thyroid cancer risk was eligible for inclusion, and no restrictions were placed on language or publication status (published or in press). A systematic electronic search of the PubMed, EmBase, and the Cochrane Library databases was performed for eligible studies from inception to July 2016. The following key words and medical subject headings were jointly used: (“diabetes” OR “fasting glucose” OR “hyperglycemia” OR “metabolic syndrome” OR “risk factor”) AND (“cancer” OR “carcinoma” OR “tumor” OR “neoplasm”) AND “thyroid” AND “cohort.” The reference lists of selected studies were manually screened for potentially relevant records. All analyses were based on previously published studies, and no ethical approval or patient consent was required.

The literature search and study selection were independently carried out by 2 reviewers using a standardized approach. Any inconsistencies were settled by group discussion until a consensus was reached. Inclusion criteria for studies were: a cohort design; assessment of thyroid cancer development in individuals with and without DM; and report of odds ratios (ORs), hazard ratios (HRs), relative risks (RRs), and standard incidence ratios (SIRs), or presentation of raw data that could produce crude effect estimates. Exclusion criteria were: a case-control or cross-sectional design; included patients with other diseases; and effect estimates not obtained or calculated.

2.2. Data collection and quality assessment

Two reviewers independently screened titles and abstracts of the eligible studies, and extracted the data. Any disagreement was resolved by group discussion until a consensus was reached. The following study characteristics were extracted: name of the first author or study group, publication year, country, sample size, mean age at baseline, proportion of males, body mass index (BMI), numbers of thyroid cancer, follow-up duration, adjustment factors, and effect estimates. Study quality was assessed by the modified Newcastle-Ottawa scale (NOS),^[27] which is quite comprehensive and has been partially validated for assessing the quality of observational studies in meta-analyses. The NOS encompasses the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items). A “star system” (range, 0–9) was developed for the assessment (Table 1).

2.3. Statistical analysis

All included studies with a cohort design and effect sizes presented HR, OR, RR, and SIR values. Because of the low incidence of thyroid cancer, the RR was approximated as OR, HR, and SIR. The maximum adjusted RR was pooled in the meta-analysis to avoid bias caused by adjustment factors. The relationship between DM and thyroid cancer risk was examined based on effect estimates and 95% confidence intervals (CIs) in various studies. When only raw data were available, crude ORs were calculated by the random Mantel-Haenszel method.^[28] When the effect estimate was reported separately in an individual trial, the fixed-effects model was used to pool summary RRs and 95% CIs for overall effect estimate in each study.^[28] Then, the random-effects model was used to assess summary RRs and 95% CIs for DM versus non-DM and thyroid cancer risk.^[29] Heterogeneity between studies was investigated by the Q-statistic, and $P < .10$ was considered to

indicate significant heterogeneity.^[30,31] Subgroup analyses were conducted for associations of country, mean age, effect estimate, and follow-up. Further, as the degree of adjustment and variables entering into the regression models varied between the included studies, stratified analyses were also performed based on important confounders, including adjusted BMI, and smoking status. Sensitivity analyses were conducted by removing each individual study from the meta-analysis.^[32] Several methods were used to evaluate potential publication bias. Visual inspection of funnel plots was conducted. Further, the Egger^[33] and Begg^[34] tests were used to statistically assess publication bias. Two sided $P < .05$ was considered statistically significant for all included studies. Statistical analyses were performed with the STATA software (version 12.0; Stata Corporation, TX).

3. Results

3.1. Study selection

The study-selection process is shown in Fig. 1. A total of 981 articles were identified from the electronic search, of which 895 were excluded because of insufficient or irrelevant data. Therefore, 86 potentially eligible studies were selected. Further, 39 articles not reporting any desirable outcomes, 27 including participants from the same population, and 4 with a meta-analysis design were excluded. A manual search of the reference lists of these studies yielded no new eligible studies. Finally, 16 studies were included into the meta-analysis.^[20–25,35–44] The general characteristics of the included studies are presented in Table 1.

3.2. Study characteristics and quality assessment

All included studies had a cohort design with worldwide distribution; they comprised 6 studies performed in USA or Canada, 5 in European countries, and 5 in Asian countries. The sample sizes ranged from 22,946 to 4,501,578 with thyroid cancer cases ranging from 19 to 3568; follow-up duration ranged from 3.5 to 27.0 years. In quality assessment, the included studies had low to moderate risk of bias, with scores ranging from 6 to 8. A study with a score of 7 or greater was considered to be of high quality. Overall, seven^[23,24,35,40,41,43,44], six^[20,22,25,36,39,42] and the remaining three^[21,37,38] studies had scores of 8, 7, and 6, respectively.

3.3. DM and thyroid cancer risk

All included studies reported an association of DM with thyroid cancer risk. Summary RR showed that DM was associated with increased risk of thyroid cancer (RR = 1.20; 95% CI 1.09–1.33; $P < .001$; Fig. 2), although substantial heterogeneity was detected across the included studies ($P = .001$). Sensitivity analysis was performed; and excluding each study sequentially from the pooled analysis did not affect the overall conclusion. Subgroup analyses demonstrated that DM had no significant impact on thyroid cancer risk in studies using SIR as effect estimate (RR = 1.54; 95% CI 0.99–2.39; $P = .057$), with follow-up duration exceeding 10 years (RR = 1.08; 95% CI 0.98–1.19; $P = .113$), and adjusting for smoking status (RR = 1.14; 95% CI 0.96–1.36; $P = .121$) (Table 2).

3.4. DM and thyroid cancer risk in men and women

A total of 8 cohort studies assessed the association of DM with thyroid cancer risk in men. Pooled analysis indicated no association of DM with thyroid cancer risk in

Table 1
Baseline characteristics of studies included in the systematic review and meta-analysis.

Study	Publication, y	Country	Sample size	Mean age at baseline	Percentage male, %	BMI, kg/m ²	Number of thyroid cancer cases	Follow-up duration, y	Adjusted factors	NOS score
US veterans ^[23]	2011	USA	4,501,578	52.3	100	NA	1053	11.7	Age, time, latency, race, number of visits, diagnoses of alcohol-related conditions, obesity, and chronic obstructive pulmonary disease	8
NHI Program ^[20]	2013	China	1,790,868	60.5	49.1	NA	1309	3.5	Sex, age, urbanization, hypertension, and hyperlipidemia	7
US RTS ^[24]	2010	USA	90,713	40.2	23.4	NA	282	15.8	Birth year, smoking status, BMI, number of personal radiographs to the head or neck, and cumulative occupational radiation dose	8
Tulinus ^[21]	1997	Iceland	22,946	50.4	49.5	25.2	83	4.0–27.0	Age	6
Wideroff ^[25]	1997	Denmark	109,581	66.5	49.8	NA	31	NA	BMI	7
Me-Can ^[35]	2009	Norway, Austria, and Sweden	549,944	44.9	49.8	25.3	277	10.4	Cohort, sex, birth year, adjusted for baseline age, BMI, and smoking status	8
MHS ^[36]	2010	Israel	100,595	61.6	52.6	NA	114	8.0	Age, region, SES level, use of health care services a year prior to index date, BMI, and history of cardiovascular diseases	7
BCLHD ^[37]	2011	Canada	370,200	60.7	54.3	NA	126	4.3	Sex, birth year, and index year	6
Adam ^[38]	1991	Sweden	51,008	>20.0	45.4	NA	19	5.2	Age and sex	6
PLCO ^[39]	2013	USA	48,497	62.5	52.0	NA	51	10.5	Sex, education, race, marital status, cigarette smoking, body mass index, alcohol intake, and cohort	7
Hemminki ^[22]	2010	Sweden	125,126	>39.0	NA	NA	71	5.0	Obesity	7
NIH–AARP Diet and Health Study ^[40]	2011	USA	496,548	62.0	59.6	27.1	525	10.0	Age, sex, smoking status, race/ethnicity, family history of cancer, BMI, and education	8
JPHC ^[41]	2006	Japan	97,771	51.6	47.6	NA	103	10.7	Age at baseline, study area, history of cerebrovascular disease, history of ischemic heart disease, smoking, ethanol intake, BMI, leisure-time physical activity, green vegetable intake, and coffee intake	8
Dankner ^[42]	2016	Israel	2,186,196	46.6	47.3	NA	3568	11.0	Age, socioeconomic status, and ethnic group	7
WHI ^[43]	2016	USA	147,934	63.2	0.0	27.9	391	15.9	Age at enrollment, ethnicity, education, smoking status, recreational physical activity, alcohol intake, history of HT use, previous thyroid disease, and BMI	8
Xu ^[44]	2015	China	36,379	59.0	44.4	NA	29	3.8	Age and gender	8

BMI = Body mass index, COPD = chronic obstructive pulmonary disease, HT = hormone therapy, NA = not available, NOS = Newcastle–Ottawa scale.

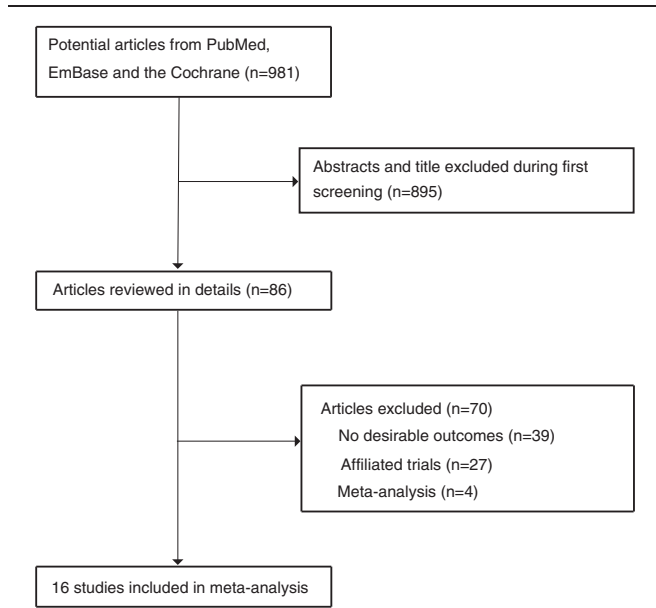


Figure 1. Study selection process.

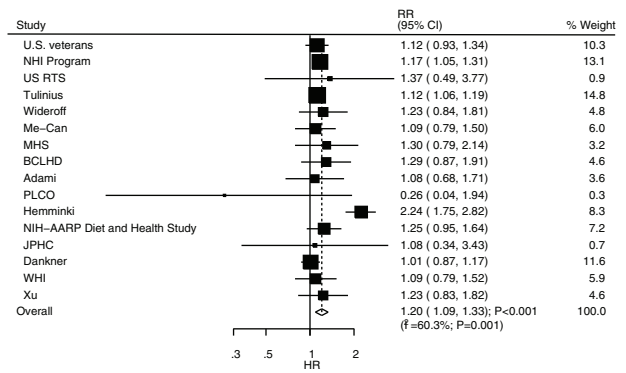


Figure 2. Diabetes mellitus (DM) and thyroid cancer risk.

men (RR=1.14; 95%CI 1.00–1.30; $P=.057$; Fig. 3). No evidence of heterogeneity was found ($P=.575$). Subgroup analysis indicated that DM was associated with increased risk of thyroid cancer in men in studies performed in Western countries (RR=1.19; 95%CI, 1.01–1.42; $P=.043$; Table 2).

Table 2

Subgroup analysis of relative risk (ratios) for thyroid cancer in men, women, and total cohort.

Factors	Subsets	Group	RR and 95% CI	P value	I ² , %	P value for heterogeneity
Country	Western countries	Men	1.19 (1.01–1.42)	.043	7.4	.365
		Women	1.09 (0.89–1.35)	.405	23.6	.257
		Total cohort	1.24 (1.06–1.45)	.006	70.8	<.001
	Eastern countries	Men	1.01 (0.78–1.32)	.922	0.0	.816
		Women	1.06 (0.92–1.24)	.415	0.0	.462
		Total cohort	1.12 (1.03–1.22)	.009	0.0	.552
Age at baseline	≥60	Men	1.08 (0.77–1.51)	.667	0.0	.761
		Women	1.26 (1.03–1.54)	.025	0.0	.641
		Total cohort	1.18 (1.08–1.29)	<.001	0.0	.791
	<60	Men	1.17 (0.97–1.41)	.105	20.6	.283
		Women	1.00 (0.87–1.15)	.986	0.0	.526
		Total cohort	1.11 (1.05–1.16)	<.001	0.0	.954
Effect estimate	SIR/SMR	Men	1.16 (0.63–2.13)	.627	0.0	.448
		Women	1.25 (0.92–1.70)	.156	0.0	.821
		Total cohort	1.54 (0.99–2.39)	.057	80.8	.005
	OR, RR, or HR	Men	1.14 (0.99–1.31)	.071	2.3	.402
		Women	1.07 (0.92–1.24)	.397	13.8	.322
		Total cohort	1.12 (1.07–1.17)	<.001	0.0	.898
Follow-up duration, y	≥10	Men	1.16 (0.96–1.40)	.136	36.3	.194
		Women	1.05 (0.88–1.26)	.587	25.8	.241
		Total cohort	1.08 (0.98–1.19)	.113	0.0	.742
	<10	Men	1.01 (0.55–1.86)	.975	0.0	.707
		Women	1.24 (0.94–1.65)	.131	0.0	.623
		Total cohort	1.36 (1.04–1.78)	.023	79.3	<.001
Adjusted BMI	Yes	Men	1.19 (0.98–1.44)	.077	14.0	.325
		Women	1.14 (0.93–1.40)	.198	17.1	.300
		Total cohort	1.27 (1.03–1.58)	.028	67.5	.001
	No	Men	1.05 (0.81–1.36)	.724	0.0	.765
		Women	1.04 (0.89–1.20)	.653	0.0	.526
		Total cohort	1.12 (1.07–1.17)	<.001	0.0	.668
Adjusted smoking	Yes	Men	1.38 (0.77–2.46)	.278	69.7	.069
		Women	1.07 (0.77–1.47)	.702	50.8	.107
		Total cohort	1.14 (0.96–1.36)	.121	0.0	.709
	No	Men	1.10 (0.95–1.27)	.201	0.0	.945
		Women	1.08 (0.94–1.23)	.300	0.0	.687
		Total cohort	1.23 (1.09–1.39)	.001	74.1	<.001

BMI = body mass index, CI = confidence interval, HR = hazard ratio, OR = odds ratio, RR = relative risk, SIR = standardized incidence ratio, SMR = standardized mortality ratio.

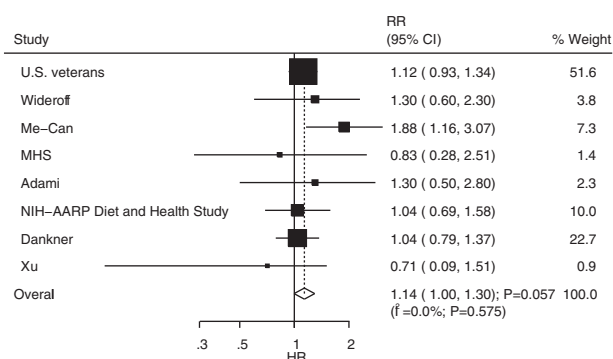


Figure 3. Diabetes mellitus (DM) and thyroid cancer risk in men.

A total of 11 cohort studies evaluated the association of DM with thyroid cancer risk in women. Pooled analysis of thyroid cancer risk in women indicated that DM versus non-DM had a harmful effect (RR = 1.11; 95% CI 1.06–1.17; $P < .001$; Fig. 4). Although no evidence of heterogeneity was noted, sensitivity analysis was performed; after excluding the study by Tulinus et al,^[21] which only adjusted for age, we found a significant difference between the DM and non-DM groups for thyroid cancer risk in women (RR = 1.08; 95% CI, 0.96–1.22; $P = .194$; Fig. 4). Subgroup analysis suggested that DM was associated with increased risk of thyroid cancer in women in participants averaging more than 60 years old (RR = 1.26; 95% CI 1.03–1.54; $P = .025$; Table 2); no other significant differences were observed.

3.5. Publication bias

Review of the funnel plots could not rule out the potential for publication bias (Fig. 5). The Egger^[33] and Begg^[34] tests showed no evidence of publication bias (P value for Egger test, .515; P value for Begg test, .753).

4. Discussion

This study was an updated meta-analysis that assessed the relationship between DM and thyroid cancer risk. Summary results indicated that DM patients had a 20% increase in thyroid cancer incidence compared with those without DM. Furthermore, when pooling for men, no significant difference was

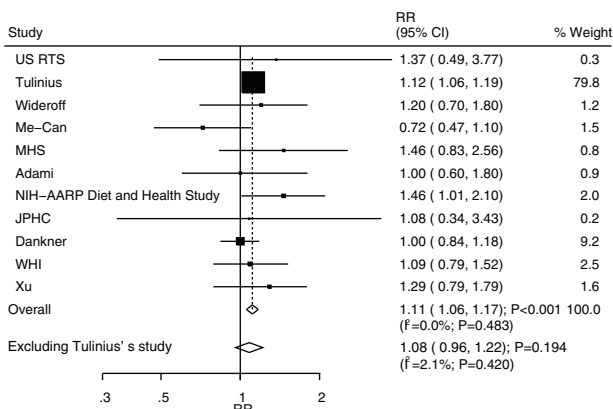


Figure 4. Diabetes mellitus (DM) and thyroid cancer risk in women.

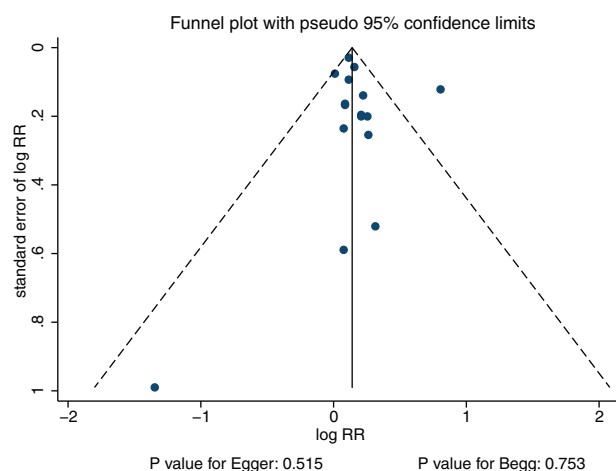


Figure 5. Publication bias for diabetes mellitus (DM) and thyroid cancer risk.

detected, whereas in women DM had a harmful impact on the risk of thyroid cancer. These associations might differ according to country, mean age, and follow-up duration.

The source of heterogeneity was explored using sensitivity and subgroup analyses. In sensitivity analysis, no substantial change was revealed after excluding any individual study in the total cohort and men, which suggested the homogeneity of pooled effect estimates. However, after excluding Tulinus et al,^[21] the conclusion changed for women. Furthermore, thyroid cancer incidence could differ according to country and mean age. For other potential confounders, no significant differences were found between respective subsets because the numbers of eligible studies in corresponding groups were rather small to draw firm conclusions. Finally, different adjustment factors might partly account for the heterogeneity.

Previous meta-analyses of the association of DM with thyroid cancer risk (17 studies, including 13 cohort and 4 case-control studies) have reported similar findings.^[19] Furthermore, several included studies corroborated the findings of the present meta-analysis. Lo et al^[20] analyzed the nationwide population-based database from 1996 to 2009 released by the National Health Research Institute of Taiwan, and found that individuals with DM have a modestly increased risk of thyroid (RR = 1.17; 95% CI 1.05–1.31), a harmful effect enhanced with follow-up duration. Tulinus et al^[21] indicated that the glucose level is associated with increased thyroid cancer risk in women, whereas this relationship was not observed in men. Hemminki et al^[22] performed a large-scale cohort study covering approximately half of the Swedish diabetic patients and found elevated thyroid cancer risk after hospitalization, suggesting the profound metabolic disturbances of the underlying disease. The present study also demonstrated that DM significantly increased the risk of thyroid cancer. Such increase might be due to DM patients having variable serum insulin levels, affecting the progression of thyroid cancer through enhanced cancer cell proliferation or reduced apoptosis, and indirectly through insulin-like growth factor-1, estrogen, and thyroid-stimulating hormone.^[45,46]

Subgroup analysis suggested that the association of DM with thyroid cancer risk was not statistically significant for studies using SIR as effect estimate, with follow-up exceeding 10 years, and/or adjusting for smoking status. However, these conclusions might be unreliable because few studies were included in these

subsets. Furthermore, the association of DM with thyroid cancer risk in men might differ among different countries. A significant impact was found in individuals from Western countries, whereas no difference was observed in Asian patients. Such discrepancy might stem from a study by Stocks et al.^[35] reported that abnormal glucose metabolism, independent of BMI, is associated with increased thyroid cancer risk in men. The latter study covered participants from Norway, Austria, and Sweden, including 6 cohorts. Furthermore, this conclusion might be biased as it included only 3 studies assessing Asian populations. Therefore, additional large-scale studies are needed to verify the potential difference according to ethnicity. The association of DM with thyroid cancer risk in women might differ with mean age. With participants averaging more than 60 years old, DM had a harmful impact on thyroid cancer risk, whereas no effect was found for younger individuals. The NIH–AARP Diet and Health Study reported similar results and found that thyroid cancer risk is significantly increased in women compared with men.^[40] The incidence of thyroid cancer was higher in women than in men, with narrow CIs; it is easier to obtain a statistically significant difference in women. Lo et al.^[20] found that the relationships between DM and thyroid cancer risk might differ by follow-up duration, likely because the mean age and duration of diabetes course play an important role in such association. In addition, diabetes treatment might affect the progression of thyroid cancer due to insulin resistance, which is associated with increased thyroid volumes and higher risk of thyroid nodule formation.^[47–49]

The present study had 3 strengths: only cohort studies were included, which could eliminate selection and recall biases; the large sample size allowed a quantitative evaluation of the correlation between DM and thyroid cancer risk, achieving more robust findings than any individual study; stratified analyses were conducted in the whole cohort, men, and women, separately; and several important factors were assessed when evaluating the relationship between DM and thyroid cancer risk in specific populations, which could affect the present results.

The current meta-analysis also had certain limitations. The adjustment models were different across the included studies, which might influence the validity of findings. In addition, publication bias was an inevitable problem because this study was based on published reports. Finally, summary analysis was based on pooled data, and individual participant data were not available, which precluded a more detailed analysis for obtaining more comprehensive results.

In conclusion, after allowing for the risk factors for thyroid cancer, DM had a potential harmful impact on thyroid cancer risk. Physicians and health professionals should encourage diabetes prevention in all individuals, especially in men from Western countries and older women.

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