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E-cadherin expression is associated with susceptibility and clinicopathological characteristics of thyroid cancer

A PRISMA-compliant meta-analysis

Changlin Zhou, MD, Chunsheng Yang, MD, Daoqun Chong, MD*

Abstract

Background: Recently, many studies have been carried out to investigate the clinicopathological significance of E-cadherin expression in thyroid cancer. However, the results remained inconsistent. In the present study, we performed a meta-analysis to evaluate the associations of E-cadherin expression with susceptibility and clinicopathological characteristics of thyroid cancer.

Methods: Eligible studies were searched from Medicine, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The strength of associations between E-cadherin expression and susceptibility and clinicopathological features of thyroid cancer were assessed by pooled odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Forty-six studies with 1700 controls and 2298 thyroid cancer patients were included for this meta-analysis. Pooled results indicated that E-cadherin expression was significantly associated with susceptibility of papillary cancer and follicular cancer (papillary cancer, ORs = 14.31, 95% CIs = 3.42–59.90; follicular cancer, ORs = 10.14, 95% CI = 4.52–22.75). Significant association between E-cadherin expression and thyroid cancer risk was also observed in the subgroup analysis based on control group (normal thyroid tissue, ORs = 28.28, 95% CI = 8.36–95.63; adjacent thyroid tissue, ORs = 8.83, 95% CI = 3.27–23.85; benign thyroid tissue, ORs = 43.96, 95% CI = 9.91–194.95). In addition, E-cadherin expression was significantly correlated with lymph node metastasis, differentiation, and tumor-node-metastasis (TNM) stage of thyroid cancer (lymph node metastasis, ORs = 3.21, 95% CI = 1.98–5.20; differentiation, ORs = 0.25, 95% CI = 0.07–0.82; TNM stage, ORs = 4.85, 95% CI = 2.86–8.25).

Conclusions: The present study showed that E-cadherin expression was significantly associated with susceptibility and clinicopathological characteristics of thyroid cancer, which suggested that E-cadherin expression might be a potential predictive factor for clinical progression of thyroid cancer.

Abbreviations: ATT = adjacent thyroid tissue, BTT = benign thyroid tissue, CI = confidence interval, CTT = control thyroid tissue, DTC = differentiated thyroid cancer, FC = follicular carcinoma tissue, FCT = follicular carcinoma tissue, FDA = Food and Drug Administration, FTC = follicular thyroid cancer, IHC = immunohistochemistry, NOS = Newcastle–Ottawa scale, NR = not reported, NTT = normal thyroid tissue, PC = papillary carcinoma tissue, PCT = papillary carcinoma tissue, OR = odds ratio, PTC = papillary thyroid cancer, TA = thyroid adenoma, TCT = thyroid carcinoma tissue, TNM = tumor-node-metastasis.

Keywords: E-cadherin, expression, meta-analysis, thyroid cancer

1. Introduction

Thyroid carcinoma is the most common endocrine malignancy, and accounts for approximately 1% of human cancers.[1] In the past few years, the incidence of thyroid cancer has tripled.[2] Thyroid malignancies were classified into papillary thyroid cancer (PTC), poorly differentiated thyroid cancer, follicular thyroid cancer (FTC), and anaplastic thyroid cancer. Most thyroid cancer patients were PTC and FTC, which were classified as differentiated thyroid cancer (DTC).[3] In the treatment of DTC, conventional therapies such as surgery, radioactive iodine, thyroid hormone therapy, and chemotherapy, were commonly used. However, some of these therapeutic options were harmful for the human body.[4] Therefore, many studies have been carried out to explore the molecular pathogenesis mechanism of thyroid cancer, and establish relevant targeted therapies. It has been reported that epigenetic factors, genetic factors, age, gender, radiation exposure, geographical region, and histological type increased the susceptibility of thyroid cancer.[5] Many genetic alterations have been identified and played fundamental role in the tumorigenesis of thyroid cancer. A prominent example was that T1799A mutation of BRAF gene was found in 45% of PTC, which leaded to the expression of $BRAF^{V600E}$ protein and caused the activation of serine/threonine kinase.[6] And rare mutations of BRAE gene were also detected in some thyroid cancer patients.

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$BRAF^{V600E}$ protein maintained the growth of thyroid tumor cells, which was demonstrated in xenograft tumor model.[7,8] The results of clinical studies showed V600E mutation of BRAF gene was significantly associated with clinicopathological outcomes of PTC, which was demonstrated in a large meta-analysis.[9,10] Second in prevalence to BRAF mutations of thyroid cancer was RAS mutation, which caused the inactivation of GTPase. When RAS was bounded to GTP, the complex leaded to the hydrolysis of GTP and converted GTP into GDP. Published studies have found RAS activated the signal pathway of PI3K–AKT in thyroid cancer, and had significant associations with AKT phosphorylation.[11,12] Mutations of PTEN and AKT gene were common genetic alterations of PI3K–AKT signal pathway, and were often observed in thyroid tumorigenesis.[13,14] In addition, other genes such as: β-catenin (CTNNB1), epidermal growth factor receptor, isocitrate dehydrogenase 1, TP53, and anaplastic lymphoma kinase were also detected in the studies of thyroid carcinoma.[15–19] These genes mostly were involved in PI3K–AKT signaling pathway, NF-κB signaling pathway, RASSF1–MST1–FOXO3 signaling pathway, WNT–β-catenin signaling pathway, and HIF1α pathway, which revealed dysregulation of proliferation, apoptosis, and metabolism of thyroid tumor cells. In recent years, in order to clarify molecular mechanism of thyroid cancer and develop molecular targeted therapies, many studies have focused on the epigenetics modifications of thyroid cancer. Promoter hypermethylation of PTEN gene was found in about 50% papillary carcinomas and almost 100% of follicular carcinomas, which suggested that it was complicated in the thyroid tumorigenesis.[20] In addition, aberrant methylation of TIMP3, DAPK, RARβ2, and SLC5A8 were correlated with extrathyroidal invasion, tumor stage, and lymph node metastasis of thyroid neoplasms.[21] In addition to aberrant gene methylation, some studies have found aberrant pattern of histone modifications was associated with the clinical progression of thyroid cancer. For instance, EZH2 and SMYD3 were overexpressed in the tissue of thyroid cancer, and EZH2 could lead to trimethylation of histone H3 lysine 27.[22] In the meantime, histone methyltransferase encoding by SMYD3, was involved in the growth of cancer cells and was correlated with metastasis of cancer cells.[23] Although no structural mutations were detected in these genes, the levels of the genes expression have changed. In the past few years, many studies were carried out to explore the association between relevant gene expression and hallmarks of thyroid cancer. However, no effective biomarkers were observed and used in the early diagnosis and treatment of thyroid cancer.

E-cadherin protein, a single-pass transmembrane glycoprotein, was transcribed from CDH1 gene and was responsible for the adhesion of epithelial cells.[24] Calcium binded to the interdomain junctions such as: DXD, DXNDNAPXF, DRE, and further rigidified the ectodomain of E-cadherin protein, which stabilized the proteins and allowed its proper localization.[25] In recent years, many literatures have developed the notion that E-cadherin played an important role in the invasion and metastasis of tumor cells.[26,27] From study of breast cancer, scientists have found expression of E-cadherin protein in breast cancer tissues with metastases was higher than their primary counterparts.[28] Furthermore, the repression of E-cadherin protein was also observed in metastatic cells of prostate cancer when these cancer cells colonized another site.[29] Several studies have found that E-cadherin protein was involved in the invasion and metastasis of thyroid cancer, and the associations have been investigated in some published literatures. However, these results were still inconsistent. Thus, we performed this meta-analysis to explore the effect of E-cadherin protein in the clinical progression of thyroid cancer.

2. Materials and methods

2.1. Literature searching

In order to acquire available information from eligible literatures, we carried out a comprehensive electronic search on PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wanfang database on the basis of PRISMA guideline.[30] The following searching strategy was used: ("E-cadherin" or "CDH1" or "ECAD") and ("Thyroid cancer" or "Thyroid carcinoma" or "thyroid adenocarcinoma"). In addition, other search terms were also used such as: "prognosis," "survival," "outcome," "susceptibility," "risk," and "prognostic." The references of included studies and relevant review were scanned to identify additional eligible studies. The literature searching ended on August 20, 2018. Two investigators independently searched eligible studies, and relevant divergences were resolved by discussion with the 2 researchers.

2.2. Inclusion and exclusion criteria

In the present study, the included studies should meet the following inclusion criteria: relevant pathologically diagnosis was used in thyroid cancer patients; E-cadherin expression levels were detected in tissues with immunohistochemistry (IHC); cases or controls should divided into 2 groups according to E-cadherin expression level; enough data was provided to calculate odds ratios (ORs) and 95% confidence intervals (CIs); and literatures were written with English or Chinese language. Exclusion criteria were used to eliminate irrelevant studies: reviews, meta-analysis, or letters; conference abstracts; samples were not human tissues; and relevant data could not be extracted with fuzzy description.

2.3. Data extraction and quality assessment

All relevant data were extracted by 2 researchers independently, and the 2 investigators reached a consensus by discussion. The following information was extracted from eligible studies: first author, study location, ethnicity, number of cases expressing E-cadherin, year of publication, tumor type, detection method of E-cadherin expression, Newcastle–Ottawa scale (NOS) score, cutoff value, and clinical features of thyroid tumor. The methodological quality of included studies was assessed with NOS.[31] NOS scores were calculated from 3 parts: selection, comparability, and exposure of thyroid cancer patients. In addition, studies of ≥6 scores were considered as high quality.[32]

2.4. Statistical methods

Stata software (version 14.0; Stata Corporation, College Station, TX) was used to all statistical analysis. To determine whether E-cadherin expression was associated with clinical features of thyroid cancer, ORs and 95% CI were calculated for quantitative assessment of associations between E-cadherin expression and thyroid cancer.[33] Cochran's Q and I^2 statistics were applied to evaluate the heterogeneity among eligible studies, and $I^2 > 50\%$ or $P < .05$ were considered as a sign of significant heterogeneity.[34,35] If significant heterogeneity was found, the random-effect model was used, otherwise the fixed-effect model was

chosen to calculate the pooled results.[36,37] In addition, subgroup analysis and meta-regression were conducted to explore the source of heterogeneity and obtained a more accurate result. The publication bias was assessed using Begg test and Egger test.[38] Finally, in order to observe the effect of each study in the overall pooled results, sensitivity analysis was performed. $P \leq .05$ was considered as statistically significant differences Table 1.

3. Results

3.1. Study characteristics

In the present study, a total of 890 literatures were initially retrieved, then duplicates (n = 694) were eliminated. In the remaining articles, 5 articles were reviews and 1 article was meta-analysis. After removing reviews and meta-analysis, 190 literatures were obtained. These obtained articles were screened by reading titles and abstracts, and we acquired 113 studies. In order to further get available articles, the full-text of literatures were read and 67 studies did not have enough data or were not related with E-cadherin expression and thyroid cancer. Finally, 46 articles were included for the meta-analysis.[39–84] Thirty-two case–control studies were included for the analysis of correlation between E-cadherin expression and susceptibility of thyroid cancer. And 15 literatures were included to investigate the role of E-cadherin expression in the tumor-node-metastasis (TNM) stage (n = 17), lymph node metastasis (n = 30), differentiation (n = 2), T-stage (n = 4), distant metastasis (n = 5), and capsular invasion (n = 5) of thyroid cancer. IHC was applied to detect the E-cadherin expression level in all eligible studies. It was worth mentioning that the cutoff definitions were different, and therefore cutoff values were different in the eligible studies (Fig. 1, Tables 2 and 3).

4. Results of meta-analysis

The pooled results showed that E-cadherin negative expression was significantly associated with increased risk of thyroid cancer in different control sample types (normal thyroid tissue, ORs = 28.28, 95% CI = 8.36–95.63; adjacent thyroid tissue, ORs = 8.83, 95% CI = 3.27–23.85; benign thyroid tissue, ORs = 43.96, 95% CI = 9.91–194.95). Subgroup analysis based on thyroid tumor subtypes revealed that E-cadherin negative expression significantly increased the risk of papillary cancer and follicular cancer (papillary cancer, ORs = 14.31, 95% CIs = 3.42–59.90; follicular cancer, ORs = 10.14, 95% CI = 4.52–22.75). Significant heterogeneity among studies was found in the analysis for the susceptibility of thyroid cancer, thus the random effects model was used. Furthermore, significant associations of E-cadherin

Table 1

Main characteristics of the included studies for the analysis of thyroid cancer risk.

References	Design	Time	Country	Ethnicity	Method	Control	E-cadherin +	E-cadherin −	Case	E-cadherin +	E-cadherin −	Cutoff value
[39]	Case–control	2018	China	Asians	IHC	ATT	117	0	TCT	48	69	10%
[40]	Case–control	2017	China	Asians	IHC	ATT	43	9	TCT	21	31	5%
[41]	Case–control	2017	China	Asians	IHC	ATT	15	0	TCT	11	39	10%
[42]	Case–control	2017	China	Asians	IHC	BTT	20	3	TCT	32	94	50%
[43]	Case–control	2016	China	Asians	IHC	ATT	50	11	TCT	25	36	5%
[44]	Case–control	2016	China	Asians	IHC	BTT	70	0	PCT	16	128	50%
[45]	Case–control	2016	Russian	Caucasians	IHC	TA	13	0	PCT	29	0	0%
[46]	Case–control	2016	Greece	Caucasians	IHC	BTT	15	0	TCT	0	20	NR
[47]	Case–control	2015	China	Asians	IHC	ATT	10	0	PCT	14	29	10%
[48]	Case–control	2014	China	Asians	IHC	TA	65	15	FCT	12	28	25%
[49]	Case–control	2014	China	Asians	IHC	ATT	51	5	PCT	29	27	5%
[50]	Case–control	2013	USA	Caucasians	IHC	NTT	10	0	TCT	88	7	1%
[51]	Case–control	2012	China	Asians	IHC	ATT	10	2	TCT	31	34	25%
[52]	Case–control	2013	China	Asians	IHC	ATT	2	42	PCT	35	9	5%
[53]	Case–control	2013	China	Asians	IHC	ATT	22	2	PCT	21	35	0%
[54]	Case–control	2012	China	Asians	IHC	ATT	81	0	PCT	35	46	0%
[55]	Case–control	2012	China	Asians	IH	TA	17	3	PCT	11	53	50%
[56]	Case–control	2012	Latvia	Caucasians	IHC	TA	16	14	PCT	2	23	NR
[57]	Case–control	2011	China	Asians	IHC	BTT	8	2	PCT	40	196	25%
[58]	Case–control	2011	China	Asians	IHC	ATT	150	15	PCT	67	98	10%
[59]	Case–control	2011	India	Asians	IHC	BTT	11	1	TCT	66	2	0 score
[60]	Case–control	2010	Latvia	Caucasians	IHC	ATT	18	37	TCT	35	27	NR
[61]	Case–control	2010	Greece	Caucasians	IHC	BTT	30	0	PCT	5	78	NR
[62]	Case–control	2009	China	Asians	IHC	TA	34	14	TCT	33	38	5%
[63]	Case–control	2008	China	Asians	IHC	BTT	15	0	TCT	9	23	0%
[64]	Case–control	2007	China	Asians	IHC	ATT	43	14	TCT	17	40	10%
[65]	Case–control	2007	Greece	Caucasians	IHC	ATT	20	0	TCT	39	16	0%
[66]	Case–control	2005	China	Asians	IHC	ATT	20	0	TCT	31	19	10%
[67]	Case–control	2004	China	Asians	IHC	ATT	43	2	TCT	36	35	10%
[68]	Case–control	2002	Japan	Asians	IHC	TA	9	1	FCT	14	6	30%
[69]	Case–control	2002	China	Asians	IHC	NTT	9	1	TCT	17	39	0%
[70]	Case–control	2001	Japan	Asians	IHC	NTT	60	0	TCT	47	17	10%
[71]	Case–control	2000	China	Asians	IHC	NTT	10	0	PCT	9	31	50%

ATT = adjacent thyroid tissue, BTT = benign thyroid tissue, FCT = follicular carcinoma tissue, IHC = immunohistochemistry, NR = not reported, NTT = normal thyroid tissue, PCT = papillary carcinoma tissue, TA = thyroid adenoma, TCT = thyroid carcinoma tissue.

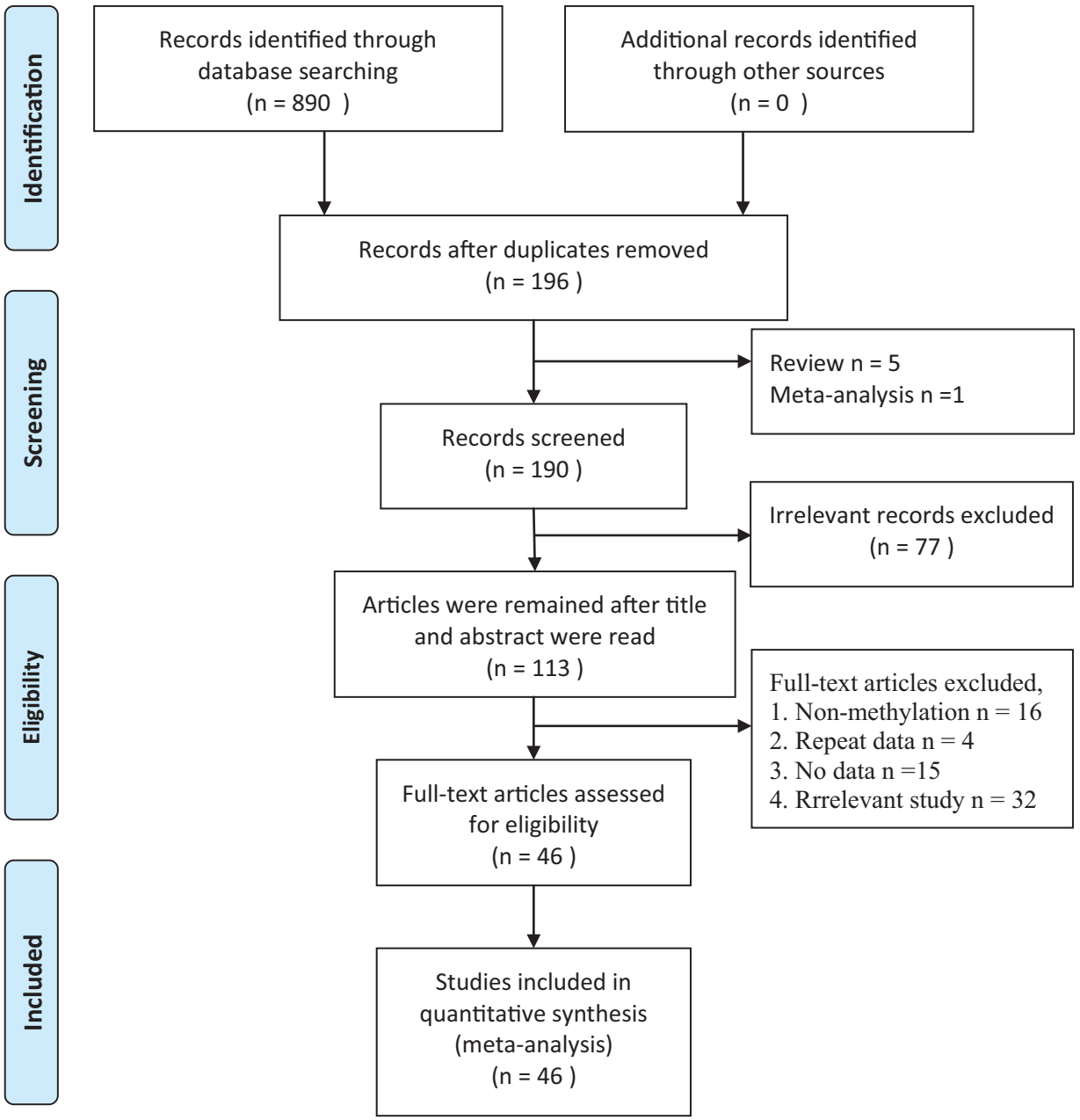

Figure 1. Flow diagram of searching eligible studies.

expression with lymph node metastasis, differentiation, and TNM stage of thyroid cancer were detected (lymph node metastasis, ORs = 3.21, 95% CI = 1.98–5.20; differentiation, ORs = 0.25, 95% CI = 0.07–0.82; TNM stage, ORs = 4.85, 95% CI = 2.86–8.25). In addition to differentiation of thyroid cancer, significant heterogeneity was observed in the analysis of lymph node metastasis and TNM stage of thyroid cancer, and the fixed effect model was applied. According to the results of meta-regression, publication year and race was not the main source of heterogeneity among included studies ($P > .05$) (Figs. 2–6, Table 3). In order to investigate the role of cutoff values in the heterogeneity among studies which evaluated the risk of thyroid cancer, we calculated the *P* value of different cutoff values in the meta-regression analysis. The results indicated that 5% cutoff values contributed to a significant heterogeneity ($P = .017 < .05$).

4.1. Publication bias and sensitivity analysis

In the overall analysis of exploring the effect of E-cadherin expression in the susceptibility of papillary cancer, significant publication bias was detected in Begg test. However, subgroup analysis based on ethnicity suggested that no significant publication bias was found in Caucasians and Asians. No significant publication bias was found in other analysis. In addition, the results of sensitivity analysis revealed that the pooled overall result was stable by eliminating each individual study (Figs. 2–6).

Table 2

Characteristics of included studies for the analysis of clinical characteristics of thyroid cancer.

References	Time	Country	Ethnicity	Method	Histology	E-cadherin +	E-cadherin −	E-cadherin +	E-cadherin −	Cutoff value
Lymph node metastasis				N0		N1–N2				
[39]	2018	China	Asians	IHC	PC	36	27	12	42	10%
[40]	2017	China	Asians	IHC	TC	18	26	7	1	5%
[41]	2017	China	Asians	IHC	TC	10	18	1	21	10%
[42]	2017	China	Asians	IHC	TC	26	58	6	36	50%
[43]	2016	China	Asians	IHC	TC	24	27	1	9	5%
[72]	2016	China	Asians	IHC	PC	33	28	17	35	30%
[73]	2016	China	Asians	IHC	PC	15	8	9	22	NR
[74]	2015	China	Asians	IHC	PC	19	20	39	13	10%
[47]	2015	China	Asians	IHC	PC	11	13	3	16	10%
[75]	2014	Japan	Asians	IHC	TC	27	9	46	11	10%
[76]	2014	Korea	Asians	IHC	PC	68	5	67	8	NR
[49]	2014	China	Asians	IHC	PC	27	18	2	9	5%
[53]	2013	China	Asians	IHC	PC	12	9	9	26	0%
[51]	2012	China	Asians	IHC	TC	22	27	1	7	25%
[52]	2013	China	Asians	IHC	PC	21	11	3	9	5%
[54]	2012	China	Asians	IHC	PC	22	10	13	36	0%
[77]	2012	China	Asians	IHC	FC	20	11	3	8	10%
[55]	2012	China	Asians	IHC	PC	8	17	3	36	50%
[57]	2011	China	Asians	IHC	PC	4	42	39	151	25%
[58]	2011	China	Asians	IHC	PC	62	40	5	58	10%
[78]	2011	China	Asians	IHC	PC	9	8	2	17	33%
[66]	2005	China	Asians	IHC	TC	28	4	3	15	10%
[79]	2004	China	Asians	IHC	PC	4	15	8	9	5%
[80]	2002	Turkey	Caucasians	IHC	PC	23	4	10	4	40%
[81]	2002	China	Asians	IHC	TC	11	15	13	9	90%
[69]	2002	China	Asians	IHC	TC	11	10	6	29	0%
[70]	2001	Japan	Asians	IHC	TC	10	0	22	8	10%
[82]	2001	China	Asians	IHC	PC	21	6	3	28	5%
[83]	2001	China	Asians	IHC	PC	23	18	8	21	10%
[71]	2000	China	Asians	IHC	PC	8	15	1	16	50%
TNM stage					I–II	III–IV				
[39]	2018	China	Asians	IHC	PC	38	21	10	48	10%
[40]	2017	China	Asians	IHC	TC	14	34	0	4	5%
[41]	2017	China	Asians	IHC	TC	10	21	1	18	10%
[43]	2016	China	Asians	IHC	TC	25	31	0	5	5%
[72]	2016	China	Asians	IHC	PC	37	34	13	29	30%
[47]	2015	China	Asians	IHC	PC	12	13	2	16	10%
[75]	2014	Japan	Asians	IHC	TC	29	11	44	9	10%
[49]	2014	China	Asians	IHC	PC	25	16	4	11	5%
[53]	2013	China	Asians	IHC	PC	16	11	5	24	0%
[51]	2012	China	Asians	IHC	TC	22	29	1	5	25%
[54]	2012	China	Asians	IHC	PC	25	7	10	39	0%
[55]	2012	China	Asians	IHC	PC	9	25	2	28	50%
[58]	2011	China	Asians	IHC	PC	64	58	3	40	10%
[78]	2011	China	Asians	IHC	PC	10	20	1	5	33%
[66]	2005	China	Asians	IHC	TC	29	8	2	11	10%
[80]	2002	Turkey	Caucasians	IHC	PC	9	2	24	6	40%
[83]	2001	China	Asians	IHC	PC	28	27	3	12	10%
Differentiation				Poor	Well					
[84]	2002	China	Asians	IHC	FC	4	16	10	12	NR
[70]	2001	Japan	Asians	IHC	TC	1	2	41	9	10%

FC = follicular carcinoma tissue, IHC = immunohistochemistry, NR = not reported, PC = papillary carcinoma tissue, TC = thyroid carcinoma tissue.

5. Discussion

In addition to conventional therapeutic methods, some molecular-targeted agents have been developed which inhibited tyrosine kinases receptors. Tyrosine kinase was involved in the proliferation and tumorous differentiation of thyroid cancer cells, and these tyrosine kinases inhibitors could block tyrosine kinases receptors and repress the growth and angiogenesis of thyroid cancer.[85] Cabozantinib, lenvatinib, sorafenib, and vandetanib were approved by the European Medical Agency and Food and Drug Administration (FDA) to treat advanced intolerance of differentiated thyroid carcinoma (RAI-R) and medullary thyroid carcinoma.[86] These agents were developed according to different biological targets, and influenced the function of relevant protein or signal pathway. Moreover, some studies were conducted to develop relevant targeted agents such as: axitinib, bevacizumab, imatinib, motesanib, nintedanib, pazo-

Table 3

Main results of association between E-cadherin expression and clinical parameters of thyroid cancer.

Clinical parameter	No. of patients	Chi-squared test					Heterogeneity	Begg test	Egger test
		OR	95%CI	Z-value	*P*	I^2	*P*	*P*	*P*
Risk (NTT vs. TCT)	326	28.28	8.36–95.63	5.38	.00	0.06	.37	1.00	.62
Risk (ATT vs. TCT)	1085	8.83	3.27–23.85	4.29	.00	0.90	.00	.42	.35
Risk (BTT vs. TCT)	858	43.96	9.91–194.95	4.98	.00	0.73	.00	.06	.59
Overall risk (CTT vs. PTC)	1123	14.31	3.42–59.90	3.64	.00	0.87	.00	.00	.89
Risk (CTT vs. PTC) in Caucasians	314	63.41	7.58–530.27	3.83	.00	0.73	.01	.17	.50
Risk (CTT vs. PTC) in Asians	809	7.61	1.29–44.75	2.24	.03	0.89	.00	.18	.95
Overall Risk (CTT vs. FTC)	253	10.14	4.52–22.75	5.62	.00	0.48	.09	.35	.59
Risk (CTT vs. FTC) in Asians	196	8.62	3.73–19.95	5.03	.00	0.40	.15	.62	.44
Lymph node metastasis (N0 vs. N1–N2)	2224	3.21	1.98–5.20	4.73	.00	0.76	.00	.17	.89
Distant metastasis (M0 vs. M1–M2)	291	1.11	0.48–2.54	0.24	.81	0.00	.98	.62	.14
Differentiation (poor vs. well)	95	0.25	0.07–0.82	2.27	.02	0.00	.49	.32	–
Capsular invasion (no vs. yes)	602	3.63	0.60–22.00	1.40	.16	0.91	.00	.33	.41
T stage (T1–T2 vs. T3–T4)	223	0.89	0.47–1.68	0.37	.71	0.00	.76	.50	.13
TNM stage (I–II vs. III–IV)	1205	4.85	2.86–8.25	5.84	.00	0.56	.00	.46	.14

ATT = Adjacent thyroid tissue, BTT = benign thyroid tissue, CTT = control thyroid tissue, FTC = follicular thyroid cancer, NTT = normal thyroid tissue, TCT = thyroid carcinoma tissue, TNM = tumor-node-metastasis.

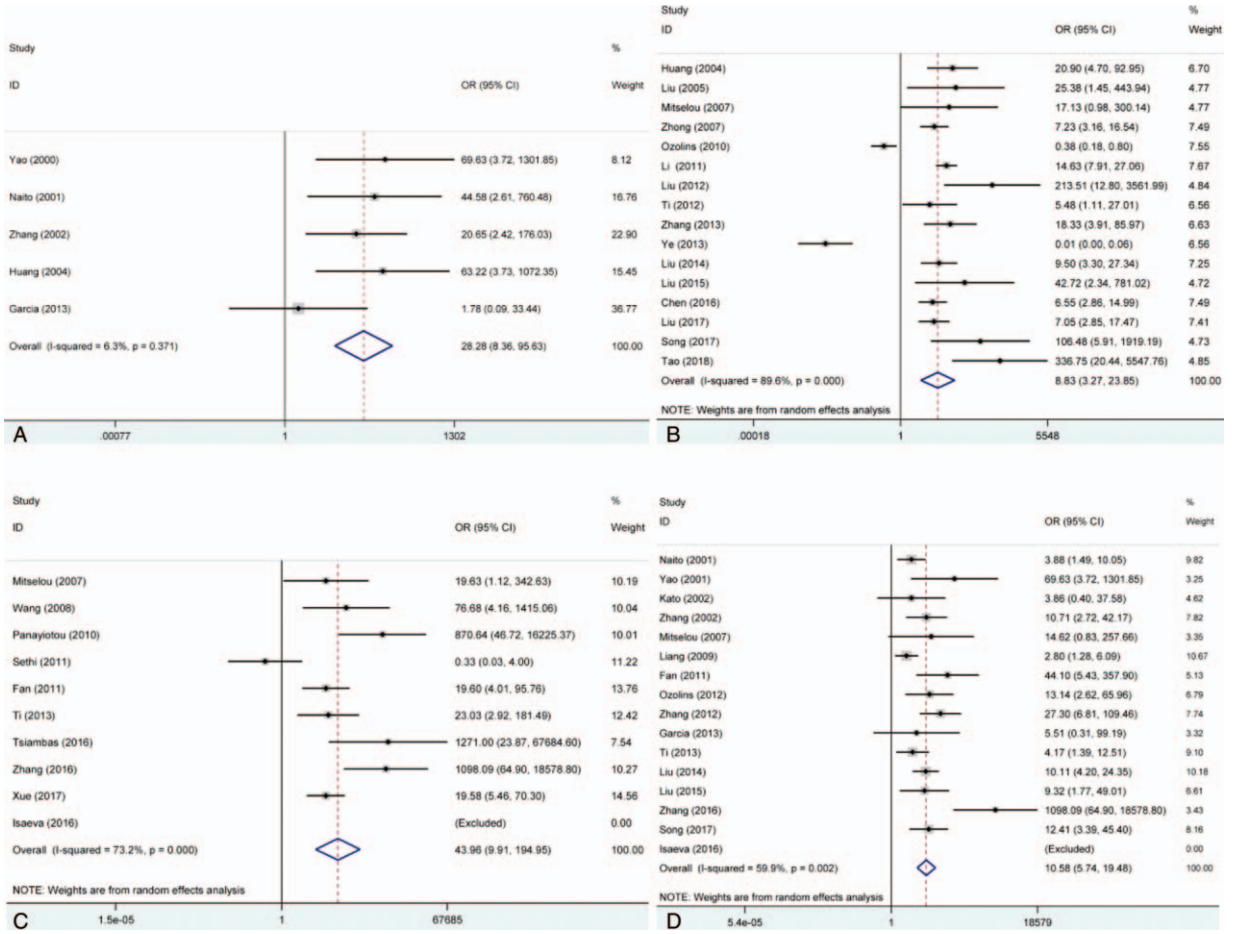

Figure 2. Forest plot of the association between E-cadherin expression and risk of thyroid cancer. (A) Normal thyroid tissue vs. thyroid cancer tissue; (B) adjacent thyroid tissue vs. thyroid cancer tissue; (C) benign thyroid tissue vs. thyroid cancer tissue; and (D) thyroid adenoma tissue vs. thyroid cancer. CI = confidence intervals, OR = odds ratios.

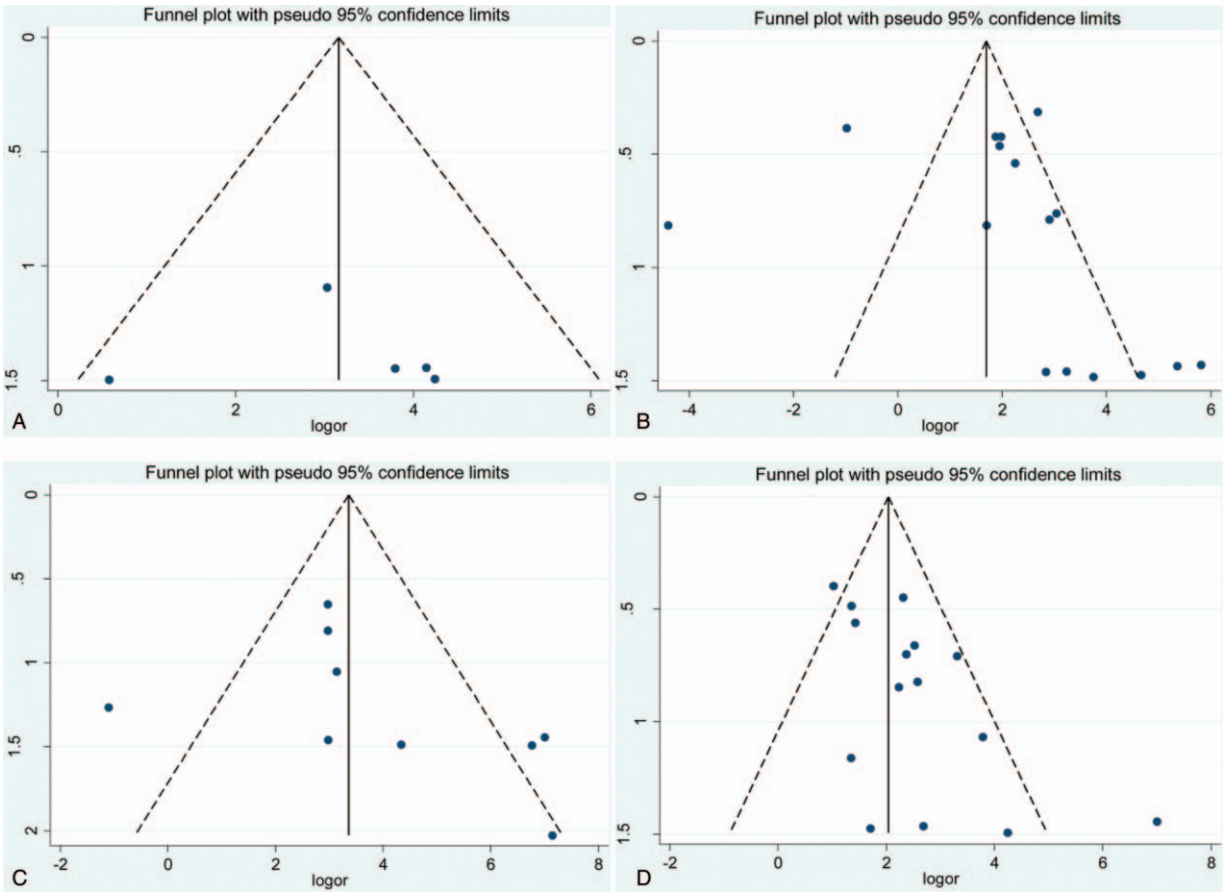

Figure 3. Funnel plot of association between E-cadherin expression and risk of thyroid cancer. (A) Normal thyroid tissue vs. thyroid cancer tissue; (B) adjacent thyroid tissue vs. thyroid cancer tissue; (C) benign thyroid tissue vs. thyroid cancer tissue; and (D) thyroid adenoma tissue vs. thyroid cancer.

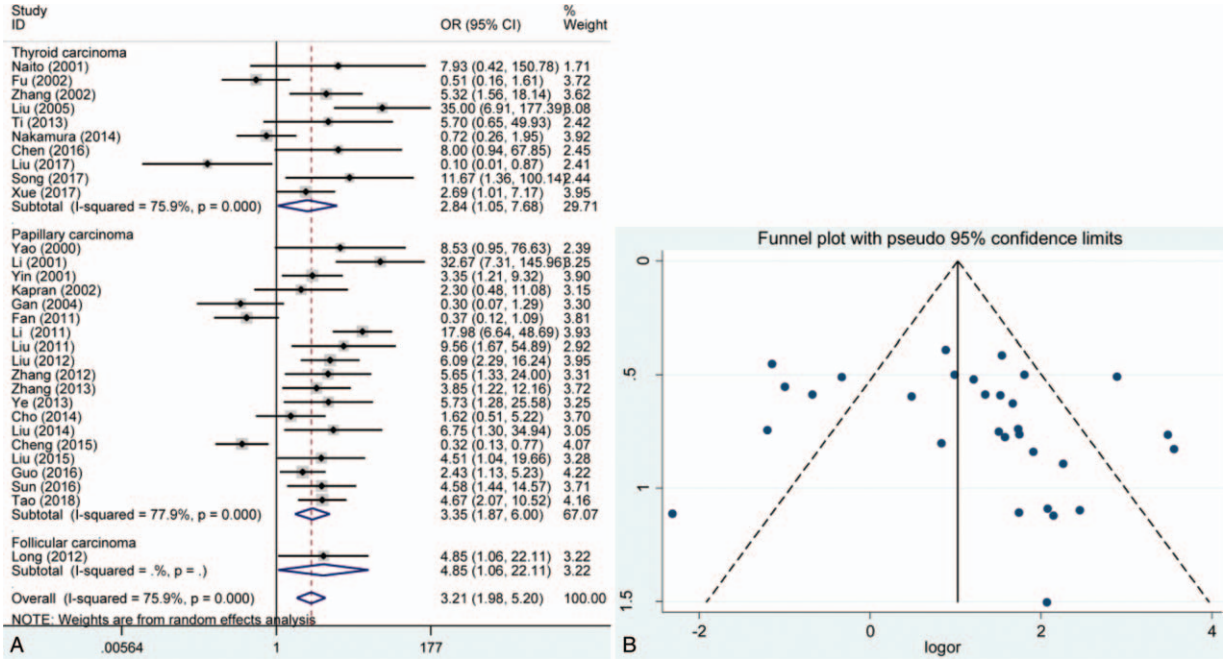

Figure 4. Meta-analysis of the effect of E-cadherin expression in lymph node metastasis of thyroid cancer patients. (A) Forest plot and (B) funnel plot. CI = confidence intervals, OR = odds ratios.

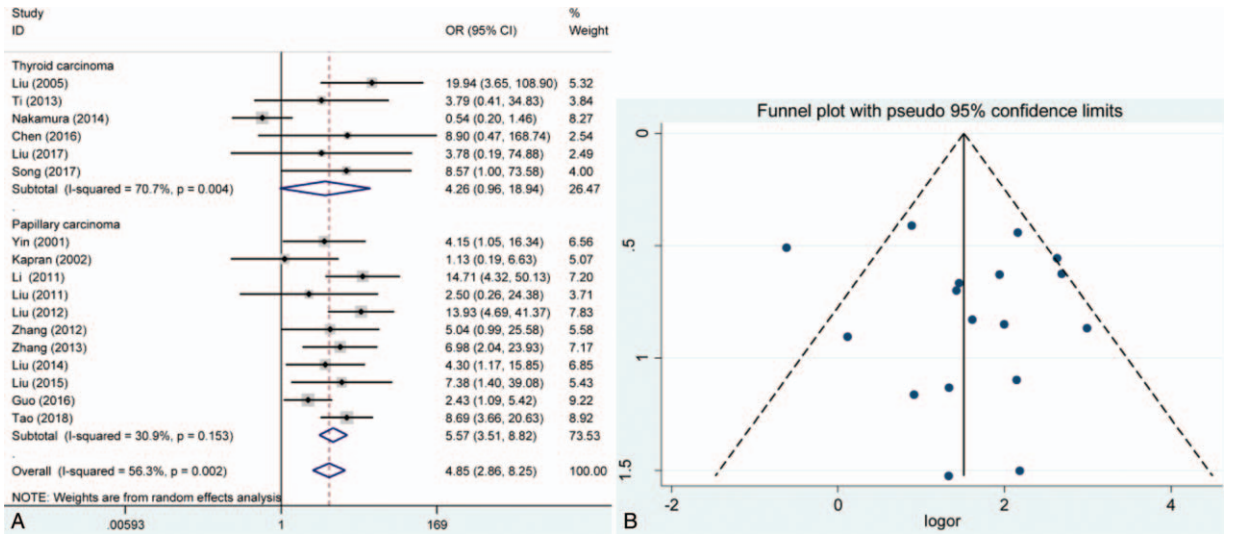

Figure 5. Meta-analysis of the effect of E-cadherin expression in tumor-node-metastasis stage of thyroid cancer patients. (A) Forest plot; (B) funnel plot. CI = confidence intervals, OR = odds ratios.

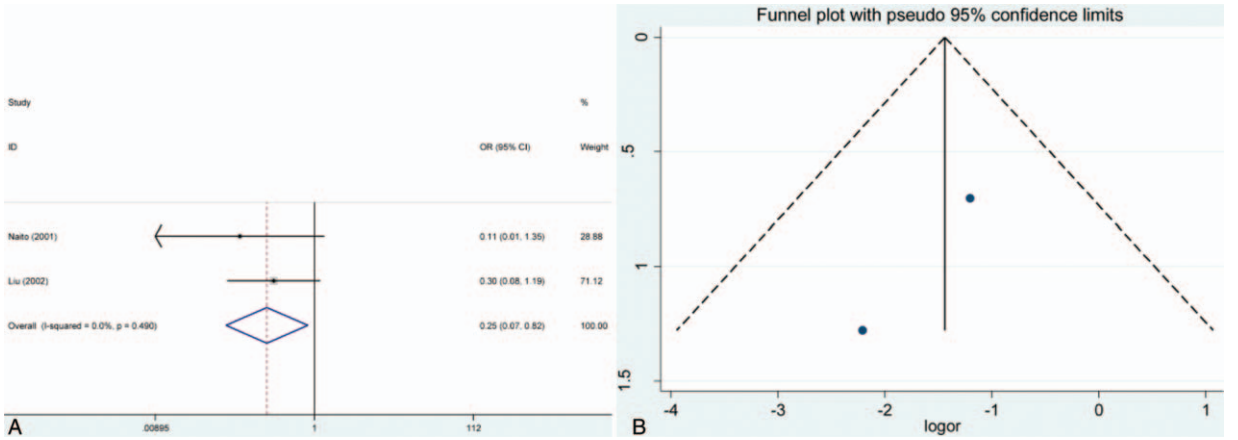

Figure 6. Meta-analysis of the effect of E-cadherin expression in differentiation of thyroid cancer patients. (A) Forest plot; (B) funnel plot. CI = confidence intervals, OR = odds ratios.

panib, ponatinib, selumetinib, sunitinib, vemurafenib, everolimus, and temsirolimus. The molecular targets of these drugs included dual PI3K/mTOR, MET, RET-KIF5B rearrangement, Bcr-Abl, RET-KIF5B, CCDC6-RET, NcoA4-RET rearrangement, FLT3, KIT, MEK, Raf, BRAFV600E, and CRAF.[2] From published clinical study, aberrant signaling pathways were involved in the progression and invasiveness of thyroid cancer. Mutations in BRAF gene and RAS gene and rearrangement of the RET proto-oncogene were common in thyroid cancer.[87] In fact, these genes mutations were also significantly associated with reduced expression of some genes. For example, the BRAF V600E mutation was related with the low expression of iodine-metabolism genes.[88] The lower expression of NIS was observed in Ki-ras-transformed rat thyroid cells.[89] In addition, several lines of evidence demonstrated that epigenetics was complicated in the thyroid tumorigenesis. Some findings have found the promoter hypermethylation and silencing of TSHR gene in thyroid cancer.[90] A large meta-analysis has found that methylation of CDH1 gene was significantly associated with risk of thyroid cancer, which might change the level of E-cadherin protein expression in thyroid cancer.[91] Therefore, clarifying the levels of E-cadherin protein expression in different stage of thyroid cancer was important for the diagnosis and treatment of thyroid carcinoma.

In this meta-analysis, a systematic review and pooled analysis was performed and the result suggested that E-cadherin negative expression had a worse impact on the susceptibility of thyroid cancer. The type of control group of eligible studies included thyroid adenoma, adjacent thyroid tissue, normal thyroid tissue, and benign thyroid tissue. Subgroup analysis was carried out according to these control groups, and significant association between E-cadherin expression and risk of thyroid cancer was still observed. The results of Begg test and Egger test did not show significant publication bias, and sensitivity analysis indicated that the overall OR was stable. However, significant heterogeneity among studies was observed. Subgroup analysis based on

ethnicity suggested that Caucasians and Asians were not the main source of heterogeneity. In order to explore the influence of E-cadherin expression in papillary carcinoma and follicular carcinoma, we conducted stratified analysis according to type of thyroid carcinoma. The results indicated that E-cadherin negative expression was a risk factor for susceptibility of thyroid cancer. The similar results were also found in breast cancer and colorectal cancer.[92,93] However, the significant heterogeneity was still detected, which indicated that some factors might cause the heterogeneity and affect the accuracy of results. The results of meta-regression showed ethnicity and publication year other than cutoff value were not the main source. Thus, relevant unified evaluation criterion of IHC should be established and applied in the future studies.

Additionally, it was found that E-cadherin negative expression significantly correlated with lymph node metastasis, differentiation, and TNM stage of thyroid cancer. The forest plot revealed that these results of included studies were inconsistent, and negative results and positive results could be found in the forest plot. As mentioned above, E-cadherin could promote the cell adhesion, and the loss of E-cadherin might lead to the tumor metastasis and invasion of cancer cells which was consistent with the results of the meta-analysis. Interestingly, we did not find that E-cadherin expression was associated with capsular invasion of thyroid cancer. However, 2 included studies still found E-cadherin negative expression had a significant association with capsular invasion of thyroid cancer,[20,44] while 1 included study obtained opposite result.[19] Considering only 5 studies were included for the analysis of association of capsular invasion of thyroid cancer with E-cadherin expression, the result might be taken into consideration carefully. Furthermore, E-cadherin negative expression significantly repressed differentiation of cancer cells according to the pooled results. As we all know, cells with lower differentiation were more likely to transform into cancer cells and metastasize other sites. Thus, E-cadherin positive expression might prevent normal cells from transformation of cancer cells. Unexpectedly, E-cadherin expression did not have a significant association with distant metastasis of thyroid cancer. After reading the eligible studies, all included 5 studies have found that there was no significant association between E-cadherin expression and distant metastasis of thyroid cancer. One conventional theory was that distant metastasis originated from lymph node metastasis, but a study which was published on Science journal has observed that independent subclones resulted in lymphatic and distant metastases in colorectal cancer.[94] In this published study, common variants in hypermutable DNA regions of 213 biopsy samples were used to reconstruct high-confidence phylogenetic trees, and 2 different lineage relationships between distant and lymphatic metastases were found. The results of our meta-analysis might reflect the similar phenomenon in thyroid cancer. Although significant heterogeneity was found in most studies, almost no obvious publication bias was observed, which revealed the overall results were stable and credible.

In the present study, some limitations should be noted. First, the significant heterogeneity might influence the accuracy of results. However, the main source of heterogeneity was not observed, so other studies with more clinical or therapeutic information should be conducted to acquire a more accurate result. Second, information of differentiation, TNM stage, T-stage, distant metastasis, capsular invasion, and hormone level of thyroid cancer patients were still insufficient. Third, most population of eligible studies were from Chinese, so the result might tend to be more accurate to Chinese population. Fourth, evaluation criterion of E-cadherin expression by IHC was not inconsistent, which might partly cause heterogeneity among eligible studies.

Conclusively, our meta-analysis first systematically investigated the associations of E-cadherin expression with susceptibility and clinical progression of thyroid carcinoma. According to the pooled data, we find that E-cadherin expression is significantly associated with susceptibility, lymph node metastasis, differentiation, and TNM stage of thyroid cancer. However, considering the limitation of the present study, more studies with large population, clinical information, multicenter design, and high quality should be carried out to confirm these findings.

Author contributions

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Investigation: Changlin Zhou, Chunsheng Yang.
Methodology: Changlin Zhou.
Software: Changlin Zhou.
Supervision: Daoqun Chong.
Visualization: Chunsheng Yang.
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