

Supplementary

Incidental thyroid carcinoma in surgery-treated hyperthyroid

patients with Graves' disease: a systematic review and meta-analysis of cohort studies

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Database information & Search Strategy

Electronic database was used in the literature searching, including EMBASE and PubMed. Last search was updated to January 23, 2018. The combination of the keywords was used as follow:

PubMed: (hyperthyroidism OR Graves OR autoimmune thyroid disease OR toxic diffuse goiter OR toxic and diffuse goiter with hyperthyroidism) AND (thyroid cancer OR thyroid carcinoma). The Medical Subject Heading (MeSH) was also used during search when available.

EMBASE:

1. hyperthyroidism/
2. Graves disease/
3. autoimmune thyroid disease.mp.
4. toxic diffuse goiter.mp.
5. (toxic and diffuse goiter with hyperthyroidism).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
6. thyroid cancer/
7. thyroid carcinoma/
8. 6 or 7
9. 1 or 2 or 3 or 4 or 5
10. 8 and 9

Table S1 Definition of hyperthyroidism, GD, Indication for surgery of included studies

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
Wahl (1982)	Not mentioned.	Not mentioned.	Hyperthyroidism patients undergo surgery.	Not available.
Ruggieri (1999)	Evaluation of T3, T4, FT3, FT4, TG, and TSH level. US, Tc 99 or 131I thyroid scanning were evaluated.	Not mentioned TPOAb, TgAb was evaluated.	Hyperthyroidism patients undergo surgery.	16: 66
Terzioglu (1993)	Clinical features and physical examination.	Not mentioned	Hyperthyroidism patients undergo surgery.	Not available.

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
Ocak S (2014)	Not mentioned.	Not mentioned	Hyperthyroidism patients undergo surgery.	25: 152
Linos (1997)	Not mentioned.	Not mentioned	Hyperthyroidism patients undergo surgery.	25: 375
Pradeep (2007)	Not mentioned.	Not mentioned	Hyperthyroidism patients undergo surgery. GD patients: 1) Relapse after ATD therapy 2) Persistent hyperthyroidism	93: 205

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
			<ul style="list-style-type: none"> 3) Large goiter (grades II and III) 4) Allergic reactions to thionamides 5) Drug noncompliance 6) Nodule 7) Eye disease (infiltrative ophthalmopathy) 8) Pregnancy current/planned 	

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
			For Toxic MNG& AFTN ptients: 1) Retrosternal extension 2) Compressive symptoms 3) Large goiter.	
Mittendorf (2001)	Evaluation of FT4, TSH level.	Not mentioned. Presence of ophthalmopathy was noted	1) Hyperthyroidism patients undergo surgery. 2) Massive thyroid enlargement with compression symptoms	9: 45

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
			3) A dominant nodule 4) Patient preference 5) Failure of radioiodine treatment 6) Concerns about radioiodine-induced aggravation of ophthalmopathy	
Dobyns (1974)	Not mentioned.	1) Diagnosed or treated at the first time at the clinic 2) Presence of eye signs	Not mentioned.	Not available.

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
Zanella (2001)	Evaluation of TT3, TT4, and TSH level. 131I thyroid scan and US evaluation.	Not mentioned	Patients with hyperthyroidism.	Not available.
Quérat (2015)	Not mentioned.	Not mentioned	1) Desire for pregnancy. 2) Carbimazole-induced agranulocytosis 3) Compressive signs 4) Suspect cytology 5) Ophthalmopathy	35: 165
Kunjumbame	Not mentioned.	Not mentioned	Patients with hyperthyroidism.	Not available.

Articles	Definition of hyperthyroidism	Definition of GD	Indication for thyroidectomy	Type of thyroidectomy (total: subtotal)
d (2015)			Exclusion: non-toxic goiter or Hashimoto's thyroiditis with thyroid cancer	

ABBREVIATION: ATD: antithyroid drug therapy; T3: triiodothyronine; T4: thyroxine; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; TG: thyroglobulin; TgAb: anti-thyroglobulin antibody; TPOAb: anti-peroxides antibody; US: ultrasonography.

Table S2 Histological classification of the included studies.

Articles	Histological definition of thyroid cancer	Histological classification
Wahl (1982)	Not mentioned.	Papillary carcinoma, Follicular carcinoma, Undifferentiated carcinoma
Ruggieri (1999)	Not mentioned.	Papillary carcinoma, Follicular carcinoma, Medullary carcinoma
Terzioglu (1993)	Not mentioned.	Papillary carcinoma, Follicular carcinoma
Ocak S (2014)	Not mentioned.	Papillary carcinoma, Follicular carcinoma
Linos (1997)	Not mentioned.	Papillary carcinoma, Follicular carcinoma, Medullary carcinoma
Pradeep (2007)	Not mentioned.	Papillary carcinoma, Follicular carcinoma, Medullary carcinoma
Mittendorf (2001)	Not mentioned.	Papillary carcinoma, Follicular carcinoma, incidental occult microscopic papillary carcinoma, incidental medullary carcinoma,

Articles	Histological definition of thyroid cancer	Histological classification
Dobyns (1974)	Not mentioned.	Follicular carcinoma, Papillary carcinoma, Mixed papillary carcinoma & Follicular carcinoma, Adenocarcinoma, Embryonal carcinoma, Carcinoma simplex, “Cancer”, Anaplastic carcinoma
Zanella (2001)	According to the standard approach published by Rosai and WHO classification.	Papillary carcinoma, Hürthle cell malignant lesion, Follicular thyroid carcinoma
Quérat (2015)	Not mentioned.	Papillary carcinoma
Kunjumbamed (2015)	Not mentioned.	Papillary carcinoma, Follicular variant of papillary thyroid cancer

Fig. S1 Subgroup analysis

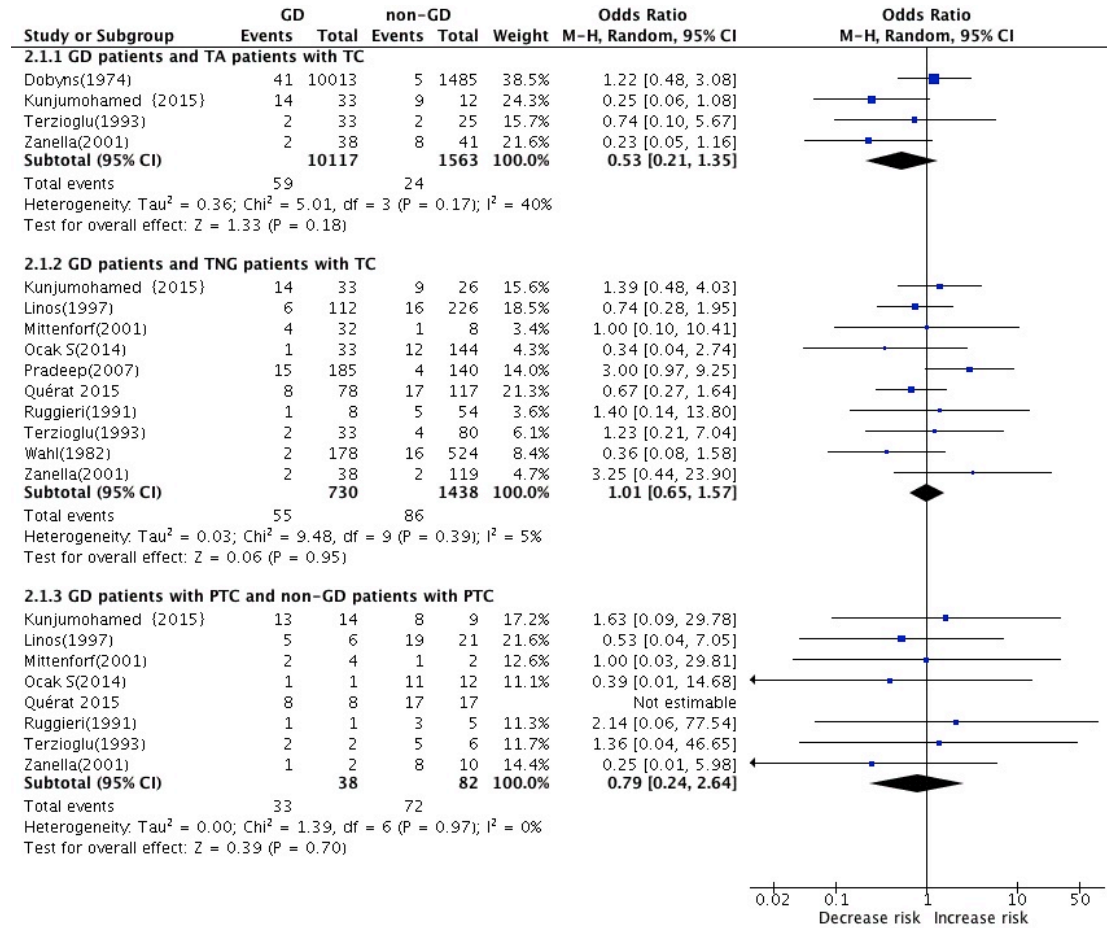
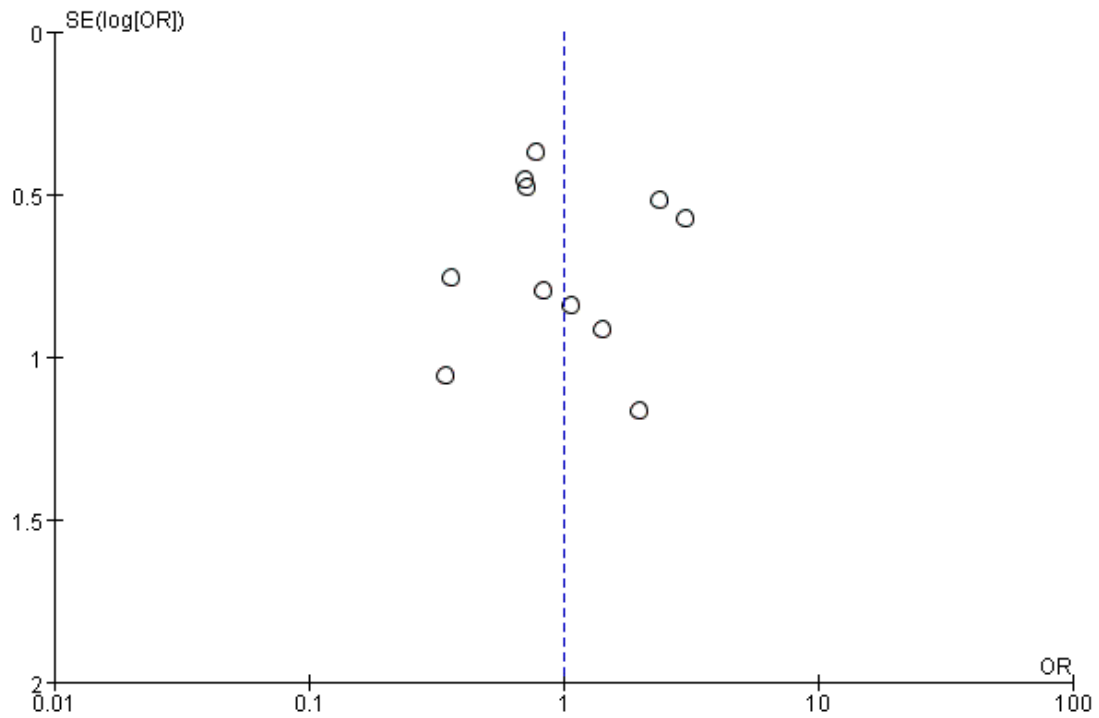


Fig. S2 Publication Bias

S2.1 Funnel plot



S2.2 Begg's test

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Begg's Test

adj. Kendall's Score (P-Q) =    13
  Std. Dev. of Score =    12.85
  Number of Studies =     11
           z =     1.01
  Pr > |z| =     0.312
           z =     0.93 (continuity corrected)
  Pr > |z| =     0.350 (continuity corrected)

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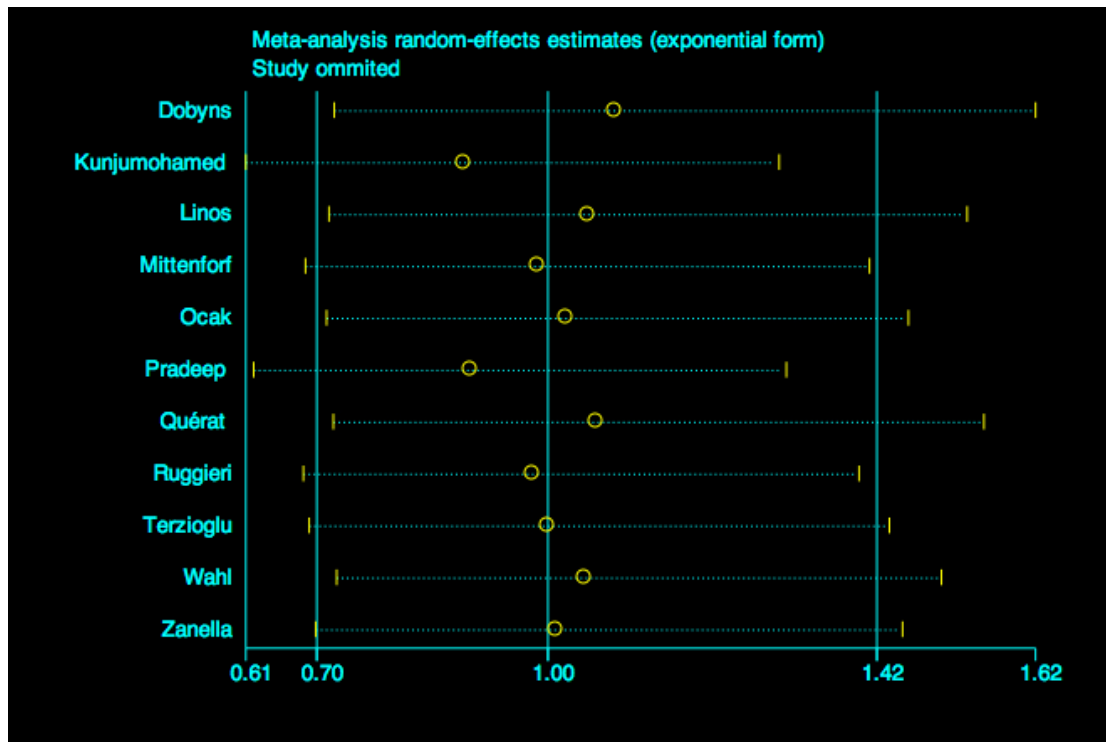
S2.3 Egger's test

Egger's test

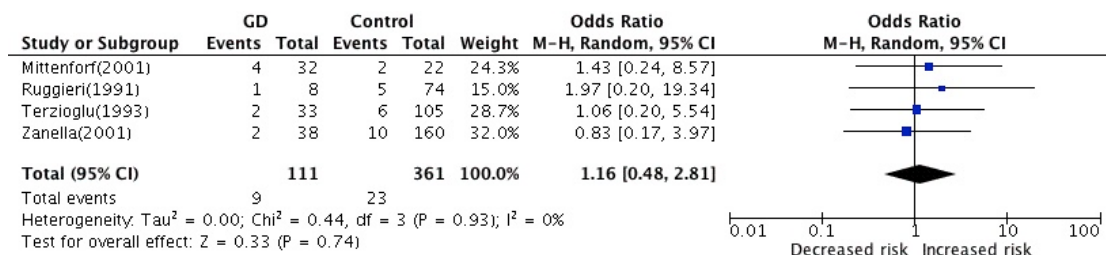
Std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
slope	-.1991965	.6232603	-0.32	0.757	-1.609109	1.210716
bias	.328923	1.111371	0.30	0.774	-2.185174	2.84302

Fig. S3 Sensitivity analysis

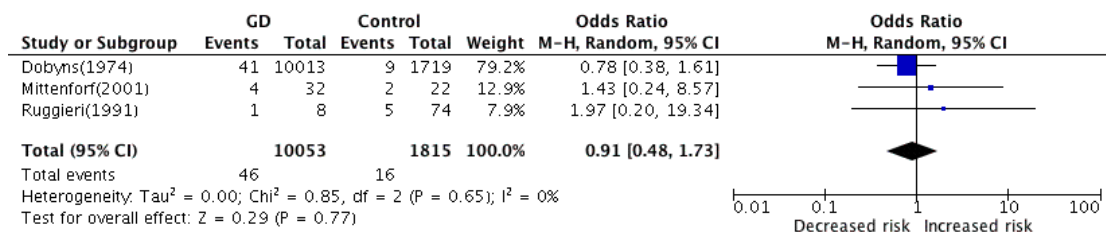
S3.1 Remove-one sensitivity analysis



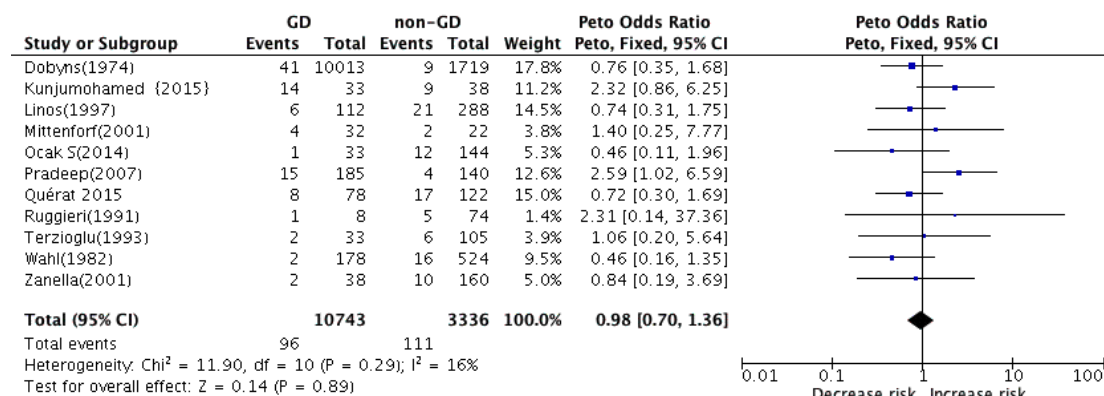
S3.2 Sensitivity analysis excluding studies with unclearly defined hyperthyroidism



S3.3 Sensitivity analysis excluding studies with unclearly defined GD



S3.4 Overall estimates of the effects of the association of GD and thyroid carcinoma using Peto fixed-effect model.



S3.5 Overall estimates of the effects of the association of GD and thyroid carcinoma using M-H fixed-effect model.

