

Suppl. Table S2. Overview of large international studies on routine Ctn measurement in nodular thyroid disease (only studies with at least 1000 patients).

Abbreviations: AFTN=autonomous functioning thyroid nodule; AIT=autoimmune thyroiditis; f=females; GD=Grave's disease; ICMA=immunochemiluminometric assay;

IRMA=immunoradiometric assay; m=males; PPI=proton pump inhibitors. *1 additional patient had been diagnosed with MEN but refused thyroidectomy (Ctn 81.9 pg/ml); **including 2 histologically discovered MTC cases without elevated basal Ctn values.

| first author publication year | country (region) | recruitment period | follow- up period | patients total | m:f | age [yrs.] | inclusion criteria | exclusion criteria | Assay | Basal Ctn cutoff [pg/ml] | Basal Ctn patients >cutoff n (%) | patients with elevated Ctn lost to follow- up or with incomplete data | MTC prevalence | proportion of sporadic MTC |
|--|-------------------------------|-----------------------|-------------------------|-------------------|--------|-----------------|---|---|--|-----------------------------------|--|--|----------------------|----------------------------------|
| Hahm 2001 [34] | Korea (Seoul) | 6/1998- 1999 | not described | 1,448 | 1:4.08 | 14-86 | nodular thyroid disease | not specified | IRMA (Medgenix CT- U.S., BioSource) | 10 (m/f) | 56 (3.9 %) | not described | 10/1,448 (0.69%) | 80 % |
| Hatzl- Griesenhofer 2002 [61] | Austria (Linz) | 1/1999- 12/2001 | not described | 3,899 | 1:3.72 | 6-90 | nodular thyroid disease | not specified | ICMA (Nichols Institute Diagnostic) | 4.6 (f) 11.5 (m) | 230 (5.9%) f:140 (4.6%) m:90 (10.9%) | 23 | 12/3,899 (0.31%) | 75 % |
| Elisei 2004 [4] | Italy (Sienna) | 1991- 1998 | 3 - 6 yrs. | 10,864 | 1:4.00 | 12-82 | nodular thyroid disease | not specified | IRMA (ELSA hCT, CIS- Biointernational) | 20 (m/f) | 47 (0.4%) | 1 | 40/10,864 (0.37%) | 80 % |
| Vierhapper 2005 [35] | Austria (Vienna) | 8/1994- 8/2004 | not described | 10,157 | 1:3.97 | not reported | nodular thyroid disease | known Ctn elevation or C-cell neoplasia | 1994-1999 IRMA (CIS-Biolnt) 1994-2004 ICMA (Nichols Institute Diagnostics) | 10 (m/f) | 507 (5.0%) | 18 | 32/10,158 (0.32%) | 91 % |
| Papi 2006 [62] | Italy (Rome/ Modena) | 4/2003- 3/2004 | not described | 1425 | 1:4.07 | 18-91 | nodular thyroid disease (non- palpable nodules <10 mm only in case of suspicious ultrasonogr. features) | known Ctn elevation or C-cell neoplasia, family history of MEN, patients in follow-up for thyroid diseases | ICMA (Nichols Institute Diagnostics) | 5 (m/f) | 23 (1.6%) | not described | 9/1,425 (0.63%) | 100 % |
| Costante 2007 [36] | Italy (various regions) | 1/2001- 12/2004 | 2 - 4 years | 5,817 | 1:4.24 | 11-72 | nodular thyroid disease | known MTC or family history of MTC, renal failure | ICMA (Nichols Advantage, Nichols Institute Diagnostics) | 10 (m/f) | 282 (4.8%) | 45 | 15/5,817 (0.26%) | not reported |
| Rink 2009 [27] | Germany (Rhine- Main) | 7/2000- 10/2006 | up to 87 months | 21,928 | 1:3.32 | 8-97 | nodular thyroid disease | not specified | IRMA (1. Calcitonin- IRMA, IBL; 2. Calcitonin- IRMA magnum, Medipan) | 10 (m/f) | 885 (4.0%) | 509 | 28/21,928 (0.13%) | 80 % |

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|--|--------------------------------|-------------------------------|----------------------------------|---------------------------|-----------------|-----------------------|--|---|---|---|--|--|---------------------------|---|
| Herrmann 2010 [28] | Germany (Bochum) | 6/2005- 9/2009 | not described | 1,007 | 1:1.29 | 55±14 | nodular thyroid disease | known Ctn ele- vation, impaired renal function, GD, AIT, pseudo- hypoparathyroidism, alcohol or drug abuse, PPI | ICMA (Immulite 2000, Siemens) | 10 (m/f) | 17 (1.7%) | none | 2/1,007 (0.2%) | 100 % |
| first author publication year | country (region) | recruitment period | follow- up period | patients total | m:f | age [yrs.] | inclusion criteria | exclusion criteria | Assay | Basal Ctn cutoff [pg/ml] | Basal Ctn patients >cutoff n (%) | patients with elevated Ctn lost to follow- up or with incomplete data | MTC prevalence | proportion of sporadic MTC |
| Grani 2012 [37] | Italy (Rome) | 5/2005- 2/2010 | up to 36 months | 1,073 | 1:4.96 | 56±13 | patientes referred to FNAC because of suspicious nodules | not specified | ICMA (automated two- site immunoassay) | 10 (m/f) | 41 (3.8%) | 2 | 2*/1,073 (0.19%) | not reported |
| Schneider 2012 [29] | Germany (Cologne) | 1/2004- 12/2010 | up to 1 year | 11,270 | not reported | not reported | nodules ≥2 mm | MTC or family story of MTC, renal insufficiency, bacterial infection, alcohol abuse, PPI therapy, GD or AIT | ICMA (Immulite 2000, Siemens) | 13 (m/f) | 32 (0.3%) | 2 | 12**/11,270 (0.11%) | not reported |
| Giovanella 2013 [38] | Switzerland (Bellinzona) | 1/2008- 12/2010 | 24 – 35 months | 1,236 | 1:1.20 | 53±17 | nodular thyroid disease | pulmonary or pancreatic tumours, kidney failure, sepsis, alcohol abuse, smoking, PPI therapy, AFTN, GD or AIT | ICMA (Immulite 2000, Siemens) | 10 (m/f) | 14 (1.1%) | none | 2/1,236 (0.16%) | 100 % |
| Silvestre 2019 [39] | Portugal (Lisboa region) | 1/2011- 12/2015 | not described | 1504 | not reported | not reported | nodular thyroid disease | not specified | ICMA (Immulite 2000, Siemens) | 10 (m/f) | 69 (4.6%) | 49 | 12/1,504 (0.80%) | 86 % |
| Storani 2019 [63] | Argentina (Buenos Aires) | 1/2009- 6/2017 | up to 6 yrs. | 1,017 | 1:7.07 | 18-88 | nodules >2 mm | known C-cell neoplasia, chronic kidney failure, PPI therapy | ICMA (Immulite 2000, Siemens) | 12 (f) 18 (m) | 4 (0.4%) | none | 2/1,017 (0.2%) | 50 % |
| present study | Germany (Rhine- Ruhr) | 11/2009- 11/2014 | up to 13 yrs. | 12,984 | 1:3.98 | 18-90 | nodules >2 mm | known Ctn elevation or C-cell neoplasia, advanced kidney disease | IRMA (SELco Calcitonin, Medipan) | 10 (f) 15 (m) | 207 (1.6%) | 83 | 16/12,984 (0.12%) | 82 % |