Title: Rare thyroid malignancies in Europe: data from the information network on rare cancers in Europe (RARECAREnet)

Running title: Rare thyroid malignancies in Europe

Keywords:

Thyroid cancer; epidemiology; incidence; medullary thyroid cancer; anaplastic thyroid cancer; cancer registries

List of abbreviations:

ASR, Age-Standardised Rate

ATA, American Thyroid Association

ATC, Anaplastic Thyroid Cancer

CR, Cancer Registry

DTC, Differentiated Thyroid Cancer

ERN, European Reference Network

EU, European Union

EURACAN, European Reference Network on Rare Cancers

FTC, Follicular Thyroid Cancer

ICD, International Classification of Diseases

MTC, Medullary Thyroid Cancer

NGS, Next Generation Sequencing

PDTC, Poorly Differentiated Thyroid Cancer

PTC, Papillary Thyroid Cancer

RARECARENET, Information Network on Rare Cancers

TC, Thyroid Cancer

UK, United Kingdom

Article category: Research article, cancer epidemiology

Abstract

Objective. Limited information is available on the incidence of rare thyroid cancer (TC) subtypes: anaplastic (ATC) and medullary (MTC). The aim of this study was to describe incidence variations and trends across European countries of all TC subtypes.

Materials and Methods. We used the RARECAREnet database including 80,721 TC incident cases in the period 2000-2007 from 77 population-based cancer registries (CRs) in Europe. In the trend analyses, we included 68,890 TC cases from 53 CRs with at least 6 years of incidence data in the years 2000-2007.

Results. In Europe age-standardised incidence rates (ASR) in women were <0.3/100,000 for MTC and ATC whereas ASR were 5.3/100,000 for papillary thyroid cancer (PTC) and 1.1/100,000 for follicular TC (FTC). Corresponding ASRs in men were <0.2/100,000 for MTC and ATC, 1.5 for PTC and 0.4 for FTC. Across countries and in both sexes the incidence of FTC and MTC was moderately correlated (r~0.5) with that of PTC, while a less marked correlation (r<0.4) emerged for ATC ASRs. The changes of the PTC ASRs across countries and time were weakly (r<0.3) or moderately (r~0.5) correlated to the changes of the other subtypes for both sexes.

Conclusion. The huge increase and heterogeneity between countries of PTC incidence has a small influence on the trends and variations of MTC and ATC in Europe. Large-scale epidemiological and clinical registry-based studies are warranted to increase knowledge about the rarest TC subtypes. This information would be fundamental for the design of new clinical trials and for inference.

Introduction

Thyroid cancers (TCs) include follicular cell-derived carcinomas, classically defined as differentiated thyroid cancer (DTC) (i.e. papillary thyroid cancer (PTC); follicular thyroid cancer (FTC); Hürtle cell carcinomas and poorly differentiated thyroid cancer (PDTC)) and medullary thyroid cancer (MTC) which arises from the neuroendocrine parafollicular C cells. Anaplastic thyroid cancer (ATC) is a very rare entity supposed to derive from undifferentiated epithelial cells [1].

Worldwide trends in TC incidence have been largely driven by an increase in PTC as opposed to other histological types [2 3 4 5]. Thus, much attention has been given to PTC with controversy surrounding the likely reasons for the observed epidemic [6]. Increased medical surveillance and widespread use of ultrasound [7 5] are likely explanations [8].

Ionising radiation exposure, mainly in childhood and adolescence [5], represents the most accepted risk factor associated with DTC, especially PTC [9 10]. Among eating habits, iodine intake represents one of the most discussed elements, because its deficiency is associated with FTCs, while there is some weak evidence that observed increases in dietary iodine intake may be responsible for the increasing incidence of PTC[11]. Evidence for other risk factors such as low intake of fruits and vegetables; cruciferous vegetables intake; alcohol consumption, sex hormones [12] and obesity [13 14] remains controversial [5 15 16].

In contrast, limited information is available on the incidence, trends and risk factors of the rarest TC subtypes: anaplastic thyroid cancer (ATC) and medullary thyroid cancer (MTC) [17 18 19]. It is not clear whether the widespread use of ultrasound and fine needle biopsies on thyroid nodules is affecting the incidence of FTC, MTC [20] and ATC. Against this background, our aim was to describe the overall incidence and changes in incidence over time of all TC subtypes in Europe and across European countries.

Material and methods

We used the database of the RARECAREnet (www.rarecarenet.eu) project, which includes incidence and follow-up data provided by 94 European population-based cancer registries (CRs) for patients with cancer diagnosed between Jan 1, 1978, and Dec 31, 2007. Our analyses refer to the period 2000-2007. To analyse incidence, we used 77 CRs with data for at least 3 years of incidence between 2000 and 2007, including all the 24 countries contributing to RARECAREnet (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Switzerland, The Netherlands and United Kingdom) and 45% of EU28 population (excluding Norway, Switzerland, and Iceland, which are not EU members) (Supplementary Table 1). We excluded 11 anatomical-site-specific CRs to avoid any incomplete coverage of some cancers affecting multiple sites and six CRs because the percentage of unspecified morphologies (ICD-O3 codes: 8000-8010) was >15%. To analyse incidence trends over time, we used 53 CRs, with data available for at least 6 years of incidence in the study period (2000-2007) (Supplementary Table 1).

Incident TC cases were defined according to ICD-O-3 topography code C73. Morphologies were grouped into major similar histological types [21] including papillary (8050,8052,8260,8263,8340-8344,8350,8450), follicular (8290,8330-8335), medullary (8246,8345-8347,8510) anaplastic including poorly differentiated (8012,8020-8035,8190,8337) and unspecified (8000-8010). All the remaining morphologies were combined into the group "all other morphologies". Cases first discovered at autopsy or by death certificate only were excluded (n=1,235 from the incidence analyses and n=1,134 from the incidence trends analyses), leaving 80,721 TC cases in the incidence analyses and 68,890 in the incidence trend analyses.

Age-standardised incidence rates (ASR) per 100,000 person-years were standardised to the European population (1960). Analysis of incidence trends was performed for Europe as a whole and by country, according to three time intervals (2000-2002; 2003-2004; 2005-2007). The statistical significance of incidence

differences (ASR variation % in 2005-2007 versus 2000-2002) was tested with the Z-test [22]. Pearson correlation coefficients (r) of PTC versus each of the other subtypes were estimated across countries, in the overall period of the study (years 2000-2007) and per each time interval included in the trend analysis (2000-2002; 2003-2004; 2005-2007).

Results

TC incidence

In Europe, in 2000-2007, the TC incidence rate was 7.1/100,000 in females and 2.4/100,000 in males with a female to male ratio of 2.97 (Table 1). PTC was the most common subtype constituting 73% and 63% of all TCs in females and males, respectively. FTC was the second most common subtype; however, its incidence rate was 5 times lower than that of PTC in females (1/100,000) and about 4 times lower in males (0.4/100,000). ASRs ≤0.3/100,000 in both females and males emerged for MTC (0.3 and 0.2/100,000, respectively) and ATC (0.1 and 0.1/100,000, respectively) (Table 1). The female to male ratio differed for MTC and ATC with female incidence rates 1.4 times that of males.

Figure 1 reports TC incidence rates by age group and subtype in both females and males. The incidence peak differed across subtypes and by sex; PTC was most common in females aged 50-54 years and males aged 55-59 years, FTC in females aged 70-74 years and males aged 75-79 years, MTC in females aged 65-69 years and males aged 70-74 years and ATC in both females and males aged 80-84 years.

PTC demonstrated the widest variability across Europe with an approximately 8-fold difference in ASRs across countries (Figure 2). In females, PTC ASRs ranged from 2/100,000 in the UK, Ireland and The Netherlands to >10/100,000 in Italy, Iceland, Portugal and France. In males, PTC ASRs ranged from 0.7 in Bulgaria, Northern Ireland and Wales to 4 in Italy and Iceland (7-fold higher).

FTC ASRs across countries varied by 3 times in females; ranging from <0.6/100,000 in The Netherlands, Bulgaria and Malta to >1.5/100,000 in Austria, Latvia and, Lithuania (Figure 2). In males, FTC ASRs ranged from 0.2/100,000 in Norway, Poland and Bulgaria to 0.7 and 0.8/100,000 in Switzerland and Austria, respectively (an almost 5-fold difference).

MTC and ATC ASRs were low (≤0.5/100.000) with limited differences across countries in both sexes. In females, MTC ASRs ranged from 0.1/100,000 in Bulgaria and Malta to 0.5/100,000 in Croatia and Austria (Figure 2). In males, MTC ASRs were 0.3-0.4/100,000 in Austria, Italy and France. ATC ASRs were <0.3/100,000 in women and <0.2/100,000 in men in all countries and <0.1/100,000 in both sexes in Croatia, Scotland, England, Latvia, and Bulgaria and Finland (Figure 2). Note: In Finland coding problems could not be ruled out completely.

Across countries and in both sexes the incidence of FTC and MTC was moderately correlated (r~0.5) with that of PTC, while a less marked correlation (r<0.4) emerged for ATC ASRs (Figure 2).

TC incidence trends

In Europe, TC ASRs increased in the years 2000-2007 in both females and males (variations +25% and +26%, respectively; p<0.01 for both) (Table 1). PTC was the subtype with the highest and most significant ASR increase (+33% and +39% in females and males, respectively). Significant but smaller increases were observed for FTC in females (ASR from 0.9/100,000 to 1/100,000) and for MTC in males (ASR from 0.17/100,000 to 0.19/100,000). No significant changes over time in ASRs were observed for the other subtypes in females or males.

In females (Figure 3), the PTC ASR significantly increased in most countries but with different magnitudes. The variation of ASRs between 2000-2002 and 2005-2007 was >50% in Portugal, Lithuania, Slovenia, Czech Republic, Latvia, Belgium and Ireland and, about 40% in Italy, Croatia, Austria, Switzerland, Bulgaria, England and Netherlands, and <30% in Slovakia, Germany, Scotland and Poland (Supplementary Table 2). In some

other countries (e.g. France, Spain), the PTC ASR did not significantly increase over the study period. The FTC ASRs increased in Ireland, England and Austria (77%, 32% and 25%, respectively), while they decreased in Latvia (-45%), Germany, Slovakia and Poland (-30%) (Supplementary Table 2). The ASRs of the MTC and ATC did not significantly change over time across countries. Moreover, the changes of the PTC ASRs across countries and time were weakly ($r<0.3$) or moderately ($r\sim0.5$) correlated to the changes of other TC subtypes (Figure 3).

In males (Figure 4), the PTC ASR significantly increased in most countries with variations >100% in Latvia, Portugal, Switzerland, and Malta, and about 40-50% in most of the other countries investigated (Supplementary Table 2). Variations <25% were observed in Netherlands, Germany and Finland, while a significant decrease was observed only in Spain (ASR from 2.3 to 1.3; -45%). FTC ASRs significantly increased only in Ireland (147%), Wales (107%), Portugal (92%) and Austria (28%), while they decreased in Slovenia (-63%) and Germany (-28%). MTC ASRs increased in Croatia and Belgium (213% and 70%, respectively) and decreased in Norway and Austria (-49% and -31%, respectively) (Supplementary Table 2). ATC ASRs increased only in England (97%) and decreased in Scotland and Germany (-68% and -49%, respectively) (Supplementary Table 2). The changes of the PTC ASRs across countries and time were weakly ($r<0.3$) or moderately ($r\sim0.5$) correlated to the changes of the other subtypes (Figure 4).

Discussion

This is the first study, to our knowledge, to report incidence and incidence trends of rare thyroid histotypes in Europe and in each EU country. ATC and MTC ASRs have limited geographical variations across European countries in both sexes and incidence trends are stable. ATC trends in Europe are coherent with those observed in the USA [23, 24] and in the Republic of Korea [25]. Regarding MTC, in the USA an increase of MTC

was observed [26] whereas in Europe, we observed a significant increase of MTC only in males in Belgium and Croatia. The present study confirms a large variation of PTC and FTC incidence across European countries and in both sexes. Finally, the moderate correlation ($r<0.5$) of PTC ASRs with the ASRs for other TC subtypes across countries, supports the hypothesis that recent PTC epidemic is not affecting the incidence of rarest TC subtypes.

The study confirms that in Europe PTC and FTC were much more frequent compared to MTC and ATC, were diagnosed at younger ages, and were more common in females than in males. These differences have been largely attributed to the age related differences in the use of health services [27]. Intense surveillance of thyroid nodules and thyroid function tend to occur in young and middle-age women due to events related to reproduction and perimenopausal and postmenopausal symptoms. The role of female hormones has also been suggested in the aetiology of DTC, however, conclusive studies are still lacking [28]. Conversely, men make frequent medical visits after middle age because of various chronic conditions [29].

Differences across countries in incidence and trends were almost exclusively limited to PTC. Substantial evidence suggests that overdiagnosis is a likely culprit for the different TC incidence across countries, almost exclusively limited to PTC [8]. Diagnostic changes accounted for 60% of TC cases diagnosed in 2003–2007 in women aged under 80 years in France, Italy, the United States, Australia, and the Republic of Korea, and approximately 50% in other countries, except Japan (30%) [30] [8]. Overdiagnosis has led to an increase of treatment procedures such as surgery and radioactive iodine treatment during the recent years [5] [31], leading scientific societies to update guidelines in order to avoid any unnecessary diagnostic procedures on incidental thyroid nodules [32] [33] [24]. The American Thyroid Association (ATA) guidelines [34] and the American College of Radiology [35] have recently stressed the importance of the sonographic pattern of the thyroid nodules for patient risk stratification.

While the epidemiological studies on DTC are numerous [5], limited information are available on risk factors for the rarest TC subtypes, as MTC and ATC. MTC may exist as a hereditary tumour (about 25% of cases) within the complex of multiple endocrine neoplasia type 2A (MEN 2A) and type 2B (MEN 2B) and, more commonly, as a sporadic form (70% of cases). For this latter type, aetiological factors are not fully known except for somatic *RET* or *RAS* mutations [36]. An association between sporadic MTC (sMTC) and history of thyroid nodules or adenomas (12-fold risk) was reported in the past [17]. More recently, Kalezic et al. [18] confirmed that history of goitre and thyroid nodules (OR 11.29, 95% CI 1.16 - 73.45, p<0.001) were independent risk factors for sMTC. Smoking history was associated with a reduced risk for sMTC in both papers [17] [18]. Authors postulated an ability to decrease thyroid-stimulating hormone secretion and an innate anti estrogenic effect of smoking [18]. Additionally, other risk factors such as menarche after 14 years [18], height (higher risk in taller subjects), hypertension, gallbladder disease and allergies have been reported [17]. Interestingly, an average prevalence of 0.14% of occult MTC has been reported in a series 7897 autopsies in patients without known thyroid disease and authors demonstrated that routine calcitonin screening applied to general population with nodular thyroid disease would be not cost effective [20].

ATC is one of the most aggressive malignant tumours in humans, with a median overall survival of no more than 6 months [21]. A next generation sequencing (NGS) analysis on a large series of ATC recently demonstrated that ATC can be divided into 3 clusters according to the genetic features from which ATC derives [37] supporting the hypothesis of ATC as the final event of a pre-existing PTC or FTC rather than a *de novo* tumour. Not surprisingly, ATC is typically diagnosed in elderly patients with 67% of ATC patients diagnosed at age >70 years. A history of goitre, low educational level and type B blood group have been recognized as independent prognostic factors in a large case-control study [19].

The major strengths of this study are the population based design and the availability of the largest well documented TC series (70,000 cases in 8 years) in Europe. The main limitation is the period analysed.

Indeed, we report on patients diagnosed from 2000 to 2007. However, these are the only and most recent available data that allow studying TC incidence by subtype across Europe.

In conclusion, MTC and ATC incidence trends in Europe are stable and not correlated to the incidence increase of PTC. Epidemiological data on MTC and ATC are currently still scant. Thus, collaboration with clinical registries will be essential to enrich population-based data with information on risk factors, tumour dimension, stage, pathological and molecular features and treatment especially for MTC and ATC for which knowledge is still limited. To this end we call the European Reference Network (ERN) on rare cancers (EURACAN) to prioritise the development of clinical registries on the rarest TC subtypes.

References

1. Mahkamova K, Latar NM, Aspinall S, Meeson A. Side population cells in anaplastic thyroid cancer and normal thyroid. *Experimental cell research* 2019;**374**: 104-13.

2. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N, Zhang Y. International patterns and trends in thyroid cancer incidence, 1973-2002. *Cancer causes & control : CCC* 2009;**20**: 525-31.

3. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *Journal of cancer epidemiology* 2013;**2013**: 965212.

4. Sanabria A, Kowalski LP, Shah JP, Nixon IJ, Angelos P, Williams MD, Rinaldo A, Ferlito A. Growing incidence of thyroid carcinoma in recent years: Factors underlying overdiagnosis. *Head & neck* 2018;**40**: 855-66.

5. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. *Nature reviews Endocrinology* 2016;**12**: 646-53.

6. Brito JP, Davies L. Is there really an increased incidence of thyroid cancer? *Current opinion in endocrinology, diabetes, and obesity* 2014;**21**: 405-8.

7. Busco S, Giorgi Rossi P, Sperduti I, Pezzotti P, Buzzoni C, Pannozzo F. Increased incidence of thyroid cancer in Latina, Italy: a possible role of detection of subclinical disease. *Cancer epidemiology* 2013;**37**: 262-9.

8. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. *The New England journal of medicine* 2016;**375**: 614-7.

9. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassov O, Bouville A, Goulko G, et al. Risk of thyroid cancer after exposure to 131I in childhood. *Journal of the National Cancer Institute* 2005;**97**: 724-32.

10. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, McGale P, Cain TM, et al. Cancer risk in 680,000 people exposed to computed

279 tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ (Clinical*
280 *research ed)* 2013;**346**: f2360.
281 11. Nettore IC, Colao A, Macchia PE. Nutritional and Environmental Factors in Thyroid
282 Carcinogenesis. *International journal of environmental research and public health* 2018;**15**.
283 12. Zabuliene L, Jasilionis D, Miseikyte-Kaubriene E, Stukas R, Kaceniene A, Smailyte G. Parity and
284 Risk of Thyroid Cancer: a Population-Based Study in Lithuania. *Hormones & cancer* 2017;**8**: 325-9.
285 13. Peterson E, De P, Nuttall R. BMI, diet and female reproductive factors as risks for thyroid cancer: a
286 systematic review. *PloS one* 2012;**7**: e29177.
287 14. Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, Tjonneland A,
288 Halkjaer J, Lukanova A, Kaaks R, Bergmann MM, Boeing H, et al. Body size and risk of differentiated thyroid
289 carcinomas: findings from the EPIC study. *International journal of cancer* 2012;**131**: E1004-14.
290 15. Cordina-Duverger E, Leux C, Neri M, Tcheandjieu C, Guizard AV, Schvartz C, Truong T, Guenel
291 P. Hormonal and reproductive risk factors of papillary thyroid cancer: A population-based case-control study in
292 France. *Cancer epidemiology* 2017;**48**: 78-84.
293 16. Bosetti C, Negri E, Kolonel L, Ron E, Franceschi S, Preston-Martin S, McTiernan A, Dal Maso L,
294 Mark SD, Mabuchi K, Land C, Jin F, et al. A pooled analysis of case-control studies of thyroid cancer. VII.
295 Cruciferous and other vegetables (International). *Cancer causes & control : CCC* 2002;**13**: 765-75.
296 17. Negri E, Ron E, Franceschi S, La Vecchia C, Preston-Martin S, Kolonel L, Kleinerman RA,
297 Mabuchi K, Jin F, Wingren G, Hallquist A, Levi F, et al. Risk factors for medullary thyroid carcinoma: a pooled
298 analysis. *Cancer causes & control : CCC* 2002;**13**: 365-72.
299 18. Kalezic NK, Zivaljevic VR, Slijepcevic NA, Paunovic IR, Diklic AD, Sipetic SB. Risk factors for
300 sporadic medullary thyroid carcinoma. *European journal of cancer prevention : the official journal of the*
301 *European Cancer Prevention Organisation (ECP)* 2013;**22**: 262-7.
302 19. Zivaljevic V, Slijepcevic N, Paunovic I, Diklic A, Kalezic N, Marinkovic J, Zivic R, Vekic B, Sipetic S.
303 Risk factors for anaplastic thyroid cancer. *International journal of endocrinology* 2014;**2014**: 815070.

20. Valle LA, Kloos RT. The prevalence of occult medullary thyroid carcinoma at autopsy. *The Journal of clinical endocrinology and metabolism* 2011;**96**: E109-13.

21. Dal Maso L, Tavilla A, Pacini F, Serraino D, van Dijk BAC, Chirlaque MD, Capocaccia R, Larranaga N, Colonna M, Agius D, Ardanaz E, Rubio-Casadevall J, et al. Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5. *European journal of cancer (Oxford, England : 1990)* 2017;**77**: 140-52.

22. Parkin DM, Hakulinen T. Cancer registration: principles and methods. Analysis of survival. *IARC scientific publications* 1991: 159-76.

23. Lin B, Ma H, Ma M, Zhang Z, Sun Z, Hsieh IY, Okenwa O, Guan H, Li J, Lv W. The incidence and survival analysis for anaplastic thyroid cancer: a SEER database analysis. *American journal of translational research* 2019;**11**: 5888-96.

24. Lin JS, Bowles EJA, Williams SB, Morrison CC. Screening for Thyroid Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2017;**317**: 1888-903.

25. Oh CM, Park S, Lee JY, Won YJ, Shin A, Kong HJ, Choi KS, Lee YJ, Chung KW, Jung KW. Increased prevalence of chronic lymphocytic thyroiditis in Korean patients with papillary thyroid cancer. *PloS one* 2014;**9**: e99054.

26. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *Jama* 2017;**317**: 1338-48.

27. Ahn HS, Kim HJ, Kim KH, Lee YS, Han SJ, Kim Y, Ko MJ, Brito JP. Thyroid Cancer Screening in South Korea Increases Detection of Papillary Cancers with No Impact on Other Subtypes or Thyroid Cancer Mortality. *Thyroid : official journal of the American Thyroid Association* 2016;**26**: 1535-40.

28. Zamora-Ros R, Rinaldi S, Biessy C, Tjonneland A, Halkjaer J, Fournier A, Boutron-Ruault MC, Mesrine S, Tikk K, Fortner RT, Boeing H, Forster J, et al. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. *International journal of cancer* 2015;**136**: 1218-27.

29. Wang Y, Hunt K, Nazareth I, Freemantle N, Petersen I. Do men consult less than women? An analysis of routinely collected UK general practice data. *BMJ open* 2013;**3**: e003320.

30. Vaccarella S, Dal Maso L, Laversanne M, Bray F, Plummer M, Franceschi S. The Impact of Diagnostic Changes on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Selected High-Resource Countries. *Thyroid : official journal of the American Thyroid Association* 2015;**25**: 1127-36.

31. Panato C, Serraino D, De Santis E, Forgiarini O, Angelin T, Bidoli E, Zanier L, Del Zotto S, Vaccarella S, Franceschi S, Dal Maso L. Thyroid cancer in Friuli Venezia Giulia, northeastern Italy: incidence, overdiagnosis, and impact of type of surgery on survival. *Tumori* 2019: 300891619839307.

32. Husson O, Haak HR, van Steenbergen LN, Nieuwlaat WA, van Dijk BA, Nieuwenhuijzen GA, Karim-Kos H, Kuijpens JL, van de Poll-Franse LV, Coebergh JW. Rising incidence, no change in survival and decreasing mortality from thyroid cancer in The Netherlands since 1989. *Endocrine-related cancer* 2013;**20**: 263-71.

33. Pacini F, Castagna MG, Brilli L, Pentheroudakis G. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology* 2012;**23 Suppl 7**: vii110-9.

34. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid : official journal of the American Thyroid Association* 2016;**26**: 1-133.

35. Hoang JK, Langer JE, Middleton WD, Wu CC, Hammers LW, Cronan JJ, Tessler FN, Grant EG, Berland LL. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *Journal of the American College of Radiology : JACR* 2015;**12**: 143-50.

36. Lloyd RV OR, Klöppel G, Rosai J. *WHO Classification of Tumours of Endocrine Organs*, 4th ed., vol. 10, 2017.

37. Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, Schweppe RE, Fishbein L, et al. Genetic Analysis of 779 Advanced Differentiated and

Anaplastic Thyroid Cancers. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2018;**24**: 3059-68.

374 **Tables and Figures legends**

375

376 **Table 1.** Number of incident cases and age-standardised incidence rates (ASR)* together with incidence
377 trends in Europe by thyroid cancer histological type in females and males. Europe, 2000-2007

378 * Per 100,000, age-standardised to the European population (1960)

379 ** ASR in 2005-2007 versus 2000-2002

380 *** including poorly

381

382 **Figure 1.** Incidence rate by age group by thyroid cancer histologycal type in females (A) and males (B)

383

384 **Figure 2.** Age-standardised incidence rates (ASR)* by country and thyroid cancers histological type§ in
385 females and males with correlation coefficients with PTC ASR

386 * Per 100,000, age-standardised to the European

387 § Note: a different scale has been used for ASR in TC subtypes

388

389 **Figure 3.** Thyroid cancers age-standardised incidence rates (x 100,000) in females, by subtype, country*,
390 period of diagnosis of PTC versus each of the other subtype

391 * Countries are ranked by incidence rate in 2005-2007. Arrow pointing upwards identify significant increase;
392 arrow pointing downwards identify significant decrease

393

Figure 4. Thyroid cancers age-standardised incidence rates (x 100,000) in males, by subtype, country*, period of diagnosis of PTC versus each of the other subtype

* Countries are ranked by incidence rate in 2005-2007. Arrow pointing upwards identify significant increase; arrow pointing downwards identify significant decrease

Supplementary Table 1. Cancer registry (CR) included in the incidence and trends analysis together with the mean population and the proportion (%) of national population covered abd the years included in the analyses

Supplementary Table 2. Age-standardised incidence rates (ASR)* and number of incident cases for thyroid cancer by histoligical type, country and period in females and males with Pearson correlation coefficients (r) between papillary with the other histological type per each time period (2000-2002; 2003-2004; 2005-2007). Countries are ranked by incidence rate in the last period in decreasing order

Data availability statement

Data available on request from the authors.