Abstract

Objective: Decreasing tumor size in a population over time is widely interpreted as a measure of effectiveness of cancer screening programs. Nonetheless, thyroid cancer size is rarely analyzed as a function of time. This study aimed to explore secular trends of thyroid cancer diameter in Germany.


Methods: Calculation of largest tumor diameters for each type of cancer as a function of time periods and birth cohorts.

Results: Over the past 25 years, subdivided into 5-year periods by year of thyroidectomy (1985–1989; 1990–1994; 1995–1999; 2000–2004; 2005–2009), tumor diameters diminished from 25 to 16 mm ($P=0.025$) for medullary thyroid cancer and from 28 to 18 mm ($P=0.017$) for papillary thyroid cancer. This reduction was greater for hereditary medullary thyroid cancer (from 27 to 11 mm; $P=0.088$) than sporadic medullary thyroid cancer (from 23 to 19 mm; $P=0.11$). No decline was observed for follicular thyroid cancer (means of 45 to 42 mm; $P=0.52$). From the first (1921–1940) to the most recent birth cohort (1981–2000), tumor size fell from 22 to 10 mm ($P<0.001$) for medullary thyroid cancer, from 24 to 22 mm ($P<0.001$) for papillary thyroid cancer, and from 49 to 38 mm ($P=0.011$) for follicular thyroid cancer. The reduction of medullary thyroid cancers affected exclusively patients with hereditary disease (from 20 to 7 mm; $P<0.001$).

Conclusion: The consistency and robustness of these data signify powerful secular trends toward smaller papillary, follicular, and medullary thyroid cancers. The causes and consequences of these trends warrant further investigation.
Patients and methods

Study population

A total of 1869 consecutive patients, having a place of residence in Germany at the time of referral to this institution, underwent cervical operations for papillary, follicular, and medullary thyroid cancers between January 1, 1995 and December 31, 2009. Information on primary tumor size was available for 1644 (88%) of these 1869 patients: specifically, for 247 (78%) of the 317 patients with follicular thyroid cancer, 583 (89%) of the 652 patients with medullary thyroid cancer, and 814 (90%) of the 900 patients with papillary thyroid cancer. These 1644 patients were included into this study. Informed consent was obtained before each surgical procedure that represented standard practice of care.

Location of the referral center within the catchment area and coverage

The Department of General, Visceral, and Vascular Surgery, serving as a tertiary surgical center with practice of care.

to the referral center (Halle) was measured with the use of an internet-based inter-city distance calculator accessible for free at http://www.postleitzahl.org/entfernung.html and rounded to the nearest kilometer (9). The calculator algorithm approximates the linear distance between two cities, the points of reference being the city centers.

The study population of 1644 patients originated from 93 of the 95 German postal code regions (Fig. 1), yielding a 98% coverage rate. Introduced in 1993, the 95 German postal code regions were designed to broadly comprise an equal number of households and residents. The two nonreferring postal code regions 82 (Garmisch–Partenkirchen) and 84 (Landshut) were from the Southern fringes of the catchment area.

Pathologic examination of surgical specimens

All specimens were subjected to histopathologic examination and embedded in paraffin. Conventional staining (hematoxylin and eosin) and thyroglobulin and calcitonin immunohistochemistry respectively were performed on every surgical specimen as appropriate. Papillary, follicular, and medullary thyroid cancers were diagnosed according to the World Health Organization’s International Histological Classification of Tumors (10, 11), subsuming poorly differentiated follicular cell-derived tumors under the category of papillary or follicular thyroid cancer as appropriate. Pathologic reports from outside institutions were reviewed as necessary. Primary tumor diameter was based on direct measurements on the surgical thyroid specimens. When multiple tumors were present, only the size of the largest thyroid cancer was taken.

Determination of the heredity of medullary thyroid cancer

All medullary thyroid cancer patients were offered genetic counseling to ascertain rearranged during transfection (RET) gene status. Before undergoing DNA-based screening, all patients or their legal guardians gave informed consent. Genomic DNA was purified from peripheral blood leukocytes using standard techniques, and amplified by means of PCR and oligonucleotide primers for exons 10, 11, 13, 14, 15, and 16. Single-strand conformation polymorphism analysis and direct sequencing were performed according to applicable national laboratory regulations. Classification of medullary thyroid cancer as hereditary disease was contingent on a positive DNA-based test involving one or more of the recognized mutational ‘hot spots’, i.e. codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, 891, or 918 (12).
Analysis of time-dependent changes

For each type of thyroid cancer, patient numbers permitting successive 5-year bands were formed:

i) For the study of changes in referral patterns, based on the year of (re-)operation at this institution (subsequently referred to as ‘5-year intervals’), and

ii) For the evaluation of advancements in diagnostic techniques over time, based on the year of thyroidectomy at any institution (subsequently referred to as ‘time periods’) (13).

Likewise, successive 20-year bands were constructed for the study of time-related changes in risk factors of the disease that cause a real change in disease rates, based on the patient’s year of birth (subsequently referred to as ‘birth cohorts’) (13).

Statistical analysis

Categorical and continuous data were tested on univariate analysis using two-tailed Fisher’s exact test and one-way ANOVA respectively. The level of statistical significance (all values were two-tailed) was set at <0.05.

Results

Clinical and histopathologic characteristics of the study population

The clinical and histopathologic breakdown for all 1644 thyroid cancer patients is given in Table 1. Perhaps having slightly higher rates of lymph node (21–58%) and distant metastases (6–22%), our study patients, with rare exceptions, were similar to other thyroid cancer patients from the international literature. Of note, the percentage of reoperations (47–76%) and the high proportion of medullary thyroid cancer patients (35%, or 583 of 1644 patients), of whom more than one-third (205 of 583 patients) had hereditary medullary thyroid cancer, were higher than described in many series. Indeed, many of our medullary thyroid cancer patients required completion thyroidectomy and systematic lymph node dissection for increased basal calcitonin levels heralding residual disease (14), or were referred for early thyroidectomy because of a positive gene test disclosing hereditable disease (12). As a matter of fact, our medullary thyroid cancer patients were referred from 87 (92%) of the 95 German postal code regions during a 15-year period across larger distances than patients with papillary and follicular thyroid cancer (means of 225 vs 161 and 158 km).

Changes in referral patterns by type of thyroid cancer and year of referral

For each type of thyroid cancer, referral patterns to this institution were analyzed by grouping all study patients into three 5-year intervals (1995–1999, 2000–2004, and 2005–2009) (Table 2).

Medullary thyroid cancer

Steady referral patterns were seen for patients with medullary thyroid cancer, both in terms of absolute numbers (163, 202, and 218 patients) and mean referral distance (227, 236, and 213 km; P=0.15), covering 55 (58%), 67 (71%), and 72 (76%) of the 95 German postal code regions. Referral patterns of patients with sporadic and hereditary medullary thyroid cancers were essentially the same (Table 2), although gene carriers travelled 20% larger distances (means of 254 vs 209 km; P<0.001).

Papillary thyroid cancer

Referrals for papillary thyroid cancer soared from 1995–1999 to 2000–2004 but seemed to have slowed down since. The significant growth in referrals (146, 279, and 389 patients) was paralleled by a concomitant expansion of

<table>
<thead>
<tr>
<th>Variables</th>
<th>Follicular thyroid cancer (247 patients)</th>
<th>Papillary thyroid cancer (814 patients)</th>
<th>Medullary thyroid cancer (583 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male, n (%)</td>
<td>98 (40)</td>
<td>256 (31)</td>
<td>247 (42)</td>
</tr>
<tr>
<td>Age at thyroidectomy, year, mean (95% CI)</td>
<td>54 (52; 56)</td>
<td>45 (44; 47)</td>
<td>44 (43; 46)</td>
</tr>
<tr>
<td>Age at referral to this institution, year, mean (95% CI)</td>
<td>55 (53; 57)</td>
<td>46 (45; 47)</td>
<td>46 (44; 47)</td>
</tr>
<tr>
<td>Reoperation, n (%)</td>
<td>187 (76)</td>
<td>514 (63)</td>
<td>272 (47)</td>
</tr>
<tr>
<td>Hereditary disease, n (%)</td>
<td>N/A</td>
<td>N/A</td>
<td>205 (35)</td>
</tr>
<tr>
<td>Largest primary tumor diameter, mm, mean (95% CI)</td>
<td>42 (39; 45)</td>
<td>20 (19; 21)</td>
<td>19 (18; 20)</td>
</tr>
<tr>
<td>Extrathyroidal tumor growth, n (%)</td>
<td>65 (26)</td>
<td>261 (32)</td>
<td>102 (17)</td>
</tr>
<tr>
<td>Lymph node metastasis, n (%)</td>
<td>53 (21)</td>
<td>387 (48)</td>
<td>340 (58)</td>
</tr>
<tr>
<td>Distant metastasis at the time of referral, n (%)</td>
<td>54 (22)</td>
<td>48 (6)</td>
<td>76 (13)</td>
</tr>
<tr>
<td>Referral distance, km, mean (95% CI)</td>
<td>158 (143; 174)</td>
<td>161 (152; 170)</td>
<td>225 (215; 235)</td>
</tr>
<tr>
<td>Postal region coverage (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>63</td>
<td>88</td>
<td>92</td>
</tr>
</tbody>
</table>

CI, confidence interval; N/A, not assessed.
<sup>a</sup>Classification based on a positive rearranged during transfection (RET) gene blood test.
<sup>b</sup>Three patients had no pertinent information regarding thyroid growth pattern.
<sup>c</sup>Number of referring relative to all 95 German postal code regions.
referral distance (means of 99, 168, and 180 km; $P<0.001$) and geographic coverage, with referrals originating from 39 (41%), 59 (62%), and 72 (76%) of the German postal code regions.

**Follicular thyroid cancer** In spite of the broadening catchment area with increasing referral distances (means of 98, 142, and 211 km; $P<0.001$), referrals for follicular thyroid cancer grew only moderately in size (69, 75, and 103 patients), coming from 23 (24%), 27 (28%), and 45 (47%) of the 95 German postal code regions.

**Changes in primary tumor size by type of thyroid cancer and year of thyroidectomy**

For evaluation of diagnostic changes over time, five 5-year time periods (1985–1989, 1990–1994, 1995–1999, 2000–2004, and 2005–2009) were constructed for each type of thyroid cancer based on the year of each patient’s thyroidectomy (Table 3; Fig. 2A and C).

Over the past 25 years, mean primary tumor diameters gradually decreased from 25 to 16 mm ($P=0.025$) for medullary thyroid cancer and from 28 to 18 mm ($P=0.017$) for papillary thyroid cancer. In absolute terms, this reduction was greater for hereditary medullary thyroid cancer (from 27 to 11 mm; $P=0.088$) than sporadic medullary thyroid cancer (from 23 to 19 mm; $P=0.11$). In stark contrast, no decline of primary tumor size was observed for follicular thyroid cancer (means of 45 to 42 mm; $P=0.52$).

**Changes in primary tumor size by type of thyroid cancer and year of birth**

For the study of time-dependent changes in environmental exposures, four successive 20-year cohorts (1921–1940, 1941–1960, 1961–1980, and 1981–2000) were formed based on the patient’s year of birth (Table 4; Fig. 2B and D).

From birth cohort to birth cohort, mean primary tumor size fell progressively from 22 to 10 mm ($P<0.001$) for medullary thyroid cancer, from 24 to 22 mm ($P<0.001$) for papillary thyroid cancer, and from 49 to 38 mm ($P=0.011$) for follicular thyroid cancer. Notably, the size reduction of primary medullary thyroid tumors occurred exclusively in patients with hereditary disease (from 20 to 7 mm; $P<0.001$), with no time trend discernable for patients with sporadic disease (Table 4). Among patients with follicular cell-derived thyroid cancers born after 1940, no further diminution of primary tumor size was observed (means of 17, 18, and 22 mm for papillary thyroid cancer, and 38, 39, and 38 mm for follicular thyroid cancer). The same applied to patients with medullary thyroid cancer born between 1941 and 1980 (means of 20 and 19 mm respectively). Intriguingly, patients with medullary

<table>
<thead>
<tr>
<th>Referral distance, km; mean (95% CI)</th>
<th>Geographic coverage, referring postal code regions, n (%)$^a$</th>
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<tbody>
<tr>
<td><strong>Cancer type</strong></td>
<td><strong>Patients, n</strong></td>
</tr>
<tr>
<td>Follicular</td>
<td>247</td>
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<tr>
<td>Papillary</td>
<td>814</td>
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<td>Medullary sporadic</td>
<td>583</td>
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<tr>
<td>Medullary hereditary$^d$</td>
<td>205</td>
</tr>
</tbody>
</table>
| CI, confidence interval. Relative to all 95 German postal code regions. | $^a$Relative to all 95 German postal code regions. $^b$One-way ANOVA. $^c$Two-tailed Fisher's exact test. $^d$Classification based on a positive rearranged during transfection (RET) gene blood test.
thyroid cancer born after 1980 harbored only cancers with tumors half the size of those from patients born in or before that year.

Patients with papillary thyroid cancer (Fig. 2B) and sporadic medullary thyroid cancer (Fig. 2D) who were in the youngest birth cohort (1981–2000) tended to have larger, more symptomatic primary tumors, presumably because these cancer types are so uncommon among patients younger than 30 years of age that they were not specifically screened for at the time.

Discussion

There were strong period effects of decreasing primary tumor size among our patients with papillary and medullary thyroid cancers, but not among those with follicular thyroid cancer. Such period effects are thought to reflect advances in diagnostic techniques, such as high-resolution cervical ultrasonography coupled with fine needle aspiration (FNA) cytology, and the increasing number of imaging studies to establish the diagnosis of thyroid cancer (1, 13). Equally powerful in this study were the birth cohort effects suggesting a gradual lessening of primary tumor size among patients with papillary, follicular, and medullary thyroid cancers. Birth cohort effects are deemed to indicate changes in environmental exposures, such as exposure to radiation or access to iodized food (13). In clinical practice, the relative contributions of period and birth cohort effects to temporal changes in primary tumor size are difficult to sort out for their complex interaction (5, 15).

Trends of primary tumor size in patients with papillary and follicular thyroid cancers

For many decades, iodine deficiency had been rampant in Germany. Only very recently has iodine supplementation, which is voluntary in Germany, reached normal levels as defined by the WHO, although by a narrow margin (16). As a corollary of this longstanding iodine deficiency in Germany, older adults still have larger thyroid glands than their younger peers (17). Increasing iodine sufficiency through iodization of agricultural animal feed and the use of iodized table salt are believed to be driving the shift from follicular thyroid cancer to papillary thyroid cancer (18). Iodine deficiency, diminishing the incidence of benign thyroid disease, should lead to smaller primary thyroid cancers — as witnessed in our birth cohort analysis (Table 4) — at least indirectly by facilitating their earlier detection. Indeed, incidence rates have risen more for smaller than larger differentiated (mainly papillary) thyroid cancers. Nevertheless, all tumor sizes have been affected by this increase (15, 18, 19), pointing to changes in environmental factors. For Italy, the Italian Network of Cancer Registries described a significant decrease in tumor diameter from 28 (1985–1994) to 14 mm (1995–2004) for papillary thyroid cancer, and from 40 (1985–1994) to 17 mm (1995–2004) for follicular thyroid cancer (20).

No such parallelism of falling papillary and follicular thyroid cancer size occurred in our institutional series, which may have included more advanced thyroid cancers. Our data confirmed the reduction of primary tumor size over time for papillary thyroid cancer, although on a smaller scale than reported from Italy. In our series (Table 3), mean size of papillary thyroid cancer fell from 28 mm (1985–1989) to 18 mm (2005–2009), whereas follicular thyroid cancer size refused to decline appreciably, with means of 45 mm (1985–1989) versus 42 mm (2005–2009). This disparity in secular trends between papillary and follicular thyroid cancers in our study, which was greatest when period effects were considered (Table 3), raises important questions. Clearly, the diagnosis of follicular-patterned thyroid tumors depends on the accuracy of high-resolution ultrasonography and fine-needle aspiration cytology. Based on WHO morphologic criteria, all epithelial thyroid tumors lacking the nuclear features characteristic of papillary thyroid cancer constitute the broad default category of follicular thyroid cancer. Such a definition, relying on the exclusion of nuclear features diagnostic of papillary thyroid cancer, has the disadvantage of combining potentially disparate tumor entities that may not hold together sufficiently as a group. Unlike nuclear features, capsular invasion and vascular invasion defy...
ascertainment cytologically, so that minimally invasive follicular thyroid cancers are frequently missed. Diagnosis of follicular thyroid cancer is more straightforward when the tumor has encroached on the juxtathyroidal tissues. For extrathyroidal growth to occur, the thyroid tumor must have reached a certain size unless it arises from the periphery of the thyroid gland.

**Trends of primary tumor size in patients with medullary thyroid cancer**

For medullary thyroid cancer, the decrease in primary tumor size over time certainly cannot be explained with increasing iodine sufficiency. This calcitonin-secreting neuroendocrine neoplasm, which does not express the sodium/iodine symporter, is unable to concentrate iodine. Conceivably, the first description of medullary thyroid cancer in 1959 as a tumor entity in its own right (21), and the subsequent availability and widespread use of sensitive calcitonin assays since the 1980s (22–26) may have prompted the more frequent and earlier detection of sporadic and hereditary medullary cancers. This drive toward early tumor diagnosis gathered additional speed with the advent of genetic testing, enabling presymptomatic identification of germ-line mutations in the RET proto-oncogene (27–29).

Intriguingly, DNA-based screening for RET germline mutations provides for the rapid and reliable identification, and hence early thyroidectomy, of asymptomatic gene carriers with occult hereditary medullary thyroid cancer, even in the presence of yet normal calcitonin serum levels (12). This evolutionary change was very apparent in German RET gene carriers born after 1980 whose mean tumor size was effectively more than halved (Table 4). Patients with sporadic medullary thyroid cancer, presenting with symptomatic disease less often in recent years than they used to in the past, experienced smaller reductions in tumor size than patients with hereditary disease who enjoyed more liberal calcitonin screening from the outset. With the German evidence-based consensus recommendation in 2004 (30) and the European Thyroid Association’s endorsement of serum calcitonin measurements for the initial diagnostic evaluation of thyroid nodules in 2006 (31), the practice of screening patients with thyroid disease routinely for increased calcitonin levels appears to have gained additional momentum. This notion is supported by the recent diminution of mean primary tumor size from 19 mm (1995–2004) to 16 mm (2005–2009), ending a 10-year period of stagnation (Table 3).

In the US, the National Cancer Institute’s SEER Program database revealed a larger annual mean tumor size in 1988 compared with the 1989–2000 period (32) for medullary thyroid cancer. No time trend was noted between 1989 and 2000 toward a smaller annual tumor size, which continued to fluctuate around a mean of 28 mm (32). In contrast, the
continuous lessening of primary tumor size was evident in our German patients with medullary thyroid cancer, falling from 25 (1985–1989) to 16 mm (2005–2009) (Table 3). The reasons underlying these disparate trends are unknown. In Europe, calcitonin screening of patients with thyroid nodules has been embraced with greater enthusiasm (30, 31) than in the US, where it is not routinely recommended because of concerns regarding its cost-effectiveness (33, 34).

**Strengths and limitations of population-based and referral-based studies**

National population-based registries, such as SEER in the US, have the great advantage of holding a large number of patients with the disease of interest. Nonetheless, there are also limitations involving nonstandardization of histopathologic diagnosis and incomplete data collection (13). The SEER data, for instance, do not contain information regarding heredity of cancers (35). Before 1988, information on tumor size and lymph nodes was not routinely collected by the SEER program (13, 15, 32). In 1992, the SEER database was enlarged by adding four additional cancer registries to the nine existing local registries, expanding coverage from ~10 to 14% of the US population (2, 15). It is not clear whether, and if so how much, this expansion of the catchment area may have altered the composition of thyroid cancer patient in the database.

Standardization of histopathologic diagnosis and completeness of data are less of an issue in institutional series. In Germany, statutory and private health insurance cover physician and hospital fees nationwide for all recognized surgical and medical treatments but not necessarily all traveling costs. Previous research has shown that, under these quasi-ideal conditions, patients are being referred more often for specialist surgical care across greater traveling distances when they are younger and have more extensive disease (8, 9). Intriguingly, primary tumor size was not a determinant of referral to our institution (8). This allowed us to study thyroid cancer size in our referral population as a function of time. Time trends based on periods should be more reliable the more the catchment area of the population of interest has remained constant. This precondition was met more for medullary thyroid cancer than papillary thyroid cancer but obviously was missed for follicular thyroid cancer. Nevertheless, the preferential referral of patients with more extensive disease (8, 9) may have enriched our study population with larger thyroid cancers, perhaps rendering it more difficult for period effects to show in this institutional series.

**Conclusion**

Powerful period (for medullary and papillary thyroid cancers) and birth cohort effects (for medullary, papillary, and follicular thyroid cancers) were noted in German thyroid cancer patients referred for specialist surgical care. The seeming failure of follicular thyroid cancers to shrink over successive time periods in this series may have been due to the preferential referral of larger thyroid cancers to this institution. The consistency and robustness of these and literature data signify strong trends toward smaller tumors for medullary, papillary, and follicular thyroid cancers. The causes underlying these secular trends, having the potential to cut cancer-specific mortality rates, warrant further investigation.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Table 4** Changes in primary tumor size by type of thyroid cancer and year of birth (n= 1619 patients).

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<tbody>
<tr>
<td>Follicular</td>
<td>241</td>
<td>49 (44; 54)</td>
<td>38 (34; 43)</td>
<td>39 (31; 43)</td>
<td>38 (22; 54)</td>
<td>0.011</td>
</tr>
<tr>
<td>Papillary</td>
<td>810</td>
<td>24 (21; 27)</td>
<td>17 (16; 19)</td>
<td>18 (16; 20)</td>
<td>22 (19; 25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medullary</td>
<td>568</td>
<td>22 (19; 26)</td>
<td>20 (18; 22)</td>
<td>19 (17; 21)</td>
<td>10 (6; 14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medullary sporadic</td>
<td>376</td>
<td>23 (19; 27)</td>
<td>21 (19; 24)</td>
<td>23 (20; 25)</td>
<td>29 (14; 43)</td>
<td>0.59</td>
</tr>
<tr>
<td>Medullary hereditary</td>
<td>192</td>
<td>20 (14; 27)</td>
<td>16 (13; 20)</td>
<td>14 (11; 16)</td>
<td>7 (3; 10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval.

²A total of 12 and 13 patients underwent thyroidectomy in or before 1920 or after 2000.

Classification based on a positive rearranged during transfection (RET) gene blood test.
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