Cancer Causes and Control **14**: 13–17, 2003.

Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland

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Received 26 February 2002; accepted in revised form 30 August 2002

Key words: incidence, papillary carcinoma, population-based, thyroid carcinoma.

Abstract

Objective: Several studies have reported upward incidence trends of papillary thyroid cancer. It is unclear whether these trends reflect a real risk increase, by some attributed to iodine supplementation, or an artificial one, due to increased diagnostic activity or changed histological criteria. This study examines if these artificial factors explain the increased papillary thyroid cancer incidence in the Swiss canton of Geneva.
Methods: All thyroid carcinomas (n = 436) recorded between 1970 and 1998 at the Geneva Cancer Registry were considered. European age-adjusted incidence trends were estimated using linear regression analysis. For papillary cancers we evaluated diagnostic modalities and way of presentation (in particular microcarcinoma < 1 cm or silent carcinoma). In addition, we reviewed the histological slides of follicular carcinomas.
Results: Papillary thyroid cancer incidence increased significantly from 0.7 to 1.8/100,000 for men and from 3.1 to 4.3/100,000 for women between 1970–74 and 1995–98. The proportion of microcarcinomas and silent carcinomas increased from 17% to 24% between 1970–79 and 1990–98. At histological review, follicular cancers were more often reclassified as papillary cancer for cases diagnosed between 1970 and 1979 than for cases diagnosed between 1990 and 1998 (45% *vs* 25%, p = n.s.).
Conclusions: The increasing papillary thyroid cancer incidence seems mainly due to changes in histological diagnostic criteria and, to a lesser extent, to increased diagnostic activity. If confirmed, the results of this study indicate that fears of increasing incidence rates of papillary thyroid cancer should not prevent implementation of adequate programs of iodine supplementation in the many areas where iodine deficiency still prevails.

Introduction

Thyroid cancer is of particular interest in Switzerland as both incidence and mortality rates are among the highest in the world [1]. Thyroid cancer includes several histological subtypes (*i.e.* papillary, follicular, anaplastic, and medullary) of which the papillary subtype is the most common one (representing 40–70% of all thyroid cancers) [2]. Over recent decades upward incidence trends of papillary thyroid cancer have been reported [3, 4] and in the Swiss canton of Geneva the incidence has also increased. It is, however, uncertain whether these trends reflect real increasing incidence rates or if the observed trends are artificial, *i.e.* caused by increased diagnostic activity or changes in histological criteria.

Development and improvement of diagnostic modalities – such as cytology, ultrasound, and scintigraphy – permit easier diagnosis of thyroid nodules. The advent of these minimally invasive techniques might have resulted in increased diagnostic activity and, consequently, in a growing diagnosis of small and/or asymptomatic papillary cancers [5].

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In addition, the diagnostic criteria for the histological classification of thyroid tumors have been subject to changes over recent decades. According to the 1974 World Health Organization (WHO) classification, follicular cancer was defined by a malignant epithelial tumor with architecture and cells similar to those normally found in an adult thyroid gland. Papillary cancer was defined as a malignant epithelial tumor with papillary structures, of which the nuclei may have a ground-glass appearance [6]. In 1988, new WHO guidelines were implemented, recommending lesions without the presence of papillae but with typical cytological features – *i.e.* ground-glass nuclei, nuclear grooves, and psammoma bodies–to be classified as papillary cancer [7]. These changes have favored the diagnosis of the papillary subtype at the expense of the follicular one, and might explain part of the increased papillary cancer incidence.

This study aims to evaluate whether changes in diagnostic facilities and histological criteria could explain the observed increased incidence of papillary thyroid cancer in Geneva. To evaluate whether the changed diagnostic facilities increased papillary thyroid cancer incidence we hypothesized that the proportion of microcarcinomas and/or silent carcinomas had increased over time. To evaluate whether changed diagnostic criteria explained the increased papillary thyroid cancer incidence, we hypothesized that many of the tumors diagnosed as follicular cancer before the change in criteria would today be diagnosed as papillary cancer.

Materials and methods

Data were derived from the Geneva Cancer Registry data set, which includes information on all cancers occurring in the resident population of the canton, approximately 400,000 inhabitants. The registry collects information from various sources and is considered very accurate with a low percentage (<2%) of cases recorded from death certificates only [8]. The data collection is based on a voluntary agreement between the recording medical institutions of the canton of Geneva and the registry. Data are abstracted systematically from all histological laboratories and public hospitals by trained registrars. These tumor registrars have access to all medical files in the public hospitals and they actively retrieve the required information. Private practitioners regularly receive inquiry forms to secure missing clinical and therapeutic data. Death certificates are consulted systematically.

Recorded data include: sociodemographic details of patients (age, gender, nationality, place of birth), diagnostic circumstances (consultation following symptoms in relation to the tumor, screening/check-up, fortuitous discovery, autopsy, death certificate), modalities of diagnostic assessment (clinical status, imaging, cytology, biopsy, surgery), tumor characteristics (including histological type and differentiation coded according to the *International Classification of Diseases for Oncology*, ICD-O) [9], stage of disease at diagnosis, treatment during the first six months after diagnosis, survival status, and second primary tumor occurrence. Tumor recurrences are not systematically recorded.

In this study we included all incident cases of histologically confirmed thyroid cancer (ICD-O code: 193) diagnosed between 1970 and 1998 (n = 436, 107 among men and 329 among women). Histological subtypes were classified into papillary carcinoma, follicular carcinoma, and other (including anaplastic carcinoma and medullary carcinoma). Trends in incidence rates (European standard) were estimated for both genders and histological subtypes by means of linear regression analysis based on the maximum-likelihood method with generalized log-linear modeling [10].

To test our first hypothesis (*i.e.* if the increased papillary thyroid cancer incidence were due to increased diagnostic activity, the proportion of microcarcinomas and/or silent carcinomas would have increased over time), we opened the clinical files of patients diagnosed with papillary thyroid cancer and retrieved additional information on method of diagnosis (especially on the use of cytology) and on the way of presentation at diagnosis. We classified papillary cancers into the following categories: (1) microcarcinoma, *i.e.* cancers with a tumor diameter $\leq$1 cm; (2) silent carcinomas, *i.e.* other tumors with no apparent symptoms (*i.e.* fortuitously discovered, detected at autopsy); and (3) clinical cancer, tumors presenting with symptoms compatible with thyroid pathology.

To test our second hypothesis (*i.e.* if the increased papillary cancer incidence were caused by changed diagnostic criteria, many of the tumors diagnosed as follicular cancer before the change in criteria would today be diagnosed as papillary cancer), we performed a histological review of thyroid cancers originally diagnosed as follicular cancer between 1970 and 1980 (early period) and between 1990 and 1998 (late period). In the early period the 1974 WHO criteria were generally used, and in the late period the 1988 WHO criteria were applied. The histological review was performed by a pathologist with extensive experience and special interest in thyroid pathology. This pathologist assesses more than 50% of all thyroid lesions that are operated in the Geneva University Hospital and is the consultant for thyroid pathology for the surgeons. The original slides

of the tumors were obtained. The revision was executed following the instructions of the Armed Forces of Pathology (AFIP) *Tumors of the Thyroid gland* [11], which are very similar to the 1988 WHO guidelines.

We calculated the proportions of reclassification of follicular cancer (with 95% confidence intervals). Finally, we estimated the incidence rates according to histological subtype, adjusting for the level of reclassification.

Results

Trends of thyroid cancer by histological subtype are presented in Figure 1. The overall incidence of thyroid cancer did not change significantly over the past three decades (linear tri-annual trend 0.99, 95% CI 0.96–1.03) and was the same for men (0.95, 95% CI 0.88–1.01) and women (1.01, 95% CI 0.97–1.05). The incidence rate of papillary cancer increased significantly over time (linear tri-annual trend 1.07, 95% CI 1.02–1.13), and was comparable for men (1.14, 95% CI 1.03–1.26) and women (1.06, 95% CI 1.01–1.12). The incidence of follicular cancer decreased (linear tri-annual trend 0.87, 95% CI 0.81–0.94). Among men there was a sharp decrease (linear trend 0.71, 95% CI 0.60–0.82), but among women the decrease was not significant (linear trend 0.96, 95% CI 0.87–1.05). The overall incidence of other histological subtypes also decreased significantly (linear tri-annual trend 0.92, 95% CI 0.86–0.99) and the trend was similar for men (linear trend 0.88, 95% CI 0.76–1.02) and women (linear tri-annual trend 0.94, 95% CI 0.86–1.02).

As expected, the use of cytology increased considerably. Between 1970 and 1974 none of the papillary thyroid cancers was diagnosed by means of cytology, whereas between 1995 and 1998 almost 50% of the papillary cancers were diagnosed cytologically (data not shown). However, the proportion of silent carcinomas and microcarcinomas increased only slightly from 17% in 1970–79 to 24% in 1990–98 (Figure 2).

Table 1 shows the results of the histological review of the thyroid tumors originally diagnosed as follicular cancer. Histological blocks were retrieved for 33 (69%) of the 48 patients diagnosed between 1970 and 1980 and 16 of the 20 (80%) patients diagnosed between 1990 and 1998. Lesions diagnosed as follicular cancer in the early period were reclassified as follows: 15 (45%) papillary carcinoma, six (18%) poorly differentiated/anaplastic carcinoma, and three (9%) as benign adenoma. In only nine (27%) patients was the diagnosis follicular cancer maintained. In the late period a substantially lower proportion of follicular cancers was re-diagnosed as papillary cancer (n = 4, 25%). In this period the initial diagnosis of follicular cancer was confirmed in 11 (69%) patients.

We used the proportions of reclassification to recalculate the crude incidence rates according to histological subtype (Table 2). The observed difference in papillary thyroid cancer incidence between the early and the late period was 1.18/100,000. After correction this difference was reduced by 36% to 0.75/100,000.

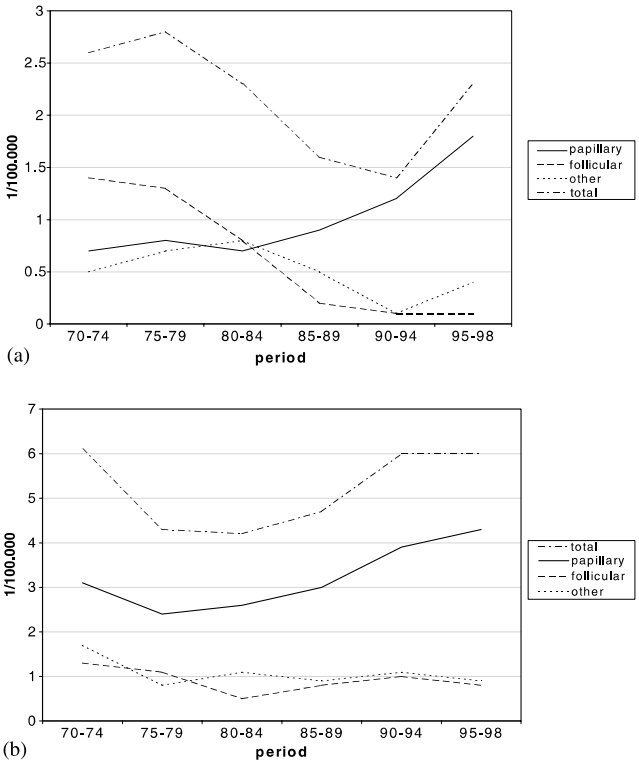

Fig. 1. Mean annual incidence rates (age standardized to European population) by histological subtype for men (panel **a**) and women (panel **b**).

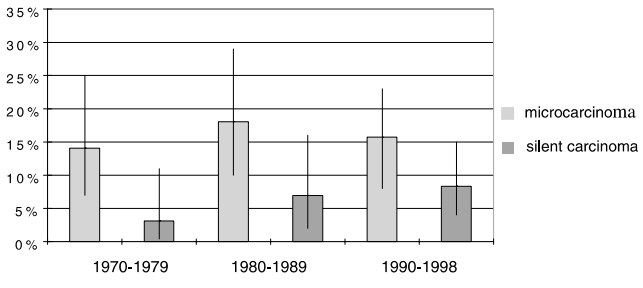

Fig. 2. Proportion (and 95% confidence intervals) of papillary thyroid cancers presenting as microcarcinomas (≤1 cm) or silent carcinoma (other tumor with no apparent symptoms of thyroid pathology) per period (both sexes together).

Table 1. Results of histological review: (re)classification of thyroid carcinomas originally diagnosed as follicular carcinoma (both sexes together)

"Follicular" carcinoma (re)classified as	1970–80 (n = 33)		1990–98 (n = 16)	
	No.	Percentage (95% CI)	No.	Percentage (95% CI)
Follicular carcinoma	9	27%, (13–46)	11	69%, (41–89)
Papillary carcinoma	15	45%, (28–64)	4	25%, (7–52)
Poorly differentiated/anaplastic carcinoma	6	18%, (7–36)	1	6%, (0–30)
Benign adenoma	3	9%, (2–24)	0	0%, (0–21)

Table 2. Observed and corrected incidence rates (1,100,000) of thyroid cancer according to histological subtype (both sexes together)

	1970–80		1990–98	
	Observed	Corrected[a]	Observed	Corrected[b]
Papillary cancer	1.88	2.46	3.06	3.21
Follicular cancer	1.29	0.35	0.62	0.43
Other cancers	1.15	1.39	0.82	0.86
Total	4.32	4.20[c]	4.50	4.50

[a] 45% of follicular cancers reclassified as papillary cancer, 18% reclassified as other cancer, 27% remained follicular cancer.

[b] 25% of follicular cancers reclassified as papillary cancer, 6% reclassified as other cancer, 69% remained follicular cancer.

[c] 9% of thyroid cancers diagnosed as follicular carcinoma between 1970 and 1980 were reclassified as benign.

Discussion

Increasing rates of papillary thyroid cancer incidence is a well-documented phenomenon in industrialized countries. Papillary thyroid cancers are in general well-differentiated tumors with an excellent prognosis [1]. Mortality rates of thyroid cancer have decreased in Switzerland over recent decades (world standardized mortality rates were 1.4/100,000 for men and 1.6/100,000 for women during the period 1955–64 and went to 0.7 and 1.0 respectively for the period 1985–89) [12].

In the USA the increasing papillary thyroid cancer incidence has been attributed to the wide use of radiation treatment for benign childhood head and neck conditions between 1930 and 1960 [1]. However, increasing incidences were also observed in the Nordic countries where, as in Switzerland, radiation therapy for benign conditions was used infrequently.

Iodine, both as deficit and excess, has also been suggested to play a role in the etiology of respectively follicular and papillary thyroid cancer [1]. Switzerland is an iodine-deficient country, and goiter and cretinism related to this deficit were especially frequent in mountainous rural areas [2]. In an attempt to prevent these diseases the Swiss authorities implemented several prophylactic programs, including the introduction of iodine-enriched salt since 1922 [13]. In previous studies for other ex-endemic goiter regions where iodine was supplemented, similar increasing papillary cancer incidence rates were reported [14, 15]. It has therefore been suggested that the increased papillary cancer incidence is caused by increased iodine intake by the population. According to this theory iodine deficiency enhances the transition from papillary carcinoma (the early carcinoma of the thyroid gland) toward less differentiated, more aggressive types. Iodine implementation might prevent this transition [3]. Data from Sweden did not suggest any enhancing effect of iodization on papillary carcinoma, as increases in papillary thyroid cancer incidence were similar in iodine-deficient and iodine-sufficient areas [16].

The present study indicates that the sharp increase in papillary thyroid cancer incidence between 1970 and 1998 in Geneva can be partly explained by changes in histological WHO criteria in 1988. The slight increase in papillary thyroid cancer that was observed before 1985 may be explained by an increased use of minimally invasive techniques, in particular fine-needle cytology. Although the use of cytology has increased tremendously, this did not significantly increase the proportion of silent papillary cancers or microcarcinomas. Probably cytology has been increasingly used as a first step in the assessment of symptomatic thyroid abnormalities (*i.e.* nodules). We nevertheless feel that the nonsignificant increase in the proportion of silent carcinomas should be interpreted cautiously. Nowadays, many frequent symptoms among women (*i.e.* disorders of menstruation, tiredness, nervousness, etc.) often lead to a search for thyroid abnormalities which might increase the number of silent carcinomas detected [17, 18].

In this study 45% of the lesions diagnosed as follicular cancer between 1970 and 1980 were reclassified as papillary cancer (compared to 25% between 1990 and 1998). In 1988, the World Health Organization implemented new diagnostic criteria for the histological classification of thyroid tumors [7]. Before the change in criteria the predominance of a papillary architectural component was mandatory to classify a lesion as papillary cancer. After the changes, lesions without the presence of papillae but with typical cytological features,

i.e. ground-glass nuclei, nuclear grooves, and psammoma bodies, were recommended to be classified as papillary cancer. Accordingly, the definition of papillary cancer was widened and lesions that were previously (correctly) classified as follicular cancer are nowadays being classified as papillary cancer [2].

Our observations are in accordance with the findings of previous investigators who also reported high levels of reclassification among tumors diagnosed as follicular thyroid cancer [4, 19]. This study additionally demonstrates a strong variation in level of reclassification over time.

Previous studies demonstrated that the diagnosis ''papillary thyroid cancer'' is maintained in the great majority of cases (93–98%) [4, 19]. We therefore assumed that reclassification of tumors initially diagnosed as papillary thyroid cancer does not have an impact on papillary cancer incidence, and limited the histological review to follicular thyroid cancer. Despite thorough research we did not find 19 histological blocks. This could introduce a bias if the missing cases presented a different histological profile than the reviewed cases. However, no differences were found in terms of sociodemographic data, method of diagnosis, or tumor characteristics as recorded by the cancer registry.

We realize that the number of cases in our histological review is too low to draw any definite conclusions. Also, we were not able to address another consequence of the changed diagnostic criteria in this study. Some benign-appearing lesions, formerly diagnosed as benign adenoma, are nowadays classified as papillary cancer [2]. As the Geneva Cancer Registry registers only malignant lesions, we were not able to evaluate whether this phenomenon attributed to the increased papillary thyroid cancer incidence. Future research is needed to elucidate this specific question.

This study evaluates to what extent changes in diagnostic facilities and histological criteria could explain the observed increased incidence of papillary thyroid cancer in a high-risk area of thyroid cancer. We conclude that the changes in histological criteria favoring the classification of the papillary type may explain an important fraction of the increase. If confirmed, the present findings are of substantial importance from a public health viewpoint. Fears of increases in the incidence of papillary carcinoma should not hamper the implementation of adequate programs of iodine supplementation in many European countries (*e.g.* France, Belgium, Italy, etc.) where iodine deficiency still prevails [20, 21].

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