# Incidence-based Mortality Trends for Thyroid Cancer: Is there a «true» Increase in Incidence of Thyroid Cancer in Switzerland?

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## Introduction

Thyroid cancer is the most important cancer among endocrine tumors. In Switzerland it accounts for less than 3% of all invasive cancers in women and for less than 1% in men. This corresponds yearly to 650 (490 women, 160 men) new cases of thyroid cancer and 60 (40 women, 20 men) deaths from thyroid cancer during 2008-2012. The yearly age standardized incidence rate in this period accounted for 11.0 and 3.6 new cases per 100'000 among women and men, respectively. Since the year 1983 this rate is only slightly increasing for men but doubled for women [1].

Similar trends are seen in other European countries, in America and Asia, which are accompanied by improving survival rates [2, 3]. In Switzerland, the 10-year survival rates between 1998 and 2012 increased too, from 79% to 88% among women and to 85% among men, respectively. In comparison to ten other European countries, the survival rate in Switzerland ranks 6$^{th}$ for women and 4$^{th}$ for men [1, 4].

The debate about the underlying causes of the observed dramatic increase in incident thyroid cancer is still ongoing. Some groups claim that the increase is only due to overdiagnosis of mainly indolent cancers of small sizes, which untreated would probably not result in death and not even in symptoms [5]. This would naturally also increase thyroid cancer survival rates. Recently, the impact of overdiagnosis possibly underlying the worldwide thyroid-cancer epidemic was quantified by comparing observed rates vs. rates expected without overdiagnosis for thyroid cancer from different countries [3]. Overall, more than 470,000 women and 90,000 men may have been overdiagnosed with thyroid cancer over two decades in the 12 countries analyzed [3]. On the other hand, some reported a «true» increase in thyroid cancer incident cases showing a positive trend in «incidence-based» mortality during 1994-2004 in the United States [6]. Therefore more studies are needed across different countries to better understand the various underlying causes of the dramatic increase in thyroid-cancer incidence in the last decades.

A recent study in Switzerland showed a large increase in the incidence of thyroid cancer during 1998-2012, limited to papillary and early stage tumors, with a three- to fourfold parallel increase in thyroidectomy. The mortality slightly decreased. The authors postulate that a substantial and growing part of the detected thyroid cancers are overdiagnosed and overtreated [7].

In our study, we focus on «incidence-based» mortality of thyroid cancer by histologic subtypes to evaluate if a part of the thyroid cancer increase observed in Switzerland could be explained by a «true» increase as it was shown by Lim et al. for the United States [6]. Moreover, we update and extend the previously reported incidence trends of thyroid cancer by sex, age and language region.

## Methods

The Foundation National Institute of Cancer Epidemiology and Registration (NICER) manages the population-based national cancer dataset, with the purpose of providing comprehensive cancer surveillance for Switzerland, as well as supporting epidemiological cancer research [8]. Population-based cantonal cancer registries collect data directly from patients' medical records and transmit a defined and pseudonymized subset of the information to NICER. Diagnoses from 1988 to 2014 in thirteen cantons where cancer registration covered at least 19 consecutive years (ZH, GR, GL, SG, AR, AI, BS, BL, VD, NE, VS, GE, and TI) are included in this report. The first eight cantons represented the German-speaking part of Switzerland, and the remaining five cantons the French/Italian-speaking part. The respective cancer registries cover about 60% of the Swiss population. Case counts for whole Switzerland are extrapolations by sex, age, tumor group, and Swiss language region.

Selection criteria were all primary tumors of malignant behavior with topography code C73 from the International Classification of Diseases for Oncology, third edition (ICD-O-3) [9]. Excluded are all systemic tumors (ICD-O-3 morphology code M9580 and higher). Almost all diagnoses were confirmed microscopically (>98%). We differentiated between papillary carcinoma (M8050, M8260,

M8340-M8344, M8350, M8450, M8452, M8453, M8460), follicular carcinoma (M8290, M8330-M8333, M8335), medullary carcinoma (M8345, M8510, M8512, M8513), anaplastic carcinoma (M8020-M8022, M8030-M8035), other specified morphologies (M8041, M8043, M8051, M8052, M8070-M8072, M8140, M8190, M8230, M8231, M8240, M8246, M8250, M8310, M8337, M8346, M8347, M8430, M8560, M8574, M8589, M8680, M8800, M8801, M8810, M8830, M8890, M8980, M9120, M9130, M9150), and unspecified cancer types (M8000-M8005, M8010-M8012).

Incidence rates are expressed as N cases per 100,000 person-years, and age-adjustment of rates for all ages combined, as well as within age groups, was based on the EU standard population [10]. The study is observational, thus confidence intervals should only be interpreted as rough descriptors of uncertainty [11].

Incidence-based thyroid cancer mortality trends are based on cantons and years of death with fewer than 15% missing information on the cause of death for registered cancer patients. These included 8 cantons (GR, GL, SG, AR, AI, VS, GE, and TI) and death years 2000-2014. For each canton, there were at least 5 years of incidence registration before causes of death analysis started in 2000. Just 0.3% of cases were based on death certificates only, i.e. the true incidence date was unknown and has been set to the day of death.

Annual percentage changes (APC) were estimated using a heteroscedastic simple linear model for logarithmic transformed age-standardized mortality rates implemented in the Joinpoint Regression Program v4.4.0.0 [12].

## Results

### A) Incidence-based mortality trends (IBM)

The analysis for trends in incidence-based mortality rates for the mortality years 2000-2014 is shown in **Table 1**, 2 and **Figure 1**.

Over 98% of thyroid cancer diagnoses were confirmed by microscopy. Histology of thyroid cancer was first divided into the following morphologic subgroups: papillary, follicular, medullary, anaplastic and unspecified histology and then constricted to three groups: papillary, non-papillary (follicular, medullary, anaplastic) and unspecified histology to achieve enough statistical power.

In our data sample, a total of 992 patients diagnosed with thyroid cancer (C73, ICD-10) have died. Half of these patients died from thyroid cancer and nearly half of other causes: the cause of death (CoD) was thyroid cancer (C73) in 486 (49.0%) patients, or 176 men (17.7%) and 310 women (31.3%) (**Tab. 1**). CoD was not C73 in 472 (47.6%) patients, and was unknown in only 34 (3.4%) patients (**Tab. 1**).

| | CoD not C73 | | CoD C73 | | CoD Unknown | | |
|---|---|---|---|---|---|---|---|
| **Thyroid Cancer (C73) Histologies** | **Men** | **Women** | **Men** | **Women** | **Men** | **Women** | **Total** |
| | **N Counts** | | | | | | |
| Papillary | 70 | 184 | 48 | 80 | 4 | 8 | 394 |
| Non-papillary | 58 | 150 | 118 | 192 | 12 | 10 | 540 |
| Unspecific histology | 6 | 4 | 10 | 38 | 0 | 0 | 58 |
| All histologies | 134 | 338 | 176 | 310 | 16 | 18 | **992** |
| | **Proportion (%) of all histologies and all Causes of Death (CoD)** | | | | | | |
| Papillary | 7.1 | 18.5 | 4.8 | 8.1 | 0.4 | 0.8 | 39.7 |
| Non-papillary | 5.8 | 15.1 | 11.9 | 19.4 | 1.2 | 1.0 | 54.4 |
| Unspecific histology | 0.6 | 0.4 | 1.0 | 3.8 | 0.0 | 0.0 | 5.8 |
| All histologies | 13.5 | 34.1 | 17.7 | 31.3 | 1.6 | 1.8 | **100** |
| | **Proportion (%) of all C73 deaths** | | | | | | |
| Papillary | | | 9.9 | 16.5 | | | |
| Non-papillary | | | 24.3 | 39.5 | | | |
| Unspecific histology | | | 2.1 | 7.8 | | | |
| All histologies | | | 36.2 | 63.8 | | | |

Tab. 1. Number of available Swiss thyroid cancer cases (C73) for the analysis for trends in incidence-based mortality rates. Data were used from eight cantons (SG/AR/AI, GR/GL, TI, VS, GE) for the death years 2000-2014 due to missing or incomplete data in other Swiss registries. CoD=cause of death.

There were 394 (39.7%) patients with papillary carcinoma, 540 (54.4%) patients with non-papillary carcinoma, and only 58 (5.8%) patients with unspecific types of thyroid cancer, indicating good quality data. More than a quarter (26.4%) of the patients who died from thyroid cancer (C73) were previously diagnosed by the histologic type of papillary carcinoma, 63.8% by non-papillary histology and 9.9% by unspecified histology type of thyroid cancer (**Tab. 1**).

The distribution patterns of these three different histology groups among those who died from thyroid cancer were very similar over the analyzed time period from 2000-2014. Histology-specific causes of death in the period 2000-2004 were 24.1%, 66.7%, and 9.2% for papillary, non-papillary, and unspecific thyroid cancer, respectively, and 24.1%, 66.3%, and 9.6% in the period 2010-2014, respectively [data not shown].

**Figure 1** shows age-standardized incidence-based mortality (IBM) rates of thyroid cancer death by year of death and by histologic type for Switzerland, based on a subset of eight cantons. The histology-based mortality trends for papillary and non-papillary histologic subtypes are interpreted as representative for whole Switzerland because the IBM trend for all histologic types was identical to the mortality trend for thyroid cancer for the death years 1988 to 2014 in the official Statistic of the Federal Office (FSO) (**Fig. 1**).

| Histologic type | Statistics* | APC** [%] | 95% CI |
|---|---|---|---|
| Papillary | IBM | -0.4 | (-6.3, 5.9) |
| Non-Papillary | IBM | -3.6 | (-6.8, -0.3) |
| All histologies | IBM | -3.0 | (-6.0, 0.0) |
| All histologies | FSO | -3.6 | (-4.2, -3.1) |

Tab. 2. Thyroid cancer as principle cause of death for different histologic types. *Statistics: IBM: Incidence-based mortality rates based on deaths during 2000-2014 and cases diagnosed 1996-2014, in a subset of 8 Swiss cantons; FSO: Mortality rates from the official vital statistics (FSO) are based on deaths during 1996-2014 from all 26 Swiss cantons. **APC: Annual percentage changes in age-standardized mortality rates.

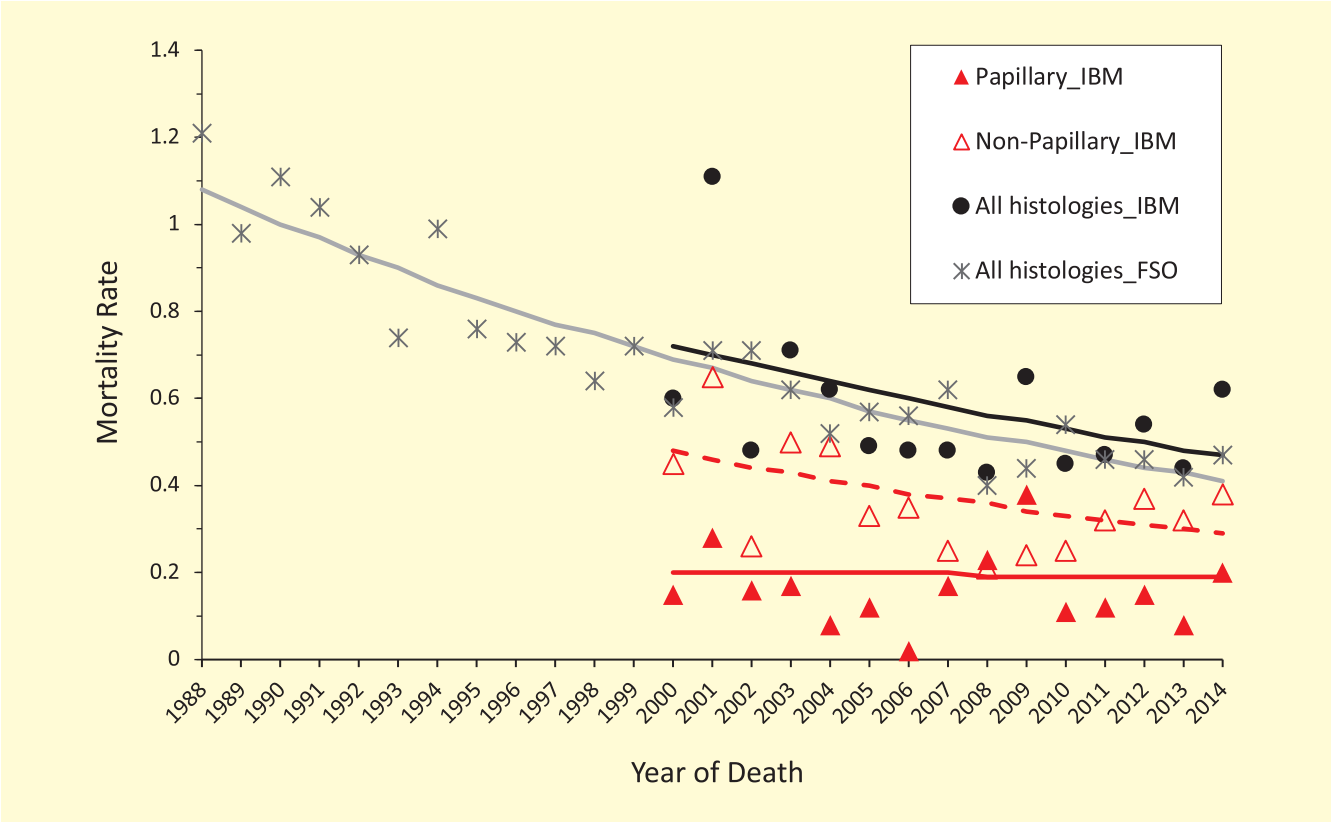


Fig. 1. Thyroid cancer as principle cause of death (CoD) for different histologic types. Age-standardized incidence-based mortality rates (IBM) are based on deaths during 2000-2014 and cases diagnosed during 1996-2014, in a subset of eight Swiss cantons. Mortality rates from the official vital statistics (FSO) are based on deaths during 1988-2014 from all 26 Swiss cantons.

The time trend for mortality of thyroid cancer over all histologies is steadily decreasing (negative), and a positive trend for the papillary histologic type alone could not be observed with the actual data from Swiss Cancer Registries. The annual percentage change of papillary IBM was -0.4 and not significantly different from zero (95%CI: -6.3, +5.9; **Tab. 2**). Due to limited data for Switzerland this analysis could not be done separately by stage of thyroid tumor. Nevertheless, the current analyses for Switzerland do not point towards a positive IBM-trend and therefore do not confirm the U.S.-results for a true incidence increase in thyroid cancer in Switzerland.

**B) Incidence trends by language region (French/ Italian-speaking vs. German-speaking regions)**

**Table 3** provides estimates for incidence and mortality rate trends for thyroid cancer separate for the two different Swiss language regions: cantons with predominantly French and Italian speaking residents (F/I region) and cantons with predominantly German speaking residents (G region). Age-standardized (European population) incidence rates per 100,000 for all morphologies combined ranges from 3.39 in the first period (1988-90) to 10.85 in the last period (2012-14) among French/Italian speaking cantons and from 4.23 to 7.42 among German speaking cantons in Switzerland

| Region | Period | Women | | | | Men | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N diagnoses* | IR# adjusted | N deaths | MR## adjusted | N diagnoses* | IR# adjusted | N deaths | MR## adjusted | N diagnoses* | IR# adjusted | N deaths | MR## adjusted |
| SL: French/Italian language region | 1988-1990 | 159 | 4.70 | 40 | 0.84 | 56 | 1.95 | 17 | 0.61 | 215 | 3.39 | 57 | 0.77 |
| | 1991-1993 | 186 | 5.39 | 43 | 0.92 | 47 | 1.56 | 22 | 0.72 | 233 | 3.59 | 65 | 0.84 |
| | 1994-1996 | 197 | 5.60 | 35 | 0.64 | 63 | 2.06 | 14 | 0.44 | 261 | 3.90 | 49 | 0.58 |
| | 1997-1999 | 226 | 6.25 | 44 | 0.78 | 82 | 2.55 | 15 | 0.44 | 308 | 4.47 | 59 | 0.65 |
| | 2000-2002 | 270 | 7.39 | 43 | 0.78 | 102 | 3.06 | 26 | 0.75 | 372 | 5.29 | 69 | 0.77 |
| | 2003-2005 | 318 | 8.68 | 26 | 0.46 | 129 | 3.78 | 17 | 0.43 | 447 | 6.30 | 43 | 0.44 |
| | 2006-2008 | 372 | 9.83 | 25 | 0.34 | 135 | 3.84 | 21 | 0.52 | 508 | 6.91 | 46 | 0.43 |
| | 2009-2011 | 560 | 14.01 | 27 | 0.40 | 157 | 4.13 | 23 | 0.54 | 718 | 9.18 | 50 | 0.48 |
| | 2012-2014 | 636 | 15.63 | 36 | 0.45 | 239 | 5.97 | 21 | 0.44 | 876 | 10.85 | 57 | 0.46 |
| SA: German language region | 1988-1990 | 496 | 5.66 | 161 | 1.30 | 190 | 2.67 | 83 | 1.08 | 687 | 4.23 | 244 | 1.23 |
| | 1991-1993 | 484 | 5.54 | 116 | 0.95 | 213 | 2.88 | 69 | 0.88 | 698 | 4.25 | 185 | 0.93 |
| | 1994-1996 | 639 | 7.30 | 124 | 0.95 | 235 | 3.04 | 68 | 0.86 | 877 | 5.24 | 192 | 0.92 |
| | 1997-1999 | 594 | 6.68 | 106 | 0.73 | 199 | 2.39 | 55 | 0.65 | 795 | 4.59 | 161 | 0.71 |
| | 2000-2002 | 646 | 7.11 | 100 | 0.72 | 213 | 2.52 | 43 | 0.48 | 861 | 4.84 | 143 | 0.62 |
| | 2003-2005 | 687 | 7.57 | 102 | 0.65 | 242 | 2.85 | 52 | 0.56 | 930 | 5.25 | 154 | 0.62 |
| | 2006-2008 | 887 | 9.54 | 90 | 0.57 | 299 | 3.32 | 54 | 0.53 | 1187 | 6.47 | 144 | 0.56 |
| | 2009-2011 | 948 | 9.97 | 96 | 0.53 | 378 | 4.00 | 47 | 0.42 | 1327 | 6.97 | 143 | 0.48 |
| | 2012-2014 | 1010 | 10.52 | 67 | 0.35 | 432 | 4.41 | 60 | 0.52 | 1441 | 7.42 | 127 | 0.44 |
| CH | 1988-1990 | 654 | 5.39 | 201 | 1.17 | 246 | 2.46 | 100 | 0.95 | 902 | 3.99 | 301 | 1.10 |
| | 1991-1993 | 670 | 5.50 | 159 | 0.95 | 259 | 2.50 | 91 | 0.84 | 931 | 4.07 | 250 | 0.90 |
| | 1994-1996 | 837 | 6.81 | 159 | 0.86 | 298 | 2.76 | 82 | 0.74 | 1137 | 4.85 | 241 | 0.82 |
| | 1997-1999 | 820 | 6.56 | 150 | 0.74 | 280 | 2.43 | 70 | 0.59 | 1102 | 4.56 | 220 | 0.69 |
| | 2000-2002 | 917 | 7.19 | 143 | 0.74 | 315 | 2.67 | 69 | 0.55 | 1233 | 4.97 | 212 | 0.67 |
| | 2003-2005 | 1005 | 7.89 | 128 | 0.60 | 370 | 3.12 | 69 | 0.52 | 1377 | 5.55 | 197 | 0.57 |
| | 2006-2008 | 1259 | 9.62 | 115 | 0.51 | 434 | 3.47 | 75 | 0.53 | 1695 | 6.59 | 190 | 0.52 |
| | 2009-2011 | 1508 | 11.14 | 123 | 0.49 | 536 | 4.04 | 70 | 0.45 | 2045 | 7.61 | 193 | 0.48 |
| | 2012-2014 | 1646 | 11.99 | 103 | 0.38 | 671 | 4.86 | 81 | 0.50 | 2317 | 8.41 | 184 | 0.45 |

Tab. 3. Number of thyroid cancer cases (N diagnoses), incidence rates (IR), number of death (N deaths) and mortality rates (MR) in Switzerland by language region, sex and time-period. SL: cantons with predominantly French and Italian speaking residents (GE, NE, VD, VS, TI). SA: cantons with predominantly German speaking residents (BS/BL, GR/GL SG/AR/AI, ZH). CH: Whole Switzerland. * Estimate for whole Switzerland. # Age-adjusted incidence rate (per 100,000). ## Age-adjusted mortality rate (per 100,000).

(**Tab. 3**). The estimated mortality rates are small as expected and almost stable resp. slightly decreasing over time.
The within-country geographical comparisons are depicted also in **Figure 2**. The much steeper thyroid cancer incidence increase in the F/I speaking cantons compared to the G region during the last 25 years is illustrated predominantly in the curve for papillary thyroid cancer incidence in women in this region (**Fig. 2**): the directly adjusted rate for F/I cantons is quadrupled in this group from 1988-2014, whereas it is tripled in the G region.

### C) Incidence trends of papillary thyroid carcinoma by sex, age and time period

To further evaluate the observed steep increase in thyroid cancer over time of predominantly papillary histologic type we compared age-specific incidence rates by sex in the first time period (1988-90) and the last (2012-14) (**Fig. 3**).
**Figure 3** demonstrates the large sex difference already seen in the overall incidence trends for thyroid cancer of combined histology types consistent with the world-wide observations: thyroid cancer is mainly a female cancer and has increased mainly in women with papillary histologic type over the last decades.

Whereas the youngest (age 0-19) and oldest (age 80-89) age group of analyzed women at the time of diagnosis have the same incidence rates today as 25 years ago, there is a great difference for the middle aged women, with a peak for the 40-60 years old. In the time period from 2012-14 there are around 4-times more female patients

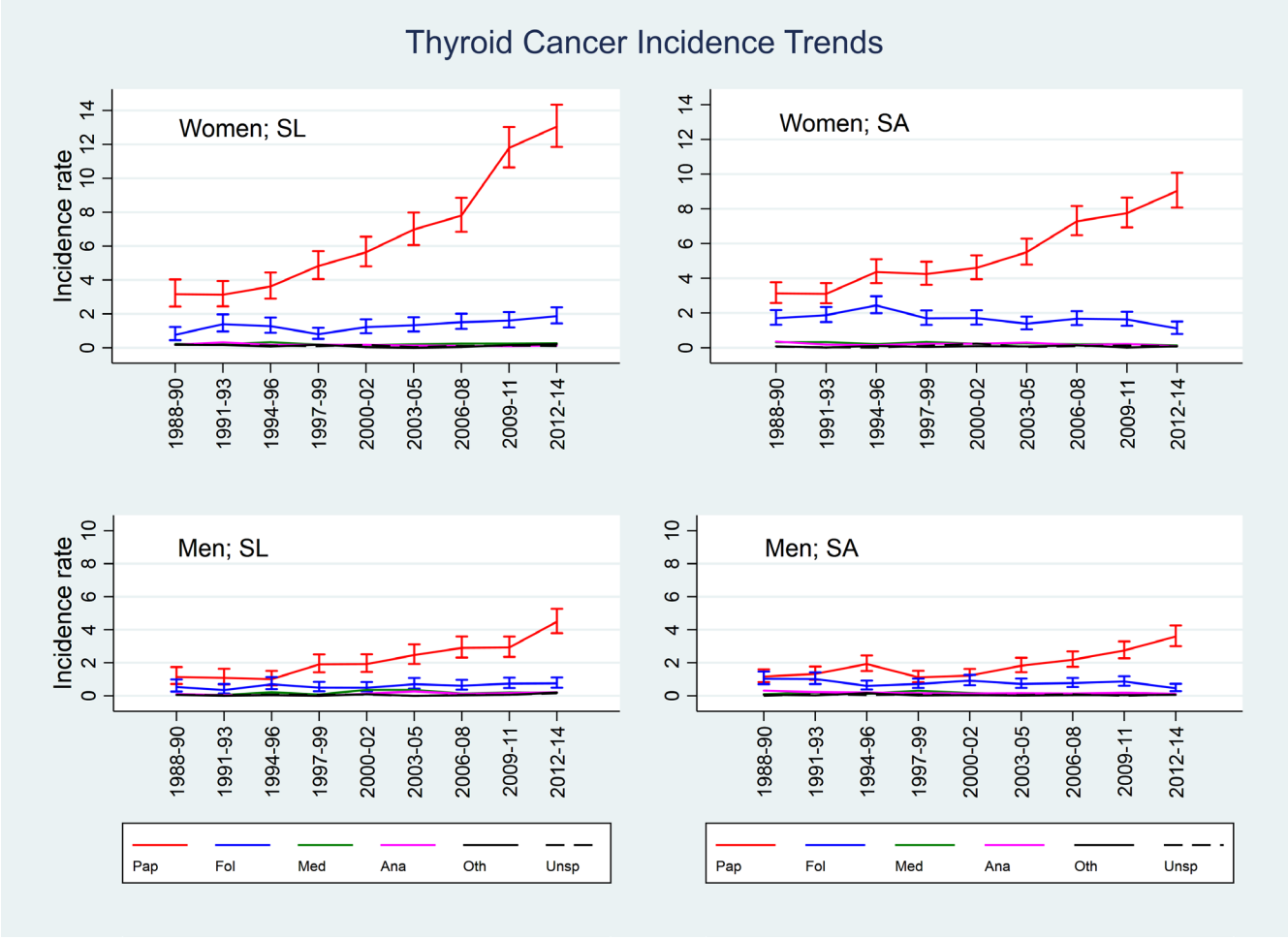


Fig. 2. Swiss thyroid cancer incidence trends by language region, sex, time period and histology types. SL: French/Italian language region, SA: German language region. Pap: papillary carcinoma, Fol: follicular adenocarcinoma, Med: medullary carcinoma, Ana: anaplastic carcinoma, Oth: other specific cancer types, Unspec: un-/poorly specified cancer. Incidence graphs for Pap and Fol are plotted with 95% confidence intervals. Included F/I speaking cantons: GE, NE, VD, VS, TI. German-speaking cantons: BS/BL, GR/GL SG/AR/AI, ZH. Incidence rates are age-standardized based on the EU standard population.

diagnosed from thyroid cancer at the age of 40-60 years than 25 years ago. Similar effects are seen for men, but much less prominent.

### Discussion

Data registered by the Cantonal Cancer Registries (F/I speaking cantons: GE, NE, VD, VS, TI and German-speaking cantons: BS/BL, GR/GL SG/AR/AI, ZH) and aggregated by NICER (National Institute for Cancer Epidemiology and Registration) from the incidence years 1988-2014 have been used to analyze trends in thyroid cancer incidence and mortality by sex, age, histology, and language region.

The findings are consistent with other Swiss reports and studies [1, 7, 15, 16, 17] and confirm the world-wide massive upward trend of thyroid cancer incidence and concomitant slight decrease of mortality trends during the last decades. The underlying mechanisms of this observation are not yet fully understood, but it is widely accepted that probably the overdiagnosis of indolent, non-lethal cancers picked up by screening are responsible for it [5]. A recent comment & response in *JAMA* [13, 14] brought up the question again: is there at least a partial «true» increase in thyroid cancer to be concerned about? Because Lim et al. [6] could show by means of a novel method of analysis for thyroid cancer mortality by tumor characteristics (histologic type and stage) at diagnosis that among patients in the United States diagnosed with thyroid cancer from 1974-2013, the overall incidence of thyroid cancer increased 3% annually, with increases in the incidence rate and thyroid cancer mortality rate for papillary thyroid cancer. The authors claim that these findings are consistent with a true increase in the occurrence of thyroid cancer in the United States.

Therefore we applied the method of Lim et al [6] in our current study to the available data in Switzerland. Due to

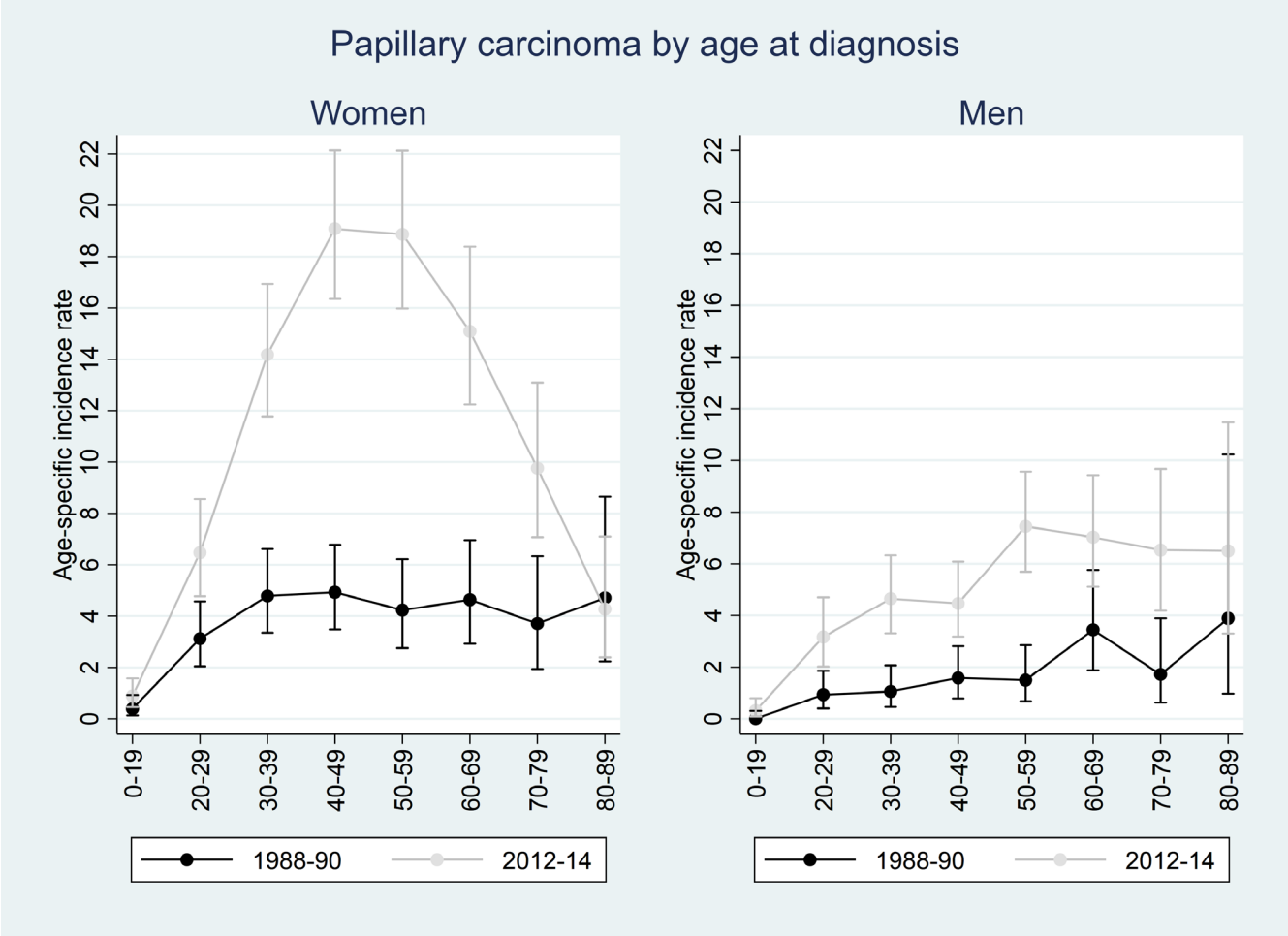


Fig. 3. Age-specific incidence rates of papillary thyroid cancer by sex, age at diagnosis and time period.

incomplete death data and to prevent the effect of underestimation, as usually found in the first years of registration, we limited our analyses to data of eight cantons (SG/AR/AI, GR/GL, TI, VS, GE) and the death years 2000-2014. We could build the histologic groups of papillary and non-papillary (medullary, follicular, anaplastic) but could not discern further subgroups as sex, or language group.

The results of the Swiss analysis could not reproduce the upward trend in mortality rates for the papillary type of thyroid cancer as found in the United States which would indicate a true increase in thyroid cancer incidence. Although a small doubt for a weak «true» effect remains because the available Swiss data had not enough statistical power to detect a very small difference and could not be analyzed separately by tumor stage. The U.S.-data analysis had shown the highest positive effect for distant stage tumors. Nevertheless, the actual evidence from the Swiss data does not reveal it, thus indicating overdiagnosis as main cause of the incident thyroid cancer increase.

An earlier study in the Swiss canton of Geneva already examined possible «artificial» factors, in contrast to a «true» increase, for the increased incidence of papillary thyroid cancer for the diagnosis years of 1970-1998. It depicts that this increase seems mainly to be due to changes in histological diagnostic criteria (follicular->papillary) and, to a lesser extent, to increased diagnostic activity [15]. The authors conclude that implementation of iodine supplementation in iodine deficiency areas should not be stopped. Similar results were shown for thyroid cancer increase for both genders in the Swiss canton of Vaud [16]. Moreover, a birth cohort study indicated similar results for thyroid cancer in Switzerland and could not definitively exclude a Chernobyl accident effect (no non-liner effect on all cohorts could be shown) [17]. Our current study confirms the above mentioned explanations.

Furthermore, our results show that the overall age-adjusted incidence rates of thyroid cancer have been increasing in Switzerland mainly for papillary carcinoma, with the greatest increase among young and middle-age women. Today there are around four times more female patients diagnosed from thyroid cancer at the age of 40-60 years than 25 years ago (**Fig. 3**). This is in accordance to the results from other high-income countries [3, 18] and the cohort effect described by Montanaro et al. for Switzerland [17]. Plausible explanations could be the improvement in diagnostic techniques, higher awareness and changes in diagnostic criteria.

Besides the enormous differences in thyroid cancer incidence by sex and age, prominent differences by language regions were observed. Overall the French/Italian-speaking cantons (F/I region) had higher age-adjusted incidence rates for thyroid cancer for both sexes in the recent years than German-speaking cantons (G region). This difference is negligible for men, but prominent for women, mainly for the papillary histologic type.
The language regional difference in the increasing incidence trend and overdiagnosis of thyroid cancer could partly be explained by the difference in the frequency of using imaging tests, which are important in thyroid cancer detection. In the F/I region imaging tests as ultrasound, computerized tomography scans and magnetic resonance imaging are in general applied more frequently than in the G region, as analysis of Swiss health insurance data in a report issued by the Federal Office of Public Health (FOPH) revealed recently [19]. Moreover, there are a number of Swiss studies and reports pointing out the cultural differences in health behavior and prevention [20, 21].

## Conclusion

Our current study supports the hypothesis of overdiagnosis as main explanation for the thyroid cancer incidence increase in Switzerland observed in the last decades, but does not definitively exclude a partly true increase. Therefore further studies with increasing power are needed to minimize the public health burden of overdiagnosis discerning the lethal from the indolent, non-lethal thyroid carcinomas and to determine any possible relations to specific exposures (e.g. ionizing events) in Switzerland due to a partly true increase of thyroid cancer.

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For additional information on cancer in Switzerland, see the NICER website at http://nicer.org/

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