original article

Incidence of thyroid cancer in Italy, 1991–2005: time trends and age–period–cohort effects

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Background: In Italy, some of the highest incidence rates (IRs) of thyroid cancer (TC) worldwide have been reported.
Patients and methods: TC cases <85 years of age reported to Italian cancer registries during 1991–2005 were included. Age-standardized IRs were computed for all TC and age–period–cohort effects were estimated for papillary TC.
Results: IRs of TC were twofold higher in 2001–2005 than in 1991–1995 (18 and 8 per 100 000 women, 6 and 3 per 100 000 men, respectively). Increases were similar in the two sexes and nearly exclusively due to papillary TC. Increases of papillary TC by birth cohort were found in both sexes and among all age groups between 20 and 79 years. Age–period–cohort models showed a strong period effect in both sexes (rate ratio for 2001–2009 versus 1991–1995 = 2.5 in women and 2.3 in men), although IRs peaked at an earlier age in women (45–49 years) than men (65–69 years).
Conclusion: The strength of the period effect in both sexes and the earlier onset in women than men strongly implicated increased medical surveillance in the upward trends of papillary TC incidence in Italy. The consequences of the current intense search for TC on morbidity and possible overtreatment, especially among young women, should be carefully evaluated.
Key words: incidence, Italy, thyroid cancer, time trends

introduction

Thyroid cancer (TC) incidence varies greatly worldwide [1] with a 10-fold difference in age-adjusted incidence rates (IRs) among women and a threefold difference in men [2, 3]. Some of the highest TC incidence worldwide has been reported in Italy [3], where below age 45 years, TC was the second most common cancer among women (after breast cancer) and the fifth most common among men [4].

Substantial increases in TC incidence have been reported in several high-resource countries over the last 30 years [5–13], whereas in some other countries increases were small [14, 15] or restricted to microcarcinomas [16]. Contrary to incidence, mortality rates for TC have declined in Europe [17] and the United States [5].

Different explanations have been proposed for the upward trends in TC incidence, including increases in medical surveillance [14, 18–21], exposure to radiation during medical procedures [22], and obesity [23, 24]. The etiology of TC, however, is not completely understood [25] except for the strong association with ionizing radiation, particularly in childhood and among young women [26].

The aim of the present study was to examine recent trends in TC incidence in Italy. For papillary TC, by far the most common histological type, standard descriptive techniques (age-standardized IRs) were supplemented with age–period–cohort analyses.

materials and methods

TC cases (International Classification of Diseases ICD-10 code C73) diagnosed between 1991 and 2005 in Italian areas covered by cancer registries were extracted from the anonymous cancer registry database of

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the Italian network of cancer registries (www.registri-tumori.it). This database includes all cancers cases reported since 1978 [4].

As of June 2009, 15 cancer registries (11.7 million people, 20% of the total Italian population) had been active for >10 years and, therefore, were included in the present study. Ten of these registries (Biella, Ferrara, Friuli Venezia Giulia, Genoa, Modena, Parma, Romagna, Turin, Varese, and Veneto) are in northern Italy, 3 (Florence and Prato, Latina, and Umbria) in central Italy, and 2 (Ragusa and Sassari) in southern Italy [3, 4]. They varied in size (190 000 to 2.1 million) and number of years of activity (11–28 years). Routine indicators of data completeness and quality in Italian cancer registries were satisfactory [3, 4].

All cases of TC that (i) occurred in patients aged 85 years or older ($n = 289$) or (ii) were first discovered at autopsy ($n = 69$) were excluded. IRs, age standardized on the basis of the 1991 (first year of observation) Italian population and by the direct method [27], were computed using SEER*Stat 6.5.1 [28]. Age-standardized rates based on the world standard or 2001 Italian population were also calculated. Since no appreciable change in trends emerged, only the estimates based on the 1991 Italian population were shown. IRs were reported by sex, histology [papillary, follicular, medullary, anaplastic, and other/not otherwise specified (NOS)] [29], and period of diagnosis (1991–1995, 1996–2000, and 2001–2005). Ninety-five percent confidence intervals (CIs) of IRs were computed according to the Poisson distribution [27]. Temporal trends were expressed as the percent change (%CH) from 1991–1995 to 2001–2005 and the joinpoint regression analysis was used to identify time points (in calendar years) where changes had possibly occurred [30].

Age–period–cohort analyses were restricted to papillary TC cases aged 15–84 years. Twenty-six papillary TC cases below age 15 years were excluded. Ten-year approximate birth cohorts were estimated by subtracting the midpoint of the 5-year age group (from 15–19 to 80–84 years) from the corresponding 5-year period.

The age effect reflects the accumulation of carcinogenic events and exposures [31]. A period effect can be caused by changes in screening practices, diagnostic techniques, or disease classification. Period effect is 'cross-sectional' as it involves all age groups and birth cohorts within a given period. Conversely, cohort effects are longitudinal because they reflect possible differences in the spread of risk factors across different birth cohorts [32].

Weighted drifts, which represent the sum of the overall slopes for period and cohort effects [32], were estimated. Two levels and a slope were fixed between age, period, and cohort [33] to deal with the nonidentifiability problem in age–period–cohort analyses and to improve estimate interpretation. The 1991–1995 period was set as a reference to allow interpreting the period effect as a rate ratio (RR). The inclusion of a slope (drift) for the period effect made the age effects interpretable as age-specific rates in the 1991–1995 period after adjustment for cohort effects. The cohort effect function was set to 1 on average with 0 slope and is interpretable as the cohort-related RR, after adjustment for age and period [33].

Age, period, and cohort estimates were modeled by natural cubic spline functions and the pointwise CIs were also computed [34]. The optimal number of knots was selected by adding an increasing number of knots at subsequent quantiles for age, period, and cohort, respectively, and the best-fitting model was defined as the one that minimized the Akaike information criterion. Age-specific female-to-male (F/M) ratios were derived from sex-specific age effects after allowance for cohort and period effects.

results

A total of 10 734 female and 3371 male TC cases below the age of 85 years were reported by Italian cancer registries between

1991 and 2005 (Table 1). IRs were approximately twofold higher in 2001–2005 than in 1991–1995 among both women (17.6 and 8.2 per 100 000) and men (5.7 and 3.1 per 100 000). Joinpoint analyses showed no departure from linear trend, implying a steady increase in the periods considered. Papillary TC was by far the most frequent histological type (73% of all TC in women and 66% in men) and the only type that showed large increases between 1991–1995 and 2001–2005 (%CH = +145%; 95% CI +130% to +160% in women; +127%; 95% CI +101% to +153% in men). IRs for medullary TC slightly increased, while IRs of follicular and anaplastic TC did not change (Table 1). IRs for the combination of other/NOS TC increased from 1991–1995 to 2001–2005 by 116% in women and 51% in men. The proportion of TC classified as other/NOS did not change within the three respective periods of diagnosis. The F/M ratio in the entire study period was 3.0 (95% CI 2.8–3.1) with higher ratios for papillary and follicular TC (3.3 and 2.6, respectively) than for medullary (1.5) and anaplastic (1.7) TC (Table 1).

Figure 1 shows age- and cohort-specific IRs of papillary TC. Age-specific IRs in women showed an inverse U-shape within all the three periods of diagnosis, with a shift of the peak from age 45–49 years to age 55–59 years (Figure 1A). Papillary TC increased less rapidly with age in men than in women and showed a plateau after age 55–59 years (Figure 1B). In both sexes, IRs of papillary TC consistently increased by birth cohort in all age groups with the possible exception of the extreme age groups (i.e. 15–19 and 80–84 years) (Figure 1C and D).

The relative contribution of age, cohort, and period effects are shown in Figure 2. Cohort effects were constrained to be 1 on average with 0 slope on account of the lack of a clear difference between cohorts in our present data (IRs in Figure 1C and D). The age effects ($P < 0.002$) were statistically significant after simultaneously adjusting for cohort and period effects (Figure 2A and B). They showed an inverse U-shape in both sexes. However, IRs increased at an earlier age in women (peak at age 45 years, Figure 2A) than in men (peak at age 65 years, Figure 2B). Cohort effects were weak in both sexes with only slightly increased RRs in the 1911–1915, 1946–1950, and 1951–1956 birth cohorts (Figure 2C and D). In contrast, period effects were strong. In comparison to 1991–1995, the RRs in 2001–2005 were 2.5 (95% CI 2.3–2.7) in women and 2.3 (95% CI 2.0–2.6) in men (Figure 2C and D). The estimated annual change (net drift) based on the period effect since 1991 and cohort effects since 1911 was +9.5% (95% CI +8.8% to +10.1%) in women and +9.0% (95% CI +7.8% to +10.2%) in men. Exclusion of patients diagnosed in the extreme age groups (15–19 and 80–84 years, with <50 cases for men) did not affect the drift estimates or the shape of curves in the remaining age groups.

Estimates of F/M ratio by age group based on age–period–cohort models are shown in Figure 3. The F/M ratio was highest (>3.5) between 35 and 54 years of age, rapidly decreasing afterward to <2 by age 75.

discussion

Incidence of TC has almost doubled in Italy between 1991–1995 and 2001–2005. Although TC was about threefold more

Table 1. Observed cases (*n*), IRs[a], %CH[b], and corresponding 95% CIs and F/M ratio for thyroid cancer by sex and histological type in Italy[c], 1991–2005

Histological type	Women				Men				F/M ratio (95% CI)
	Period of diagnosis			%CH[b]	Period of diagnosis			%CH[b]	
	1991–1995 *n* (IR)	1996–2000 *n* (IR)	2001–2005 *n* (IR)	(95% CI)	1991–1995 *n* (IR)	1996–2000 *n* (IR)	2001–2005 *n* (IR)	(95% CI)	1991–2005
Overall	2198 (8.2)	3943 (12.2)	4593 (17.6)	+115% (+102% to +127%)	734 (3.1)	1215 (4.0)	1422 (5.7)	+84% (+67% to +101%)	3.0 (2.8–3.1)
Papillary	1477 (5.7)	2828 (8.9)	3568 (13.9)	+145% (+130% to +160%)	443 (1.8)	767 (2.5)	1025 (4.2)	+127% (+101% to +153%)	3.3 (3.2–3.5)
Follicular	361 (1.3)	461 (1.4)	415 (1.5)	+15% (−2% to +32%)	123 (0.5)	164 (0.5)	146 (0.6)	+12% (−17% to +41%)	2.6 (2.3–2.9)
Medullary	86 (0.3)	126 (0.4)	153 (0.6)	+81% (+34% to +127%)	51 (0.2)	89 (0.3)	79 (0.3)	+48% (−8% to +103%)	1.5 (1.3–1.8)
Anaplastic	69 (0.2)	86 (0.2)	65 (0.2)	−14% (−43% to +16%)	31 (0.1)	37 (0.1)	31 (0.1)	−8% (−49% to +33%)	1.7 (1.3–2.1)
Other/NOS	205 (0.7)	442 (1.3)	392 (1.5)	+116% (+78% to +154%)	86 (0.4)	158 (0.5)	141 (0.6)	+51% (+10% to +93%)	2.4 (2.1–2.7)

[a]Truncated (0–84 years) rates per 100 000, age-standardized on the 1991 Italian population.
[b]2001–2005 versus 1991–1995.
[c]Fifteen cancer registries.
IR, incidence rate; %CH, percent change; CI, confidence interval; F/M, female-to-male; NOS, not otherwise specified.
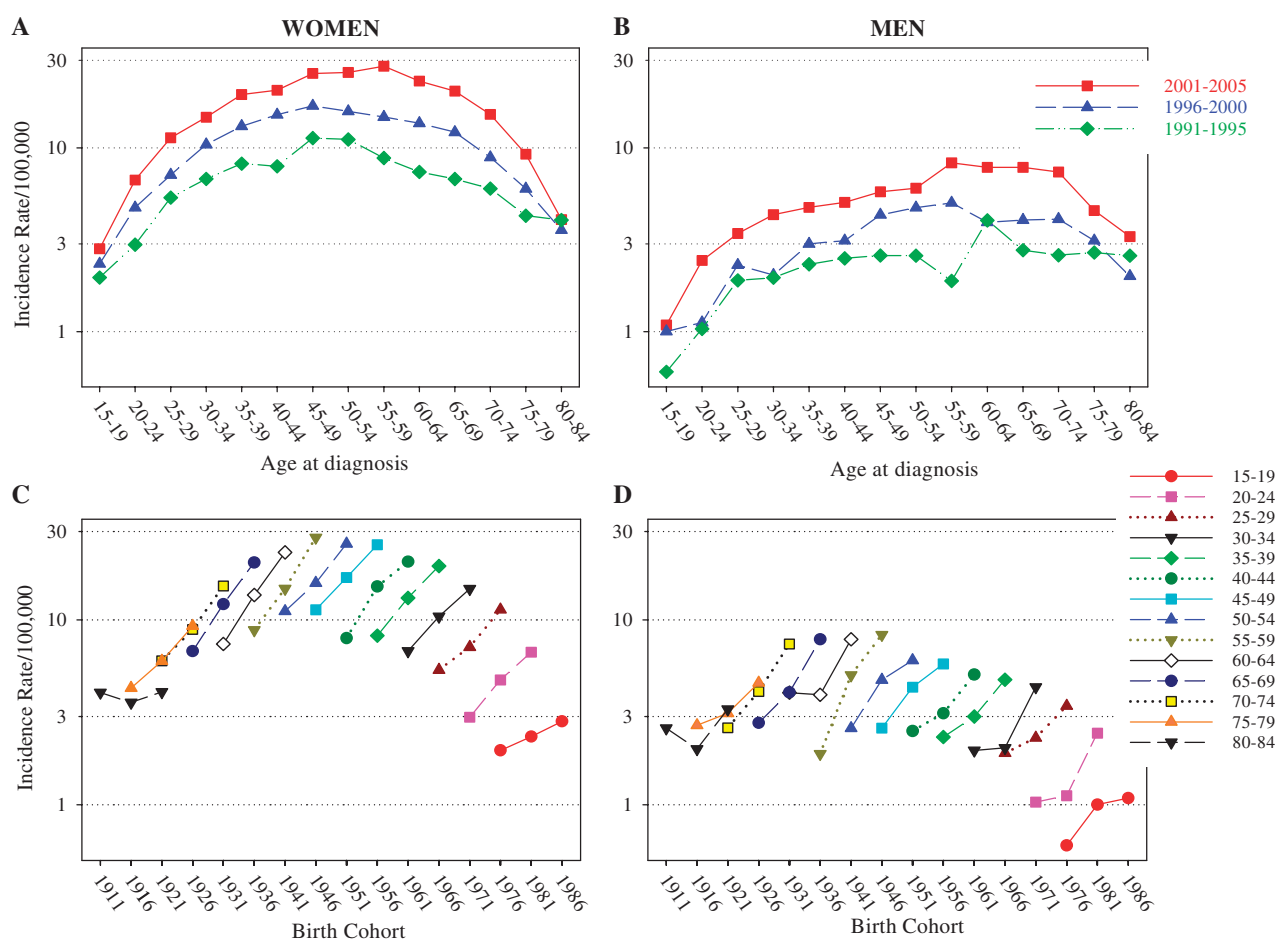
Figure 1. Age-specific incidence rates of papillary thyroid carcinoma by period of diagnosis (A, B) and birth cohort (C, D) and sex, Italy[a], 1991–2005.
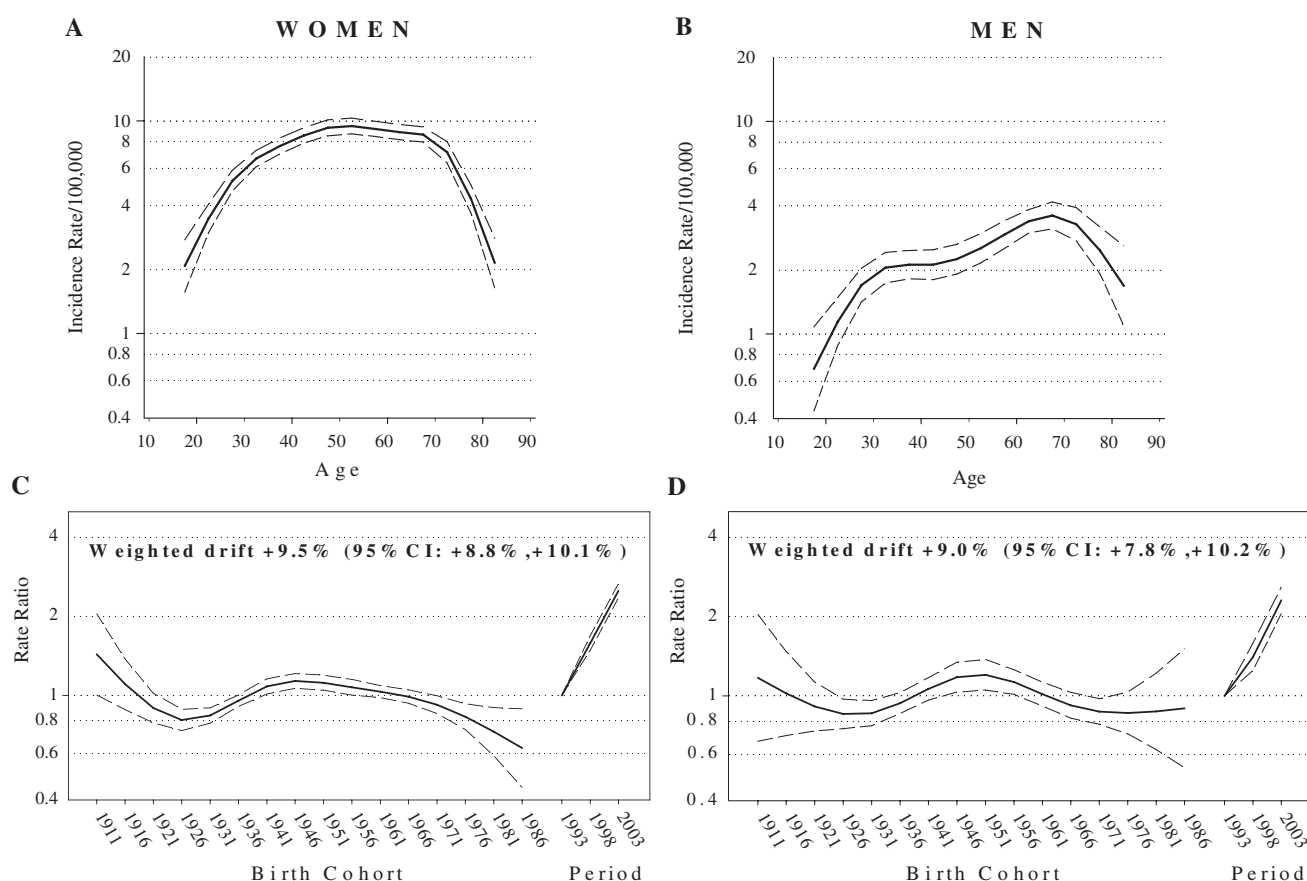[a]Fifteen cancer registries.

Figure 2. Age, cohort, and period effects[a] and weighted drift of papillary thyroid carcinoma incidence by sex, Italy[b], 1991–2005.
[a]Age effects as incidence rates for the reference period; period effects as rate ratios relative to the reference period; cohort effects constrained to be 1 on average with 0 slope. All effects are modeled by cubic splines. Dashed lines: 95% confidence interval.
[b]Fifteen cancer registries.

common in women than men in our study, incidence increases were of similar size in the two sexes and were almost exclusively due to increases in papillary TC.

The application of an age–period–cohort model to papillary TC revealed similarities as well as differences between the two sexes. The lack of a cohort effect (except for a modest peak in individuals born between 1946 and 1955) and the strong period effect (over twofold increase) were similar in men and women. The age effect, however, greatly differed by sex, as already reported in the United States [35]. In fact, TC incidence started increasing at a much younger age in women than men. After adjustment for cohort and period effects, the highest papillary TC incidence was attained at age 45–49 years in women but at age 65–69 years in men.

Although the effect of period and cohort components on drifts in age–period–cohort models is always difficult to disentangle, the strength of the period effect in both sexes in our study clearly points to a role of increased medical surveillance of thyroid nodules and symptoms potentially related to thyroid gland dysfunction [12, 18, 21, 36]. Indeed, ultrasound and thyroid hormone assays have been widely available in Italy since the early 1980s [37, 38]. Greater use

of health care services by young and middle-aged women (due to events related to reproduction and peri- and postmenopausal symptoms) than by men of the same age made the impact of diagnostic changes emerge more rapidly and at an earlier age in women. Conversely, medical surveillance in men is highest at old age [38] as was the detection of papillary TC. Indeed, some rise in TC incidence had already been seen in Italian women in 1986–1990, but findings were based on fewer (nine) cancer registries [39] than in the present report. Papillary TC are present in large proportions of individuals with no signs or symptoms of TCs as shown in autopsy-based studies [40].

Stable or decreasing TC mortality rates in Italy [41], as well as in other high-resource countries [5, 7, 11, 17, 18] also indirectly support the predominance of early-detected/good-prognosis papillary TC in the upward TC trends. Some authors [12, 16, 42] reported that the increases in papillary TC were limited or disproportionately higher for small TC, but a few studies from the Unites States [19, 43] showed that increases were seen for both small and large papillary TC in both sexes. Unfortunately, information on tumor size is not systematically collected in Italian cancer registries.
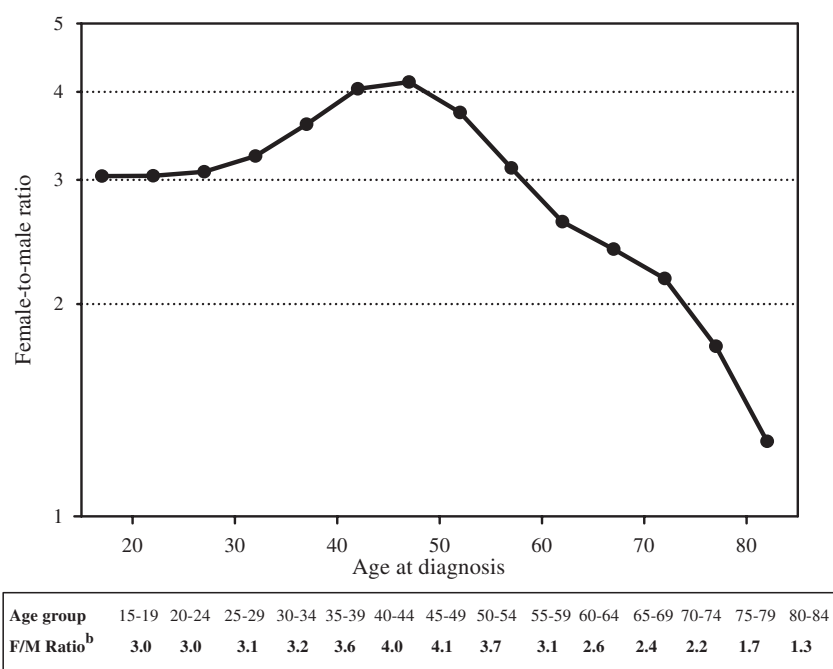
Age group	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84
F/M Ratio[b]	3.0	3.0	3.1	3.2	3.6	4.0	4.1	3.7	3.1	2.6	2.4	2.2	1.7	1.3

Figure 3. Female-to-male (F/M) ratio of papillary thyroid carcinoma by age group according to the age, period, and cohort (APC) model, Italy[a], 1991–2005.
[a]Fifteen cancer registries;
[b]Estimated using age-specific incidence rates from the age-period-cohort model (see Figure 2A and B).

Along with medical surveillance, other factors that vary with time may have also contributed to the increased incidence of papillary TC. The number of diagnostic radiology examinations has doubled in the past 10–15 years in the United States and other countries [22, 44]. Italy should be no exception, although nationwide surveys of medical radiation exposure do not exist. Subclinical iodine deficiency has been reported in many Italian areas [45], and no mass iodine supplementation effort was undertaken in Italy during the study period. Chronic iodine deficiency is a risk factor for follicular and anaplastic TC [46], but inconsistent associations with papillary TC have been reported both for low and high iodine intake [8, 14, 25]. Some evidence of an association between body size and TC is also emerging [24, 25]. Overweight is increasing in most developed countries and moderate increases in the prevalence of overweight were reported in Italy between 1983 and 2004 [47].

Trends of TC in adolescents were difficult to evaluate as only 86 and 34 papillary TC were reported in females and males, respectively, in the 15- to 19-year age group. If anything, upward trends seemed weaker in this age group than in older groups.

Our findings might have been affected by some limitation of cancer registry data; i.e. possible incompleteness of reporting and varying quality of histopathologic diagnoses. However, the completeness and quality of Italian cancer registries have been shown to be satisfactory [3, 4]. In addition, cancer incidence data were not available for some parts of Italy, notably in the south, and relatively few cancer registries had been active for >10 years. Our findings, therefore, may not be fully representative of the entire country or of early increases in TC incidence in the 1980s. However, our present study is the largest

ever on TC incidence trends in Europe and one of the first to apply age–period–cohort models to TC trends.

In conclusion, data from Italian cancer registries showed marked upward trends in TC incidence in the last 15 years, largely due to a strong period effect in papillary TC. The consequences of the current intense search for TC in terms of possible overtreatment [48], costs, and morbidity associated with thyroidectomy and thyroid hormone replacement, especially in young women, need careful evaluation.

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disclosure

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