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Original Research

The impact of overdiagnosis on thyroid cancer epidemic in Italy,1998–2012

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Abstract ***Aims:*** In Italy, incidence rates of thyroid cancer (TC) are among the highest worldwide with substantial intracountry heterogeneity. The aim of the study was to examine time trends of TC incidence in Italy and to estimate the proportion of TC cases potentially attributable to overdiagnosis.

Methods: Data on TC cases reported to Italian cancer registries during 1998–2012 aged <85 years were included. Age-standardised incidence rates (ASR) were computed by sex, period, and histology. TC overdiagnosis was estimated by sex, period, age, and Italian region.

Results: In Italy between 1998–2002 and 2008–2012, TC ASR increased of 74% in women (from 16.2 to 28.2/100,000) and of 90% in men (from 5.3 to 10.1/100,000). ASR increases were nearly exclusively due to papillary TC (+91% in women, +120% in men). In both sexes, more than three-fold differences emerged between regions with highest and lowest ASR. Among TC cases diagnosed in 1998–2012 in Italy, we estimated that overdiagnosis accounted for 75% of cases in women and 63% in men and increased over the study period leading to overdiagnosis of 79% in women and 67% in men in 2008–2012. Notably, overdiagnosis was over 80% among women aged <55 years, and substantial variations were documented across Italian regions, in both genders.

Conclusion(s): Incidence rates of TC are steadily increasing in Italy and largely due to overdiagnosis. These findings call for an update of thyroid gland examination practices in the asymptomatic general population, at national and regional levels.

1. Introduction

Incidence rates of thyroid cancer (TC) increased in recent decades in many high-resource countries, but at different magnitudes [1–5]. Italy is one of the countries showing the highest and still growing age-standardised incidence rates (ASR) worldwide [3,6,7], with a nearly 10% annual average increase from 1991–1995 (ASR = 8/100,000 women) to 2001–2005 (ASR = 18/100,000 women) [8]. TC incidence rates in 2008–2012 from 128 European cancer registries (CRs) have been recently published in the last edition of Cancer Incidence in Five Continents monograph [7], which reported the highest TC incidence in Europe by Italian registries. Moreover, GLOBOCAN [6] estimated TC incidence in Europe at national level in 2012, showing for Italy the highest TC incidence in men and the second highest in women, after Lithuania (Appendix A).

Similar to the large heterogeneity observed among [3,9] and within countries [2,10–12], a large and growing variation in TC incidence rates exists across Italian regions [13,14]. In contrast, TC mortality rates have been very low in Italy (0.3–0.4/100.000 in men and women, age-standardised to the world standard population) and stable or declining in almost all other high-income countries [5,6,15].

It is unlikely that exposure changes of known [16–19] or unknown risk factors could explain the observed

Table 1
Populations included in the study, observation period, age-standardised incidence rates (ASR)[a] for incidence of thyroid cancer, Italy, 1998–2012, age 0–84 years.

Region	Cancer Registries (CRs)	*Period of registration*	Population 2008 (0–84 years) X million	WOMEN				MEN			
				ASR				ASR			
				1998–2012	1998–2002	2003–2007	2008–2012	1998–2012	1998–2002	2003–2007	2008–2012
	All Italian CRs	1998–2012	22.36	22.5	16.2	23.1	28.2	7.7	5.3	7.7	10.1
Piedmont	Torino	*1998–2012*	0.85	**16.4**	12.9	17.6	18.8	**5.4**	3.8	5.6	6.6
	Biella	*1998–2010*	0.18	**12.9**	10.3	13.8	15.6	**5.4**	5.2	5.3	5.7
Lombardy	Brescia	*1999–2008*	1.08	**26.0**	24.9	26.0	30.2	**9.5**	8.1	10.0	11.6
	Mantova	*1999–2010*	0.39	**26.7**	21.5	26.9	33.3	**9.1**	6.8	9.4	11.1
	Milano	*1999–2010*	1.19	**13.6**	12.5	13.9	14.5	**5.8**	5.0	6.5	5.5
	Sondrio	*1998–2011*	0.18	**13.8**	13.4	15.1	12.5	**5.2**	4.4	6.6	4.2
	Varese	*1998–2012*	0.83	**13.9**	10.6	13.8	17.4	**5.4**	4.5	6.0	5.8
Trentino-Alto Adige	Alto Adige/SouthTyrol	*1998–2010*	0.48	**9.5**	8.0	10.4	10.5	**4.3**	4.1	4.2	4.6
	Trento	*1998–2010*	0.50	**15.4**	12.4	16.5	18.3	**4.9**	3.5	5.2	6.2
Veneto	Veneto	*1998–2009*	2.26	**15.5**	12.3	16.5	20.7	**5.6**	4.2	5.8	8.4
Friuli Venezia Giulia	Friuli Venezia Giulia	*1998–2010*	1.17	**15.5**	14.1	15.7	17.9	**5.2**	3.9	5.5	6.6
Liguria	Genova	*1998–2009*	0.83	**18.1**	15.7	19.1	22.3	**6.5**	4.8	7.1	8.8
Emilia-Romagna	Ferrara	*1998–2011*	0.34	**35.7**	28.4	43.1	35.9	**12.2**	9.7	13.0	14.5
	Modena	*1998–2012*	0.65	**34.2**	22.3	35.8	43.8	**12.7**	8.2	13.6	15.7
	Parma	*1998–2012*	0.40	**36.7**	21.7	44.5	43.7	**11.5**	7.7	13.9	12.8
	Reggio Emilia	*1998–2012*	0.49	**31.2**	23.8	28.9	40.0	**11.0**	7.6	10.8	14.0
	Romagna	*1998–2012*	1.13	**32.6**	20.1	33.2	42.3	**10.6**	6.0	9.0	15.7
Tuscany	Firenze-Prato	*1998–2008*	1.16	**17.0**	14.9	16.9	27.5	**5.9**	5.0	6.6	7.0
Umbria	Umbria	*1998–2011*	0.84	**18.8**	14.8	16.6	26.2	**6.9**	5.2	5.9	9.9
Lazio	Latina	*1998–2011*	0.51	**37.2**	25.5	44.2	42.0	**11.9**	6.5	14.8	14.4
Campania	Napoli	*1998–2012*	1.15	**18.1**	12.7	16.6	21.2	**7.3**	4.6	7.8	8.2
	Salerno	*1998–2009*	1.07	**19.2**	17.6	20.5	20.4	**5.9**	5.0	6.3	7.4
Sicily	Catania-Messina-Enna	*2003–2012*	1.86	**37.3**	~	36.2	38.3	**12.0**	~	9.8	14.0
	Palermo	*2003–2012*	1.21	**23.7**	~	23.1	24.4	**7.7**	~	7.1	8.3
	Ragusa-Caltanissetta	*1998–2012*	0.56	**22.9**	16.2	28.8	22.7	**6.5**	4.6	6.4	7.5
	Siracusa	*1999–2012*	0.39	**22.0**	20.0	20.8	24.6	**6.2**	4.9	6.2	7.2
Sardinia	Nuoro	*2003–2012*	0.21	**44.4**	~	35.4	53.1	**11.7**	~	8.8	14.6
	Sassari	*1998–2011*	0.46	**27.2**	18.5	28.5	35.9	**8.0**	4.7	8.6	11.1

Bold values signifies the most important information (ASR).
[a] Incidence rates per 100,000, age-standardised to the Italian population (2008).

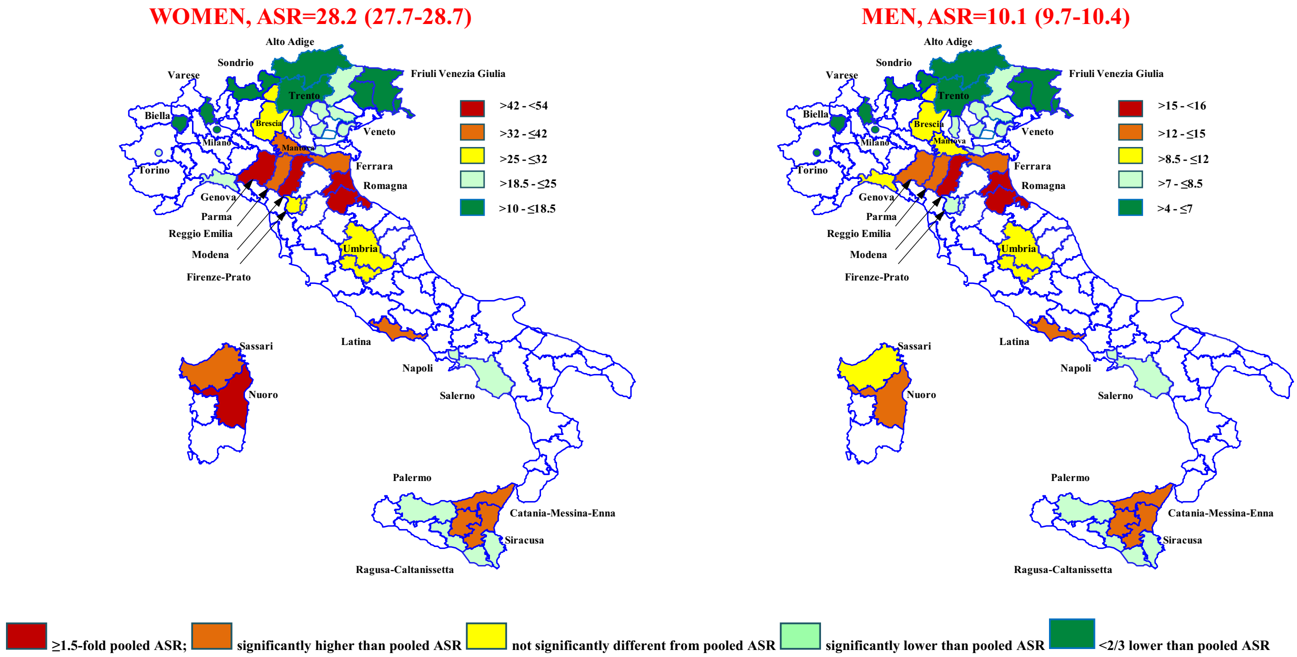


Fig. 1. Age-standardised incidence rates (ASR) (Per 100,000 age standardised to the Italian Population [2008]) and 95% confidence intervals for thyroid cancer by sex, Italy, 2008–2012, age 0–84 years.

magnitude of upward trends and regional heterogeneity in TC incidence. Conversely, technological advances in detecting small thyroid lesions and increased medical surveillance [14,16] are likely to have played a major role in the current TC epidemic [1,9], which led to overdiagnosis, i.e. the diagnosis of thyroid tumours that, if left alone, would not result in symptoms or death. Percentages of TC overdiagnosis, reported from studies using different assumptions and methodologies, range from 50% to 75% in Italy and the United States [3,9,20].

The aim of the present study was to examine TC incidence in Italy between 1998 and 2012, by sex and histological type, and across Italian areas. We have used a previously developed methodology [3,9] to estimate the proportion of TC cases attributable to overdiagnosis in Italy overall and across Italian regions.

2. Materials and methods

As of June 2016, 28 population-based Italian CRs (39% of the total Italian population) had been active for 10 years or more in the period of interest, i.e. 1998–2012, and, therefore, were included in the present study (Table 1).

Incident TC cases were defined according to International Classification of Diseases——ICD—10 code C73. Morphologies were coded according to ICDO-3 and grouped into major histological types [21,22], including papillary (8050, 8052, 8260, 8263, 8340–8344, 8350, 8450, 79.5% of cases in 1998–2012), follicular (8290, 8330–8335, 8.2% of cases), medullary (8246,8345–8347,8510, 3.4%), anaplastic (including poorly differentiated, 8012,8020–8035,8190,8337, 1.7%), and unspecified (8000–8010, 6.6%). Cases first discovered at autopsy or death certificate only (n = 149) and those occurring in patients aged ≥85 years (n = 460) were excluded, leaving 41,393 TC cases for the present analyses. The database of Italian CRs includes also cancer deaths (i.e. mortality) occurred in the areas covered by registries, based on information provided by the National Institute of Health [23] or by the Local Mortality Registries.

Age-standardised incidence and mortality rates per 100,000 person-years were standardised to the Italian and to the World standard population. Since no appreciable change in trends emerged, only the estimates based on Italian population are presented for incidence rates, calculated by sex, histology, area (registry area or region), and period of diagnosis (1998–2002, 2003–2007, 2008–2012).

Statistical methods and assumptions to estimate the fraction and number of TC overdiagnosis were previously developed and are described elsewhere [3,9]. In brief, we compared the observed shape of TC age-specific rates in Italy with the expected historical shape if detection of TC had continued occurring without the use of technological diagnostic advances and with the same level of thyroid surveillance as in the past. The expected shape was obtained by using the historical age-specific rates from the Nordic countries in 1958–1967, prior the introduction of ultrasonography. These historical rates roughly increased exponentially with age

Table 2
Number of incident cases and age-standardised incidence rates (ASR)[a] for thyroid cancer by sex, histological type and period. Italy, 1998–2012, age 0–84 years.

Histological type	Women							Men							W/M ratio (1998–2012)
	Period of diagnosis						Variation (%)[b]	Period of diagnosis						Variation (%)[b]	
	1998–2002		2003–2007		2008–2012			1998–2002		2003–2007		2008–2012			
	Cases (%)	ASR	Cases (%)	ASR	Cases (%)	ASR		Cases (%)	ASR	Cases (%)	ASR	Cases %	ASR		
Papillary	5345 (76.6)	**12.37**	10,317 (82.3)	**19.07**	9708 (83.2)	**23.49**	+90%	1438 (66.9)	**3.50**	2988 (75.0)	**5.80**	3033 (76.6)	**7.71**	+120%	**3.2**
Follicular	701 (*10.0*)	**1.63**	939 (*7.5*)	**1.73**	762 (*6.5*)	**1.84**	+13%	265 (*12.3*)	**0.66**	373 (*9.4*)	**0.73**	347 (*8.8*)	**0.88**	*+33%*	**2.2**
Medullary	227 (3.3)	**0.52**	351 (*2.8*)	**0.64**	301 (*2.6*)	**0.72**	+38%	141 (*6.6*)	**0.35**	211 (*5.3*)	**0.41**	175 (*4.4*)	**0.44**	*+26%*	**1.5**
Anaplastic	133 (*1.9*)	**0.32**	194 (*1.5*)	**0.35**	110 (*0.9*)	**0.26**	−19%	86 (*4.0*)	**0.22**	113 (*2.9*)	**0.22**	78 (*2.0*)	**0.20**	*−9%*	**1.2**
Other	28 (*0.4*)	**0.06**	45 (*0.4*)	**0.08**	38 (*0.3*)	**0.09**	+50%	23 (*1.1*)	**0.06**	30 (*0.8*)	**0.06**	35 (*0.9*)	**0.09**	*+50%*	**1.1**
NOS	547 (*7.8*)	**1.28**	683 (*5.5*)	**1.26**	749 (*6.4*)	**1.81**	+41%	195 (*9.1*)	**0.48**	271 (*6.8*)	**0.53**	290 (*7.3*)	**0.74**	*+54%*	**2.4**
Overall	**6981 (*100*)**	**16.19**	**12,529 (*100*)**	**23.12**	**11,668 (*100*)**	**28.22**	**+74%**	**2148 (*100*)**	**5.27**	**3986 (*100*)**	**7.74**	**3958 (*100*)**	**10.05**	***+91%***	**2.9**

NOS = not otherwise specified.
Bold values signifies the most important information (ASR).
[a] Per 100,000, age-standardised to the Italian population (2008).
[b] ASR in 2008–2012 versus 1998–2002.

[3], similarly to the behaviour of other epithelial cancers and in agreement with the multistage model of carcinogenicity of Armitage and Doll [24]. This model implies a linear relationship between the logarithms of age and rates. As a sensitive analysis, we also assessed the historical shape of TC age-specific profile in the two longest term Italian cancer registries (i.e. Parma and Varese) in 1978–1982, obtaining results consistent (i.e. 1.6 in women and 1.9 in men) with the Nordic countries in terms of shape of the curves and value of the slope [3].

Once defined the shape of the expected age-specific curves, we noticed that, in Italy as well as in other countries [3], the TC incidence rates in elderly people had varied only minimally across periods and birth cohorts in the study period [3,8]. We therefore set the expected incidence rates to be equal to those observed for the older age group, here chosen as the 10-year group aged 75–84 years to reduce statistical instability. For all other age groups, the expected rates were extrapolated according to the multistage model, assuming linearity on a log-log scale, with the historical slope constrained to pass by the midpoint of the older age group. We attributed to overdiagnosis the progressive excess of observed as compared to expected rates [9]. The number of TC cases attributable to overdiagnosis in the whole country was estimated by simply multiplying the observed and expected sex- and age-specific rates in areas covered by cancer registries by the corresponding national population estimates in Italy [23]. Results are also reported for Italian regions where CRs covered at least 20% of the population (i.e. 12 out of 20) to compare the possible impact of the organization and delivery of health services, such as screening and early detection programs, which are under regional authorities.

3. Results

In Italy, ASR for TC nearly increased from 16.2/100,000 in 1998–2002 to 28.2/100,000 in 2008–2012 in women and from 5.3/100,000 to 10.1/100,000 in men in the corresponding period (Table 1). A wide heterogeneity in ASR of TCs was observed across regions and CR areas (Fig. 1), with ASR >40/100,000 women in 2008–2012 in Nuoro, Latina, and CRs of Emilia-Romagna region, and <20/100,000 women in Alpine areas (i.e. Alto Adige, Biella, Sondrio, Trentino), Milano, Torino, Firenze-Prato, and Varese, Veneto, and Friuli Venezia Giulia. Notably, TC recently stabilised rates showed high incidence in 2003–2007 in some areas (i.e. Ferrara, Parma, Latina, and Catania). Similar patterns were found in men (Table 1).

In both sexes, an approximately four-fold difference in ASR emerged between Italian CRs in 2008–2012 (Fig. 1), ranging from 10.5 per 100,000 in Alto Adige to 53.1 per 100,000 women in Nuoro (and for men from

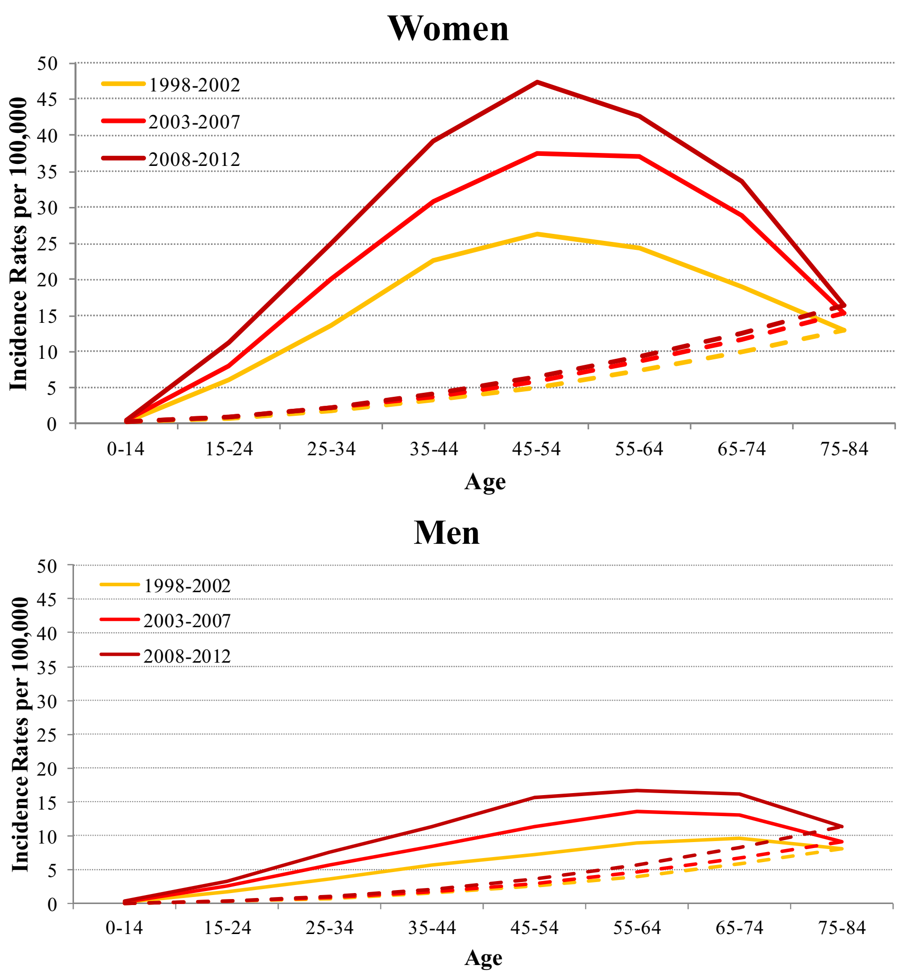


Fig. 2. Observed versus expected changes in age-specific incidence rates of thyroid cancer per 100,000 women and men (Pool of Italian cancer registries.), by period, Italy, 1998–2012, age 0–84 years. The observed rates were derived from AIRTUM database. The expected rates were based on the observation that before the introduction of ultrasonography and other novel diagnostic techniques, thyroid cancer incidence increased exponentially with age in all countries with available long-term data, in keeping with the multistage model of carcinogenesis described by Armitage and Doll (rate proportional to age^k, where the exponent k is to be estimated from incidence data) [24]. For each 10-year period, the expected age-specific rates were obtained by hypothesizing that the disease would have retained the historical age curve described by the multistage model. Since thyroid cancer incidence varied only minimally across periods among people 75–84 years of age, we added a constraint that sets as equal the expected and observed incidence rates for this age group. We hypothesised that the progressive departure of the observed rates from the multistage model was attributable to the increased detection of asymptomatic, nonlethal disease—that is, overdiagnosis.

4.2/100,000 in Sondrio to 15.7/100,000 in Romagna and Modena). ASRs significantly higher than pooled estimates emerged in the Po River plain (Brescia, Ferrara, Modena, Parma, Reggio Emilia, Romagna), Sardinia, North East Sicily, and Latina, whereas the lowest ASRs were noted in the Alpine belt. Notably, more than two-fold variations were found also within the same Region, e.g. in Lombardy or Sicily.

Papillary TC was by far the most frequent histological type (81% of all TC in women and 74% in men), showing the largest increases (+90% in women and +120% in men, from 1998–2002 to 2008–2012) (Table 2). Slight increases were observed also for follicular and medullary TC, whereas anaplastic TC rates did not show any increase. The women/men ratio in the entire study period was 2.9, higher for papillary and follicular (3.2 and 2.2, respectively) than for medullary and anaplastic (1.5 and 1.2, respectively) TC.

Fig. 2 shows the 10-year age-specific ASR from 1998–2002 to 2008–2012 in women and men. There was a gradual modification of the age curve, with incidence progressively increasing among young and middle-age adults, peaking at age 45–54 years in women and 55–64 years in men but remaining relatively constant at older ages. This pattern progressively generated an inverted U-shaped age-specific curve. Fig. 2 also shows (dotted lines) the age-specific curves expected if they had retained the historical exponential growth shape.

Table 3
Observed number of thyroid cancer (TC) cases and estimated number of cases overdiagnosed by sex, period, age, and region, Italy, 1998–2012, age 0–84 years.

	Population[a]		Women			Men		
			TC cases[b]	Attributable to overdiagnosis		TC cases[b]	Attributable to overdiagnosis	
	N (million)	In areas covered by CR (%)		N	%		N	%
Period								
1998–2012[c]	**57.27**	**39%**	**98,648**	**74,372**	**75%**	**32,176**	**20,379**	**63%**
1998–2002[d]	55.83	–	22,322	15,997	72%	6822	3915	57%
2003–2007[e]	55.95	–	32,689	24,846	76%	10,359	6849	66%
2008–2012[c]	57.27	–	41,245	32,387	79%	14,060	9402	67%
Age (years)[f]								
0–24	13.30	–	3792	3261	86%	1242	1051	85%
25–34	7.87		11,345	10,097	89%	3262	2707	83%
35–44	9.52		22,243	19,574	88%	6109	4826	79%
45–54	8.11		22,885	19,223	84%	6814	4975	73%
55–64	7.14		19,114	14,527	76%	6791	4278	63%
65–74	6.18		13,518	7705	57%	5538	2547	46%
Region[g]								
Piedmont	4.22	24%	5274	3744	71%	1749	981	56%
Lombardy	9.26	40%	12,709	8659	68%	4730	2616	55%
Trentino-Alto Adige	1.00	100%	901	601	67%	319	186	58%
Veneto	4.67	48%	5539	3734	67%	1950	1237	63%
Friuli Venezia Giulia	1.18	100%	1449	1045	72%	471	247	52%
Liguria	1.52	55%	2288	1450	63%	785	372	47%
Emilia-Romagna	4.09	74%	10,816	8062	75%	3590	2301	64%
Tuscany	3.50	33%	4722	3564	75%	1586	987	62%
Umbria	0.84	100%	1228	904	74%	435	268	62%
Campania	5.66	39%	7877	6584	89%	2539	1925	80%
Sicily	4.89	82%	10,640	8819	84%	3101	2266	76%
Sardinia	1.61	42%	3931	3047	83%	1070	595	73%

[a] Truncated 0–84 years.
[b] Estimated in Italy or regions applying age-specific ASR in CR areas.
[c] At 2008.
[d] At 1998.
[e] At 2003.
[f] Overdiagnosis was set at 0% at age 75–84 years.
[g] Regions covered by Italian CRs.

TC overdiagnosis was 75% for women and 63% for men in Italy during the entire study period (Table 3), increasing from 72% in 1998–2002 to 79% in 2008–2012 in women and from 57% to 67% in men in the corresponding period. In particular, overdiagnosis was >80% in women and >70% in men at ages <55 years. When sex-, period-, age-, and area-specific incidence rates were applied to the Italian population, we estimated that out of 98,648 TC diagnoses in women, during the study period, 74,372 were potentially attributable to overdiagnosis (Table 3). In men, overdiagnosed cases were estimated to be 20,379 out of 32,176 TC cases diagnosed in 1998–2012. Estimates of overdiagnosis showed also remarkable regional variations, with estimates of 60–70% in women living in Northern Italy (i.e. Piedmont, Lombardy, Trentino Alto Adige, Veneto, and Liguria) to 80–90% in Campania and Sicily. The pattern was similar in men, although lower in magnitude, as compared to women.

In most examined regions, TC incidence rates peaked at around 50 years of age in women (Appendix B) and approximately 10 years later in men (Appendix C).

TC mortality rates showed a consistent decrease from 0.87/100,000 in 1998–2002 to 0.76/100,000 in 2008–2012 in men (−13%) and from 0.94/100,000 to 0.77/100,000 in women (−18%) in the corresponding period (Fig. 3). Notably, incidence-to-mortality ratios were 37 in women and 13 in men in 2008–2012.

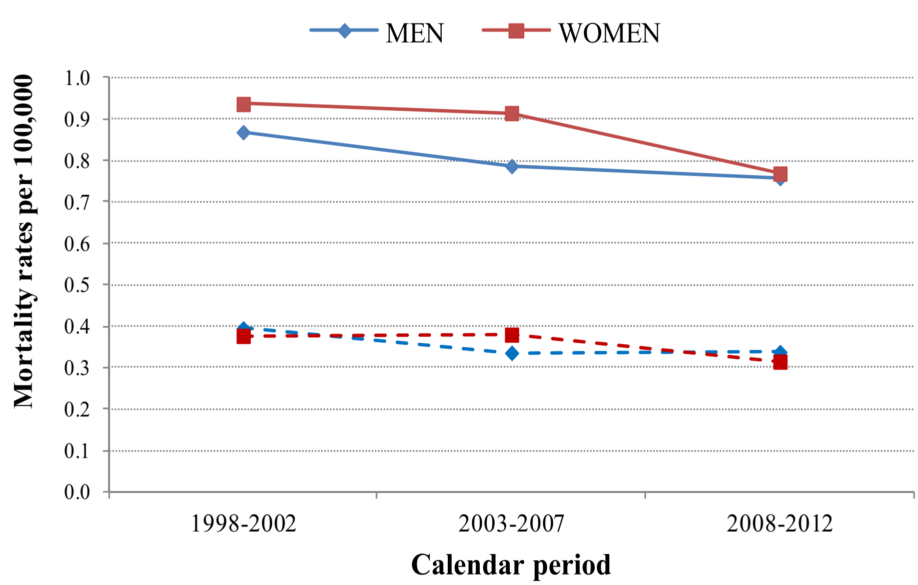
4. Discussion

TC incidence almost doubled in Italy from 1998 to 2012, an increase mainly attributable to the papillary type without indications of stabilization except from some already very high–incidence areas, in contrast with the low and decreasing TC mortality rates recorded in Italy [15], which are more pronounced among women and in the North [25].

Our findings also show a progressively increasing geographic variation of TC incidence rates. Contrary to other common epithelial cancers, TC incidence does not show a clear North (i.e. regions at highest income)–South or urban-rural gradients. The regional and local differences in TC incidence rates were also documented in other high-income countries [2,10–12,26] and suggest a major role of medical practices, rather than changes in exposure to risk factors. A very strong correlation (R = 0.77) has been shown between TC incidence and intensity of thyroid gland screening in small areas [27] in South Korea, the highest incidence country. Of note, in the USA, Schneider *et al.* [28] showed that implementation of a screening program resulted in a 17-fold increase in thyroid nodules and carcinomas in all age groups, even with the diagnostic methods available in the 1970s. This magnitude is comparable to the 10-fold increase shown in South Korea between 1996 and 2010, after the start of an opportunistic but widespread screening program in middle-aged people, and to the 30-fold excess of TC observed in the Fukushima Prefecture, Japan, following a large-scale thyroid screening of children and young adults subsequent to the nuclear accident [29].

TC overdiagnosis is the likeliest explanation for nearly 3 out of 4 cases (i.e. approximately 100,000 TC cases, or 6600 cases per year) in the last 15 years in Italy. Moreover, the temporal increase suggests that the problem of TC overdiagnosis has not been appropriately tackled yet. The fraction of TC cases attributable to overdiagnosis varies substantially at geographical level but exceeds 60% in women and 50% in men in all study regions. It is particularly severe (i.e. nearly 90%) in women aged <45 years, a group with a 10-year survival of 99% [30] and with no excess risk of death in comparison with the general population [31]. Factors other than medical surveillance that may also affect such picture cannot be excluded [16]. Among them, one can speculate that the prevalence of TC risk factors could have increased over time and could also have been highly variable among areas. The implication of iodine deficiency is ruled out by the presence of low TC rates in the Alpine belt that was formerly an endemic goitre area [13,18]. In a context where a large majority of TC cases are attributable to thyroid gland surveillance, only large and well-designed analytical studies may provide non-speculative evidence on the possible impact of spatial and temporal variations in risk factors.

The major strengths of this study are the population-based design and the availability of the largest well-documented TC series (>41,000 in 15 years) in Europe. Some limitations may be related to Italian CR data, although completeness and accuracy of histopathologic diagnoses have been considered satisfactory [7,32]. Gaps in nationwide information on the cancer incidence are the main limitations of the present study and, therefore, our findings may not be fully representative of the entire country given, in particular, the strong internal TC variability. However, the coverage of Italian CRs has increased over time and more than one-third of Italian areas (22.5 million people) contributed to the study.



	1998-2002	2003-2007	2008-2012
—— Men	0.87	0.79	0.76
—— Women	0.94	0.92	0.77
- - Men	0.40	0.34	0.34
- - Women	0.38	0.38	0.32

Fig. 3. Age-standardised mortality rates (ASR) (Age standardised to the Italian Population 2008 [——] and to the world standard population [- - -]) for thyroid cancer. Italy (Areas covered by Italian cancer registries.), 1998–2012, age 0–84 years.

Cancer overdiagnosis studies are strongly dependent on the assumptions used [33] and, consequently, the proportion of cases of TC attributable to diagnostic changes should be interpreted with caution. On these grounds, we also have chosen not to report uncertainty intervals, as these may lead to a false impression of precision of our estimates. We relied on the Nordic countries to establish the historical age curve of TC incidence prior to diagnostic changes [3]. However, when we performed a sensitivity analysis by calculating the expected age-specific profile for TC using the two longest duration Italian cancer registries, consistent estimates were obtained.

In terms of prevalence, TC represented in 2010 the fourth most commonly diagnosed cancer in women in Italy [34] and in the USA [35]. It should be borne in mind that overdiagnosed TC patients can, by definition, be considered as cured [31] since they shows no excess risk of death, in comparison with the general population. Nevertheless, most of them still undergo total thyroidectomy and, in a high proportion, also other potentially harmful treatments (e.g. neck lymph node dissection and radiotherapy) [36], meanwhile healthcare systems face the cost of unnecessary diagnoses and treatments [37]. In addition, TC survivors report, compared with the normative population, higher levels of symptoms such as fatigue [38], mouth and throat problems, and anxiety, which have a negative impact on life quality [39].

In conclusion, our findings stress the need to reconsider practices of thyroid gland examination [40], in particular, but not only, in some areas of Italy. Attention should also be paid to the possibility of less aggressive therapeutic and follow-up strategies for a disease which is rarely lethal.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.01.083.

Appendix

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