Original article

Thyroid-cancer epidemic in Italy: The impact of overdiagnosis between 1998 and 2012

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Running title: The impact of overdiagnosis on thyroid-cancer epidemic in Italy: 1998-2012

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Key message

The incidence of thyroid cancer incidence nearly doubled in Italy between 1998 and 2012, +74% in women (from 16.2 to 28.2/100,000) and +90% in men (from 5.3 to 10.1/100,000). These increases were largely documented in the papillary subtype (+90% in women, +120% in men). Between 1998-2012 in Italy, overdiagnosis accounted for 75% of thyroid cancer cases diagnosed in women and 63% in men.

Abstract

Background In Italy, incidence rates of thyroid cancer (TC) are among the highest worldwide with substantial intra-country 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.

Patients and Methods Data on TC cases reported to Italian cancer registries during 1998-2012 aged <85 years were included. Age-standardized 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 (+90% in women, +120% in men). In both sexes, more than 3-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.

Keywords: Thyroid cancer, Overdiagnosis, Incidence, Italy, Time trends

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 incidence rates worldwide [3,6], with a nearly 10% annual average increase from the 1991-1995 (IR=8/100.000 women) to 2001-2005 (IR=18/100.000 women) [7]. Similarly to the large heterogeneity observed among [3,8] and within countries [2,9-11], a large and growing variation in incidence rates in TC incidence exists across Italian regions [12,13]. In contrast, TC mortality rates have been very low in Italy (0.3-0.4/100.000 in men and women) and stable or declining in almost all other high-income countries [5,6,14].

It is unlikely that exposure changes of known [15-18] or unknown risk factors could explain the observed magnitude of upward trends and regional heterogeneity in TC incidence. Conversely, technological advances in detecting small thyroid lesions and increased medical surveillance [15] are likely to have played a major role in the current TC epidemic [1,8], 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 [3,8,19].

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 [3,8] to estimate the proportion of TC cases attributable to overdiagnosis in Italy overall and across Italian regions.

Materials and Methods

As of June 2016, 28 population-based Italian cancer registries (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 [20,21], 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-DCO (n=149) and those occurring in patients aged ≥85 years (n=460) were excluded, leaving 41,393 TC cases for the present analyses.

Age-standardized incidence rates (ASR) per 100,000 person-years standardised to the Italian population were 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 [3,8]. 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 increase exponentially with age [3], which implies a linear relationship between the logarithm of incidence rate and the logarithm of age and the consequent possibility to estimate the slope (of value approximately 2) of this log-log relationship [3]. 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 with the Nordic Countries in terms of shape of the curves and value of the slope.

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 [3,7]. 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 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 mid-point of the older age group. We attributed to overdiagnosis the progressive excess of observed as compared to expected rates [8]. The number of TC cases attributable to overdiagnosis in the whole country was estimated by simply multiplying the observed and expected sex-age-specific rates in areas covered by cancer registries by the corresponding national population estimates in Italy [22]. 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.

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 CRs areas (Figure 1), with ASR >40/100,000 women in 2008-2012 in Nuoro, Catania, Latina, and CRs of Emilia Romagna region, and <20/100,000 women in Alpine areas (i.e., Alto Adige, Sondrio, Trentino), Milan, Turin, Florence, and Varese, Veneto and Friuli Venezia Giulia. Notably, TC recently stabilized 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 4-fold difference in ASR emerged between Italian CRs in 2008–2012 (Figure 1), ranging from 10.5 per 100,000 in Alto Adige to 53.1 per 100,000 women in Nuoro (and for men from 4.2/100,000 in Sondrio to 15.7/100,000 in Romagna and Ferrara). ASRs significantly higher than pooled estimates emerged in the Po River plain (Brescia, Ferrara, Modena, Parma, Reggio Emilia, Romagna), Sardinia, North-East of Sicily, and Latina, whereas the lowest ASR were noted in the Alpine belt. Notably, more than 2-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.

Figure 2 shows the 10-year age-specific ASR from 1998-2002 to 2008-2012 in women and men. There is 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. Figure 2 also shows (dotted lines) the age-specific curves expected if they had retained the historical exponential-growth shape.

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 1), and approximately 10 years later in men (Appendix 2).

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, and are in contrast with the low and decreasing TC mortality rates recorded in Italy [14].

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 [2,9-11,23], 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 [24] in South Korea, the highest-incidence country. Of note, in the USA, Schneider et al [25] 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 [26].

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% [27] and with no excess risk of death in comparison with the general population [28]. Factors other than medical surveillance that may also affect such picture cannot be excluded [15]. 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 [12,17]. 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 strength 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 cancer Registry data, although completeness and accuracy of histopathologic diagnoses have been considered satisfactory [29]. 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.

Cancer overdiagnosis studies are strongly dependent on the assumptions used [30] 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 4th most commonly diagnosed cancer in women in Italy [31] and in the USA [32]. It should be borne in mind that overdiagnosed TC patients can, by definition, be considered as cured [28] 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) [33]. TC patients frequently face such effects of treatment and thyroid hormone replacement therapy uncertainty, and decreased quality of life [34], meanwhile healthcare systems face the cost of unnecessary diagnoses and treatments [35].

Our findings stress the need to reconsider practices of thyroid gland examination [36], 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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Disclosure

The authors have declared no conflicts of interest.

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

Region	CR	*Period*	Population 2008 (0-84 years) X million	WOMEN ASR 1998-2012	WOMEN ASR 1998-2002	WOMEN ASR 2003-2007	WOMEN ASR 2008-2012	MEN ASR 1998-2012	MEN ASR 1998-2002	MEN ASR 2003-2007	MEN ASR 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	Turin	*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
	Milan	*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-AltoAdige	Alto Adige/Sudtirol	*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	Genoa	*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	Florence-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	Naples	*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

[1]Incidence rates per 100,000, age-standardised to the Italian Population (2008).

Table 2. Number of incident cases and age-standardized incidence rates (ASR)[1] for thyroid cancer by sex, histological type and period. Italy, 1998-2012, age 0-84 years

	WOMEN Period of diagnosis							**MEN** Period of diagnosis							
Histological type	**1998-2002**		**2003-2007**		**2008-2012**			**1998-2002**		**2003-2007**		**2008-2012**			**W/M ratio 1998–2012**
	cases *%*	**ASR**	**cases** *%*	**ASR**	**cases** *%*	**ASR**	***Variation (%)²***	**cases** *%*	**ASR**	**cases** *%*	**ASR**	**cases** *%*	**ASR**	***Variation (%)²***	
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**

[1]Per 100,000, age-standardised to the Italian Population (2008)

[2] ASR in 2008-2012 vs 1998-2002.

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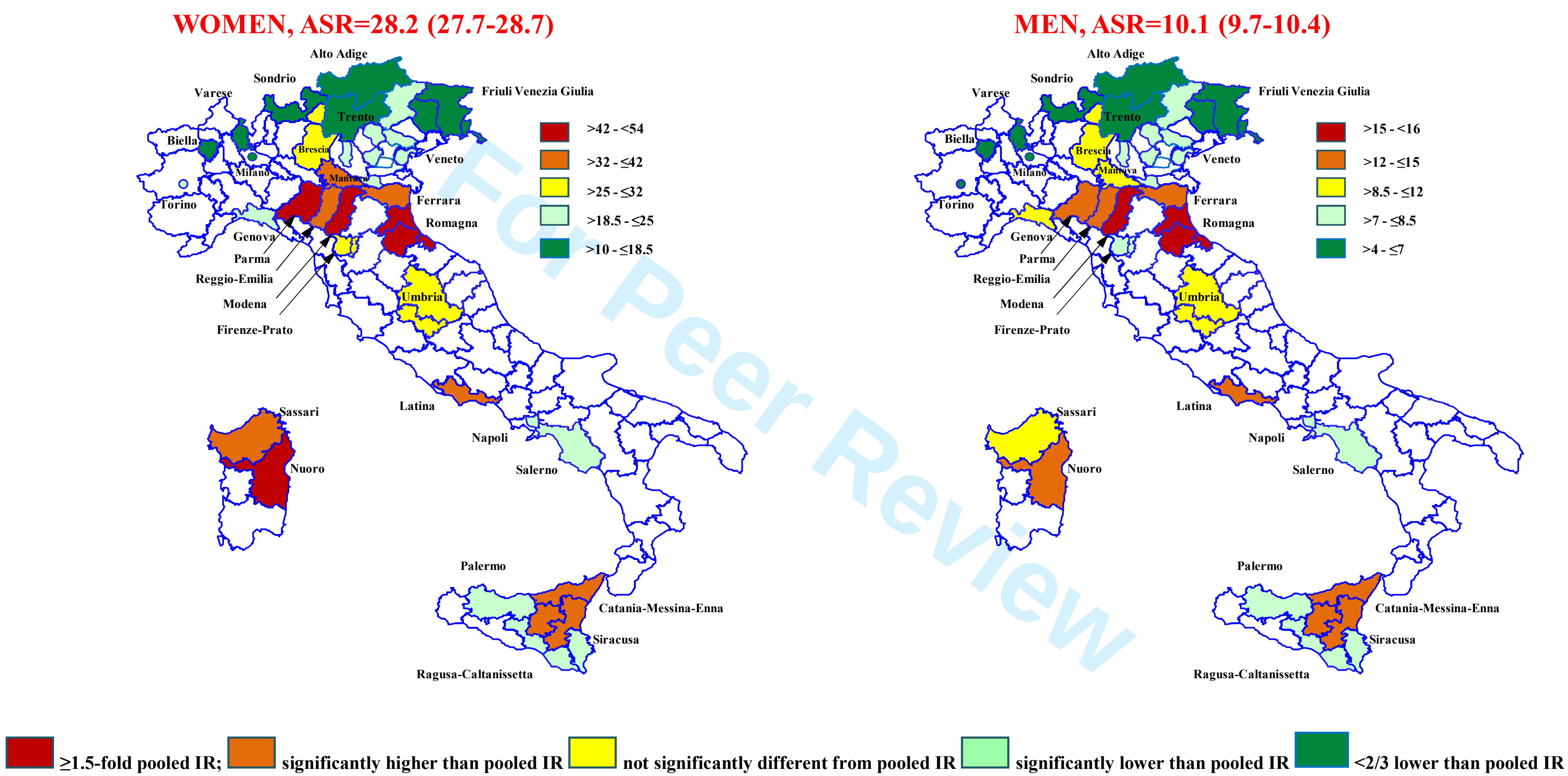
Table 3. Observed number of thyroid cancer (TC) cases and estimated number of cases overdiagnosed by sex, period, age, and Region. Italy, 1998-2012, age 0-84 years

	Population[1]		Women			Men		
				attributable to overdiagnosis			attributable to overdiagnosis	
	N (X million)	In areas covered by CR (%)	TCases[2]	N	%	TCases[2]	N	%
Period								
1998-2012[3]	**57.27**	**39%**	**98,648**	**74,372**	**75%**	**32,176**	**20,379**	**63%**
1998-2002[4]	55.83	-	22,322	15,997	72%	6,822	3,915	57%
2003-2007[5]	55.95	-	32,689	24,846	76%	10,359	6,849	66%
2008-2012[3]	57.27	-	41,245	32,387	79%	14,060	9,402	67%
Age (years)[4]								
0-24	13.30	-	3,792	3,261	86%	1,242	1,051	85%
25-34	7.87		11,345	10,097	89%	3,262	2,707	83%
35-44	9.52		22,243	19,574	88%	6,109	4,826	79%
45-54	8.11		22,885	19,223	84%	6,814	4,975	73%
55-64	7.14		19,114	14,527	76%	6,791	4,278	63%
65-74	6.18		13,518	7,705	57%	5,538	2,547	46%
Region [5]								
Piedmont	4.22	24%	5,274	3,744	71%	1,749	981	56%
Lombardy	9.26	40%	12,709	8,659	68%	4,730	2,616	55%
Trentino A.A.	1.00	100%	901	601	67%	319	186	58%
Veneto	4.67	48%	5,539	3,734	67%	1,950	1,237	63%
Friuli V.G.	1.18	100%	1,449	1,045	72%	471	247	52%
Liguria	1.52	55%	2,288	1,450	63%	785	372	47%
Emilia R.	4.09	74%	10,816	8,062	75%	3,590	2,301	64%
Tuscany	3.50	33%	4,722	3,564	75%	1,586	987	62%
Umbria	0.84	100%	1,228	904	74%	435	268	62%
Campania	5.66	39%	7,877	6,584	89%	2,539	1,925	80%
Sicily	4.89	82%	10,640	8,819	84%	3,101	2,266	76%
Sardinia	1.61	42%	3,931	3,047	83%	1,070	595	73%

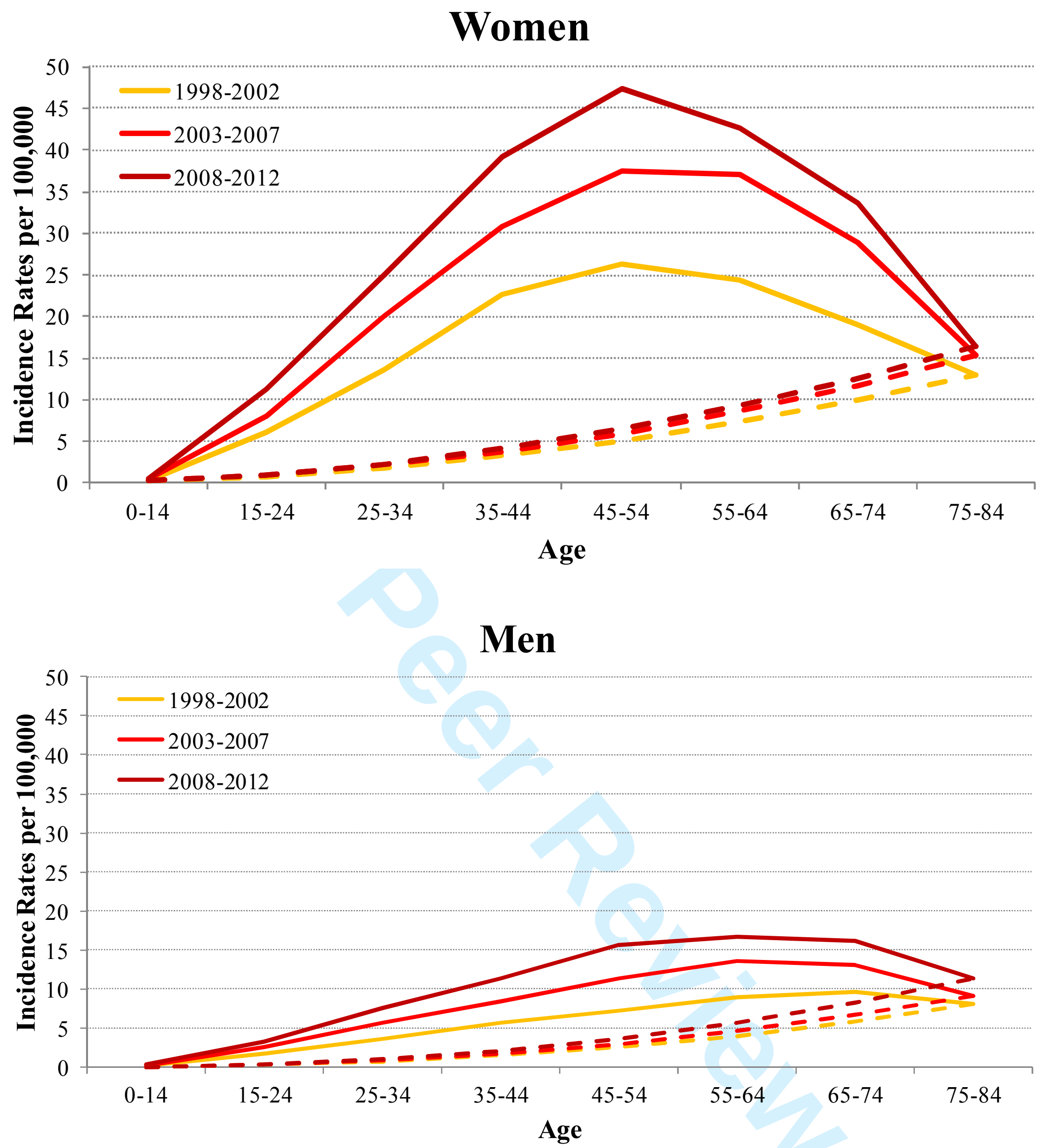
[1]Truncated 0-84 years. [2]Estimated in Italy or Regions applying age-specific IR in CR areas. [3]At 2008. [4]At 1998. [5]At 2003.
[4] Overdiagnosis=0% at 75+, by definition. [5]Regions covered by Italian Cancer registries.

Figure 1. Age-standardized incidence rates (ASR)[1] and 95% confidence intervals for thyroid cancer by sex. Italy, 2008-2012, age 0-84 years



[1] Per 100,000, age-standardised to the Italian Population (2008)

Figure 2. Observed versus Expected changes in age-specific incidence rates of thyroid cancer per 100,000 women and men[1], by period. Italy, 1998-2012, age 0-84 years



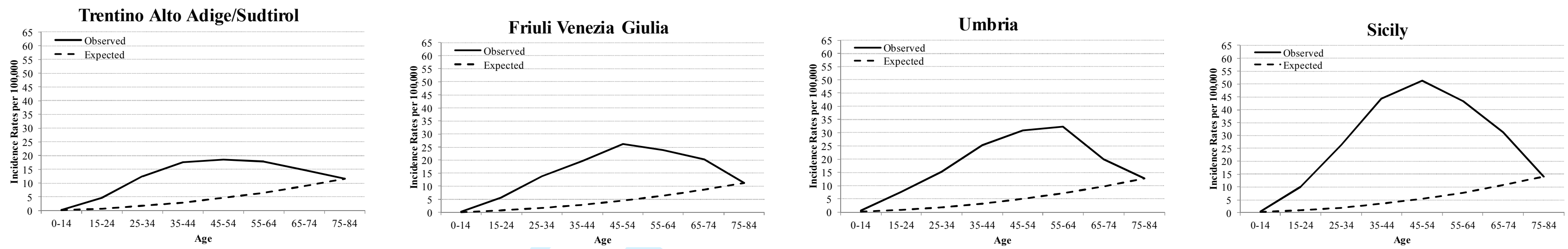
[1]Pool of Italian cancer registries.

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). 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 to 84 years of age, we added a constraint that sets as equal the expected and observed incidence rates for this age group. We hypothesized 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.

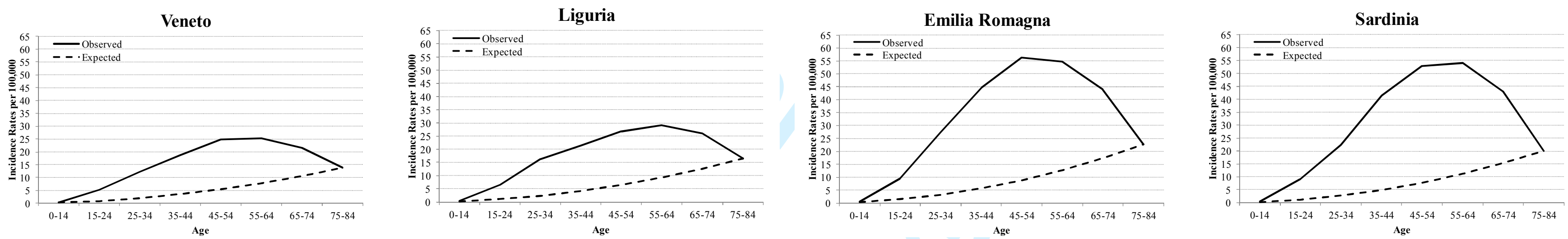
Appendix 1. Observed versus Expected age-specific incidence rates of thyroid cancer per 100,000 by region in women. Italy, 1998-2012, age 0-84 years

WOMEN

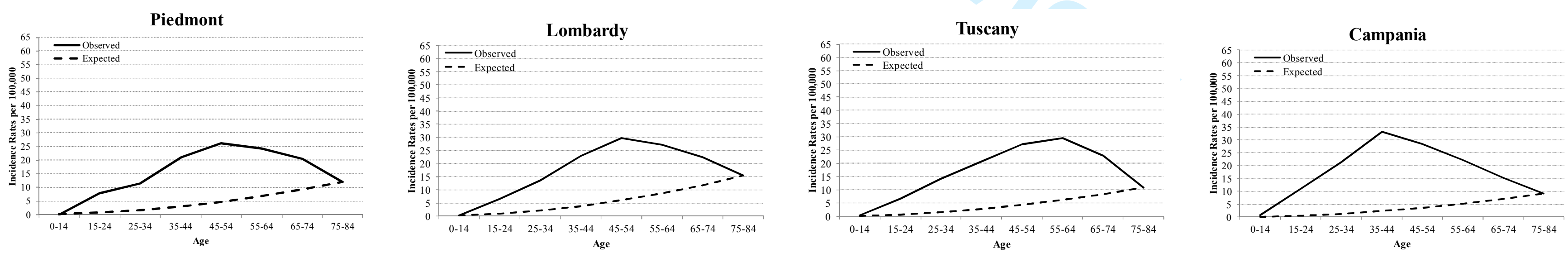
Regions with coverage >80%



Region with coverage >40% to ≤80%



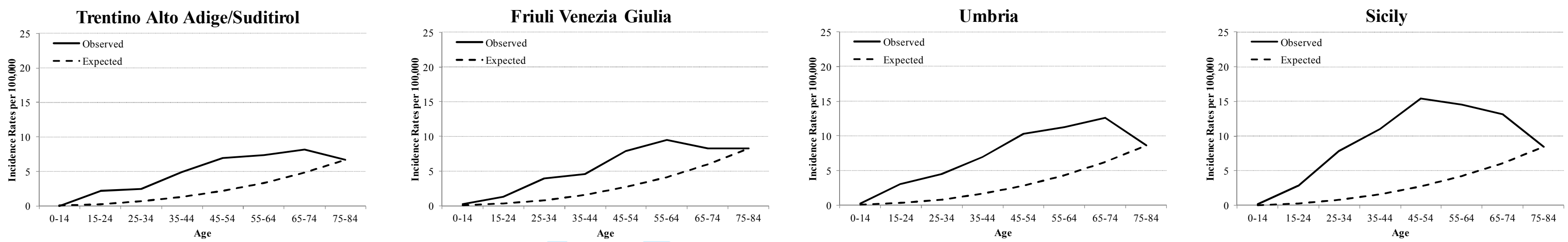
Regions with coverage >20% to ≤40%



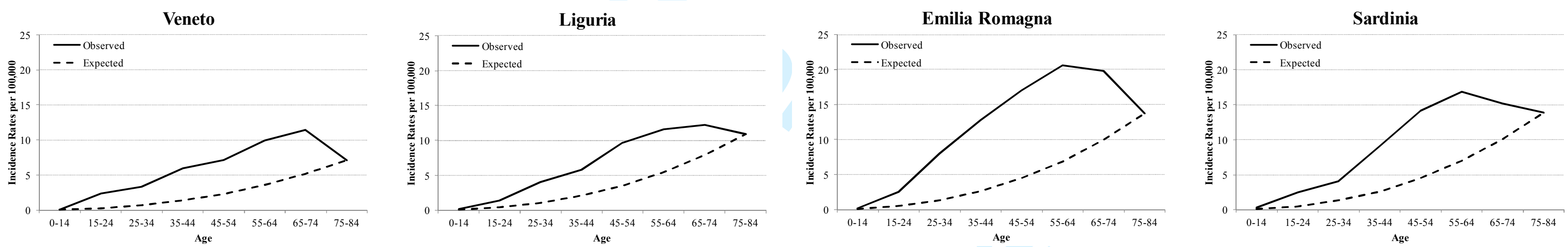
Appendix 2. Observed versus Expected age-specific incidence rates of thyroid cancer per 100,000 by region in men. Italy, 1998-2012, age 0-84 years

MEN

Regions with coverage >80%



Region with coverage >40% to≤80%



Regions with coverage >20% to ≤40%