



ORIGINAL ARTICLE

Estimates of the incidence of infection-related cancers in Italy and Italian regions in 2018

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Keywords

Cancer incidence • Chronic infections and cancer • Infection-related cancers • Italy • Regional distribution

Summary

Introduction. Chronic infections and infestations represent one of the leading causes of cancer. Eleven agents have been categorized by the International Agency for Research on Cancer (IARC) in Group 1, 3 in Group 2A and 4 in Group 2B. We previously estimated that the incidence of cancers associated with infectious agents accounted for the 8.5% of new cancer cases diagnosed in Italy in 2014.

Methods. In the present study we evaluated the incidence of cancer in Italy and in the 20 Italian regions in 2018, based on the data of Cancer Registries, and calculated the fraction attributable to infectious agents.

Results. Cancers of infectious origin contributed to the overall burden of cancer in Italy with more than 27,000 yearly cases, the

92% of which was attributable to *Helicobacter pylori*, human papillomaviruses, and hepatitis B and C viruses. With the exception of papillomavirus-related cancers, the incidence of cancers of infectious origin was higher in males (16,000 cases) than in females (11,000 cases). There were regional and geographical variations of cancers depending on the type of cancer and on the gender. Nevertheless, the overall figures were rather similar, the infection-related cancers accounting for the 7.2, 7.6, and 7.1% of all cancers in Northern, Central, and Southern Italy, respectively.

Conclusions. The estimate of the incidence of cancers attributable to infectious agents in Italy in 2018 (7.3% of all cancer cases) is approximately half of the worldwide burden, which has been estimated by IARC to be the 15.4% of all cancer cases in 2012.

Introduction

Altogether, chronic infections and infestations represent one of the leading causes of cancer worldwide. Eleven agents have been categorized by IARC (International Agency for Research on Cancer) in Group 1 (sufficient evidence of carcinogenicity to humans), 3 in Group 2A (probably carcinogenic), and 4 in Group 2B (possibly carcinogenic) [1]. Several other viruses, bacteria and protozoa have been suspected to be associated with various human cancers [2, 3].

The global burden of infection-related cancers has been estimated and periodically updated at IARC. The population attributable fraction (PAF) in the world population, in terms of incidence, was estimated to be the 15.6% in 1990 [4], 17.8% in 2002 [5], 16.1% in 2008 [6], and 15.4% in 2012 [7]. The last figure corresponds to 2 million new cancer cases of infectious origin out of 14 million cases of all cancers, with broad variations depending on the geographical region and on the developmental status. In fact, the PAFs varied from less than 5% in North America, Australia-New Zealand and some Western and Northern Europe countries to more than 50% in sub-Saharan Africa countries [7].

The PAF, indicating the proportion of cancers of infectious and parasitic origin, has been estimated in various

countries based either on morbidity and/or on mortality data. Thus, mortality PAF estimates have been made in the USA in 1981 (10%) [8], in the UK both in 1998 (10-20%) [9] and 2005 (5%) [10], in France in 2000 (3.6%) [11], and in China in 2005 (29.4%) [12]. Other studies estimated incidence data or both incidence and mortality data. For instance, the 4.1% of all new cancer cases occurring in France in 2015 were attributable to infectious agents [13]. In China, infection-related cancers accounted in 2005 for 25.9 and 29.4% of the overall cancer cases and deaths, respectively [14]. In another study in China, cancers related to the main cancer-related pathogens in men and women accounted for 17.7 and 15.4% (incidence) and 20.0 and 16.9% (mortality), respectively [15]. In the Korean population, for 2007 the fractions of all cancers attributable to infection were 25.1% and 16.8% for cancer incidence in men and women, and 25.8% and 22.7% for cancer mortality in men and women, respectively [16]. The 2.9% of cancers diagnosed in Australia in 2010 were attributable to infectious agents [17].

We previously estimated the PAF of infection-related cancers in Italy, based on 2014 national incidence data [2]. That analysis demonstrated that cancers associated with 6 pathogens accounted for 31,000 out of 365,000 new yearly cases (8.5%), 42.0% of which was

attributable to *Helicobacter pylori* (Hp), 34.7% to hepatitis B virus (HBV) and hepatitis C virus (HCV), 19.8% to human papillomaviruses (HPV), 2.9% to human herpesvirus 8 (HHV8) or Kaposi's sarcoma virus (KSHV), and 0.2% to human herpesvirus 4 (HHV4) or Epstein-Barr virus (EBV). The objectives of the present study were to reassess the incidence of infection-related cancers in Italy 4 years later and to evaluate the geographical distribution of these cancers in the 20 Italian regions. To this purpose, we made estimates of the incidence and of the attributable fractions (AFs) of cancers associated with IARC Group 1 pathogens, excepting the infestations by trematodes, which are rare in Italy, and HIV-1 infections, because HIV-related immunodeficiency requires the concomitant infection with other carcinogenic infectious agents [1].

Methods

MONITORED REGIONS AND COVERAGE BY CANCER REGISTRIES (CR)

The study covered the whole Italian territory, which includes 20 regions whose localization is shown in the map (Fig. S1). The regions were grouped according to geographic areas (North, Central or South) [18]. Northern regions include, in alphabetical order, Emilia Romagna, Friuli Venezia Giulia, Liguria (Liguria), Lombardia (Lombardy), Piemonte (Piedmont), Trentino Alto Adige (Trentino South-Tyrol), Valle d'Aosta (Aosta Valley), and Veneto, having an overall population of 27,746,158 residents as to January 2018 (Tab. SI). Central regions include Lazio (Latium), Marche (Marches), Toscana (Tuscany), and Umbria, having an overall population of 12,050,054 residents (Tab. SII). Southern and Insular regions include Abruzzo, Basilicata, Calabria, Molise, Puglia (Apulia), Sardegna (Sardinia), and Sicilia (Sicily), having an overall population of 20,697,761 residents (Tab. SIII).

The estimate of the incidence of cancers associated with chronic infections in the male and female population of whole Italy and of individual regions was based on the data available from Italian CRs, which in 2018 covered the 68% of the national population. In particular, the coverage in Northern regions was on an average 71% (Tab. SI), the coverage in Central regions was 25% (Tab. SII), and the coverage in Southern and Insular regions was 65% (Tab. SIII).

ESTIMATES OF THE INCIDENCE OF CANCERS OF INFECTIOUS ORIGIN

The evaluated agents covered DNA viruses, including HPV, HHV4/EBV, HHV8/KSHV, and HBV, either alone or in coinfection/superinfection with hepatitis D virus (HDV); RNA viruses, including HCV and human T-lymphotropic virus-I (HTLV-I); and bacteria, including Hp. The main cancers associated with the above pathogens are shown in Tables SI-SIII. The incidence estimates were selected from the AIOM-AIRTUM publica-

tion [19] for the available cancer sites (oropharynx, liver, uterine cervix, vulva, vagina, penis, Hodgkin's lymphoma, Kaposi's sarcoma). The remaining sites (non-cardia stomach, MALT, oral cavity, larynx, nasopharynx, Burkitt's lymphoma, adult T cell lymphoma/leukemia) were estimated by applying the previously described methodology [19], that is: a) preliminary time trend analysis; b) computation of regional incidence rates (with correction for incomplete coverage when necessary); c) projection of incidence rates to 2018; and d) application of rates to the resident population. A preliminary time trend analysis was made by selecting data from CRs with complete information on incidence during the 2003-2014 period. Cancer sites, three major age group (0-49, 50-69, 70+ years) and sex were considered. The average annual percent change (APC) of age-standardized incidence rates was estimate by a Joinpoint analysis [20]. APCs for the most recent period were considered for projections.

REGIONAL INCIDENCE RATES

Site-, sex-, age- and region-specific rates were computed in the calendar period 2010-14 (observed rate). Also site-, sex-, age- and geographic area- specific rates were computed for the same calendar period. Then regional rates were obtained as the weighted average between the observed rate and the area specific rates: Regional rate = α *Observed rate + (1- α)*Area specific rate, where α is the regional coverage. Consequently, in case the proportion of population covered by CRs is 0%, as it was the case for 3 regions (Marche, Abruzzo, and Molise), the regional rate equals the area specific rate, in case such a proportion is 100% the regional rate equals the observed rate. In Lazio and Campania the average rate was computed between observed rates and national pool data, instead of area specific ones.

PROJECTION OF INCIDENCE RATES TO 2018 AND APPLICATION OF RATES TO THE RESIDENT POPULATION

We assumed that incidence observed in the period 2010-2014 represent on an average the incidence of the year 2012 and that the time trend observed in the most recent time interval between 2003 and 2014 does not vary during the subsequent six years. Moreover, in order to take into account the random variability, when the site-, sex- and age- trend variation was not statistically significant (that is 95% confidence intervals include 0), the APC was constrained to 1. Therefore, incidence rates were projected to 2018 by multiplying the site-, sex-, age- and region- specific rates. The site-, sex-, age- and region-specific projected rates were multiplied by the region and age specific resident population in 2018, based on prevision from the National Statistical Institute [21].

ATTRIBUTABLE FRACTIONS

The fraction of each cancer attributable to infectious agents was inferred from data available in the literature. In particular, as detailed in Table I, the data for HBV (\pm HDV) + HCV-related liver cancer made reference to the Italian population [22]. The data for HPV-related oro-

Tab. I. Estimates of total incident cancer cases and of incident cancer cases attributable to the main cancer-associated infectious agents in Italy in 2014 and 2018.

Cancer site (ICD-10)	Infectious agent	Italy, 2014 [2]				Italy, 2018 (present study)			
		AF	Gender	Total incident cases	Infection-related cases	AF	Gender	Total incident cases	Infection-related cases
Non-cardia stomach (C16.1-C16.9)	Hp	0.90 (World [6])	M	7,500	6,750	0.89 (World [7])	M	8,156	7,259
			F	5,500	4,950		F	5,060	4,503
			M+F	13,000	11,700		M+F	13,216	11,762
MALT (C88.4)	Hp	0.86 (World [6])	M	700	602	0.74 (World [7])	M	169	125
			F	850	731		F	112	83
			M+F	1,550	1,333		M+F	281	208
Total Hp-associated cancers	Hp		M	8,200	7,352		M	8,325	7,384
			F	6,350	5,681		F	5,172	4,586
			M+F	14,550	13,033		M+F	13,497	11,970
Liver (C22)	HBV (± HDV) +HCV	0.87 (Italy [29])	M	8,600	7,465	0.68 (Italy [22])	M	8,929	6,071
			F	3,800	3,298		F	3,966	2,697
			M+F	12,400	10,763		M+F	12,895	8,768
Uterine cervix (C53)	HPV	1.00 (World [6])	F	2,200	2,200	1.00 (World [23])	F	2,241	2,241
Vulva (C51)	HPV	0.40 (World [24])	F	900	364	0.25 (World [24])	F	1,266	317
Vagina (C52)	HPV	0.61 (World [24])	F	200	122	0.78 (World [23])	F	226	176
Penis (C60)	HPV	0.47 (World [24])	M	182	85	0.50 (World [23])	M	563	282
Oral cavity (C00-C08)	HPV	0.24 (World [25])	M	2,283	537	0.04 (World [7])	M	3,034	121
			F	1,524	358		F	1,721	69
			M+F	3,807	895		M+F	4,755	190
Oropharynx (C09-C10, C12-C14)	HPV	0.36 (World [25])	M	1,214	432	0.24 (South Europe [7])	M	1,552	372
			F	348	124		F	407	98
			M+F	1,562	566		M+F	1,959	470
Larynx (C32)	HPV	0.24 (World [25])	M	3,714	891	0.05 (World [7])	M	4,076	204
			F	335	80		F	500	25
			M+F	4,049	971		M+F	4,576	229
Total HPV-associated cancers	HPV		M	7,393	1,945		M	9,225	979
			F	5,507	3,248		F	6,561	3,126
			M+F	12,900	5,203		M+F	15,786	4,105
Nasopharynx (C11)	EBV (HHV4)	0.80 (Low incidence regions [6])	M	315	252	0.80 (Low incidence regions [7])	M	452	362
			F	124	99		F	156	125
			M+F	439	351		M+F	608	487
Burkitt's lymphoma (C83.7)	EBV (HHV4) ± Pf	0.20 (USA & Europe [6])	M	200	40	0.20 (USA & Europe [6])	M	115	23
			F	100	20		F	44	9
			M+F	300	60		M+F	159	32
Hodgkin's lymphoma (C81)	EBV (HHV4)			NA	NA	0.36 (Europe [7])	M	1,228	442
							F	1,013	365
							M+F	2,241	807
Total EBV-associated cancers	EBV (HHV4)		M	515	292		M	1,795	839
			F	224	119		F	1,213	503
			M+F	739	411		M+F	3,008	1,342
Kaposi's sarcoma (C46)	KSHV (HHV8)	1.00 (World [6])	M	600	600	1.00 (World [23])	M	646	646
			F	300	300		F	280	280
			M+F	900	900		M+F	926	926
Adult T cell lymphoma/leukemia (C91.5)	HTLV1			NA	NA	1.00 (World [23])	M	12	12
							F	2	2
							M+F	14	14
All the above cancers			M	25,758	18,034		M	28,932	15,894
			F	16,831	13,194		F	17,194	11,178
			M+F	42,589	31,238		M+F	46,126	27,072

Hp: Helicobacter pylori; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus (Delta agent); HPV: human papillomavirus; EBV: Epstein-Barr virus; HHV4: human herpesvirus 4; PF: Plasmodium falciparum; KSKV: Kaposi's sarcoma virus; HHV8: human herpesvirus 8; HTLV: human T-lymphotropic virus; AF: attributable fraction; M: males; F: females.; NA: not available.

pharynx cancer were related to the South Europe population and those for EBV-related Hodgkin's lymphoma were related to the European population [7]. Those related to Burkitt's lymphoma were related to the USA and European populations [6]. All the other cancers were related to the world population [6, 7, 23-25]. As shown in Table I, the AFs for individual cancers ranged from a minimum of 0.04 for HPV-related oral cancer to a maximum of 1 for KSHV/HHV8-related Kaposi's sarcoma, HTLV-1-related adult T cell lymphoma/leukemia, and HPV-related uterine cervix cancer. However, it is known that lifestyle, environmental and genetic factors can affect the susceptibility to HPV-related cervical cancer [26].

Results

COMPARISON OF THE INCIDENCE OF INFECTION-RELATED CANCERS IN ITALY IN 2014 AND 2018

Table I compares the incidence of infection-related cancers in Italy as estimated in 2014 [2] with the one estimated in 2018 (present study). According to the more recent estimate, there was a 13% decrease in the incidence of all cancers associated with chronic infections, which accounted for a total of 31,238 cases in 2014 and a total of 27,072 cases in 2018. Such a decrease depends both on methodological issues and on variations in the AFs adopted during that period. In particular, in the case of Hp-related cancers the incidence of non-cardia stomach was very similar in 2014 and 2018. In contrast, there was a sharp drop in Hp-related MALT cases especially because of a different methodological approach. As to the liver cancers attributable to HBV and HCV, the 1.23-fold decrease in the incidence from 2014 to 2018 parallels a 1.28-fold decrease in the adopted AFs. The estimates of HPV-related cancers of female genitals were very similar in 2014 and 2018. In contrast, there was an apparent increase in HPV-related penis cancer in 2018 because of a different methodological approach. The estimate of the incidence of HPV-related cancers of the upper aerodigestive tract was much lower in 2018 because in the meantime a considerable drop of the AFs had been proposed. Some variations also occurred for EBV-related cancers because Hodgkin's lymphoma had not been included in 2014. The estimate of KSHV (HHV8)-related Kaposi's sarcoma was almost identical in 2014 and 2018, whereas very few cases of HTLV1-related adult T cell lymphoma/leukemia had not been computed in the previous study.

INCIDENCE OF INFECTION-RELATED CANCERS IN THE ITALIAN REGIONS IN 2018

Tables SI, SII and SIII report the resident male and female population in 2018 [27], the percentage of the population covered by accredited CRs, and the estimated incidence of cancers, expressed as cases/100,000 residents, attributable to infectious agents in Northern, Central and Southern Italian regions, respectively. The

panels in Figure 1 display maps that show the estimated incidence of cancers of infectious origin in the male and female population of the 20 Italian regions in 2018. As to all cancers of infectious origin (Fig. 1A), there was an evident intergender difference, which among males was characterized by a general trend to a gradient from North to South, with a maximum of 67 cases/100,000 in Veneto and a minimum of 39 cases/100,000 in Sicily. A similar picture was apparent in the female population, but with some regional exceptions. In fact, the maximum incidence was in Umbria (42 cases/100,000) but with close data in a Southern region (Basilicata). On the whole, by combining the two genders, the total number of cases/100,000 residents in Northern, Central and Southern regions were 94.4, 97.2 and 85.6, respectively. A strong difference between males and females was also evident for HBV/HCV-related liver cancer (Fig. 1B), with sharp interregional variations in the male population, where the maximum incidence values were recorded in Northwestern regions, while a more homogeneous regional distribution occurred in the female population. By combining the two genders, the number of HBV/HCV-related liver cancer cases/100,000 residents in Northern, Central and Southern regions were 31.2, 24.4 and 30.3, respectively.

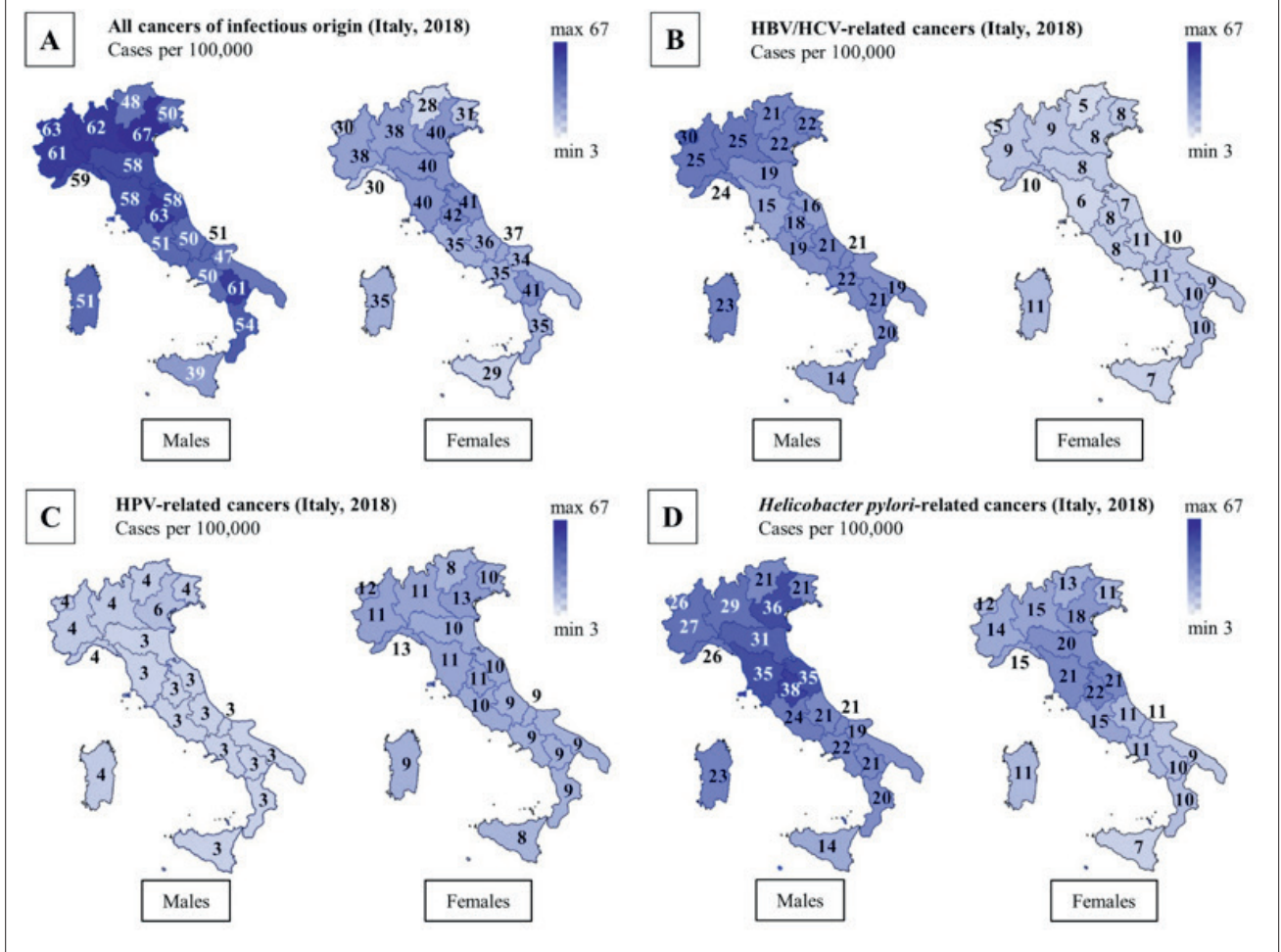
The higher incidence of all HPV-related cancers in females, compared to males, is evident from the values reported in Fig. 1C. The interregional differences were not sharp, although there was a regular gradient from North to South, especially in the female population. By combining the two genders, the number of HPV-related cancer cases/100,000 residents in Northern, Central and Southern regions were 15.2, 13.8 and 11.9, respectively. The incidence of Hp-related cancers was considerably higher in males than in females (Fig. 1D). The highest incidence values were clustered in Central Italy regions. By combining the two genders, the number of Hp-related liver cancer cases/100,000 residents in Northern, Central and Southern regions were 42.0, 52.9 and 34.3, respectively.

Table SIV reports the estimates of total incident cancer cases for the whole Italy and by region and area. By cumulating the two genders, the infection-related cancers in Northern, Central, and Southern Italy accounted in 2018 for the 7.2, 7.6, and 7.1% of all cancers, respectively. The national figure was 7.3%, corresponding to 27,381 cases of infection-related cancers out of a total of 373,300 incident cases.

Discussion

The present study estimated the incidence of the most relevant cancers associated with chronic infections over the whole national territory and, individually, in the 20 Italian regions. Drawing an up-to-date picture of the epidemiological situation is important because of the evolving estimates of PAFs and of our knowledge about the infectious origin of cancer. For instance, Hp role in gastric cancer was established in the nineties, the role

Fig. 1. Maps showing the estimated incidence of all cancers of infectious origin (A), of HBV/HCV-related cancers (B), of HPV-related cancers (C), and of Hp-related cancers (D) in the male and female population of the 20 Italian regions in 2018. The incidence is drawn with a continuous tonal gradation, ranging on a scale between a minimum of 3 and a maximum of 67. The number of new cases/100,000 is reported in each region.



of HPV in head and neck cancer has recently been assessed, and recent studies are suggesting a role for other pathogens, such as the involvement of EBV in gastric cancer development, either alone or in coinfection with Hp [28].

The overall national estimates of infection-related cancers in 2018 (present study) were slightly lower than those made in 2014 [2], with a decrease from a total of 31,238 new cases to 27,072 cases (-13%). For some cancers, such as Hp-related non-cardia stomach cancer, HPV-related uterine cervix cancer and KSHV-related Kaposi's sarcoma, the estimates were virtually overlapping in 2014 and 2018. For other cancers there were variations, mainly in the sense of a decrease, which depended either on technical issues or on the lower AFs adopted recently.

The most paradigmatic example of AF resizing is provided by liver cancer attributable to hepatotropic viruses. In the previous study, we adopted an AF of 0.87, which was based on an estimate made in Italy in 2001 [29]. Already at that time, HCV infections overwhelmed HBV infections in the causation of primary hepatocellular carcinoma in Italy [29].

Later on, the scenario has further evolved, with a progressively increasing contribution of non-viral factors and a decrease of the role of the viral etiology, which went down to 67.6% in the quinquennium 2010-2014, with the contribution of 8.6% by HBV (\pm HDV), 47.3% by HCV, 1.5% by HBV + HCV, and 10.5% classified as multi-etiology [22]. Indeed, as inferred from 770,000 cases of liver cancer occurring worldwide in 2012, the contribution of these hepatotropic viruses to liver cancer is sharply variable according to the geographical area, HBV causing approximately 2 of 3 liver cancers in developing countries but 1 in 4 cases in more developed countries [30]. Such a trend appears to be even more pronounced in Italy. Screening for HBV and HCV was introduced to reduce transmission among high risk groups. HCV screening has gained increasing diffusion because of the potential of antiviral drugs to eliminate the infection, which led WHO to pose the objective of eradication in 2030 [31].

Hp, HPV, HBV and HCV together accounted for the 92% of all infection-attributable cancers diagnosed both in the world in 2012 [7] and in Italy in 2018. However,

there are sharp differences in the overall contribution of the above agents to the incident cancers of infectious origin, which in the world and in Italy was 14.8% and 6.8%, respectively. In particular, Hp, HBV + HCV, and HPV were responsible on a global scale for the 5.4, 4.8, and 5.0% of all incident cancer cases [7], whereas in Italy they were responsible for the 3.2, 2.3, and 1.3% of cases, respectively. Another important difference is that the total numbers of infection-related cancers worldwide was equal in males and females, i.e. 1,100,000 cases each in 2012 [7], whereas in Italy there were in 2018 many more cases in males (16,000) than in females (11,000). This is likely to be ascribed to the fact that the most pronounced difference between the world and the Italian situation is related to HPV-related cancers, which displayed a female/male ratio of 3.2 in Italy and of 8.6 in the world [7]. Such a difference reflects the fact that in Italy there is a broad application both of primary prevention measures (anti-HPV vaccination) and of secondary prevention by means of oncological screenings (PAP test and HPV-DNA test).

There were evident variations in cancer incidence between the North, Centre and South of Italy and among the 20 regions, with some characteristic clusters of cancers according to the geographical localization. Thus, there was a general trend to a North to South downward gradient for all cancers of infectious origin, and especially to a lower incidence in Southern Italy. As to HBV/HCV-related liver cancer cancers, the maximum incidence was detected in Northwestern regions, at least in males, and the lowest incidence was in Central Italy. It should be noted that sub-regional variations may also occur. For instance, within the Campania region in 1998-2002 the incidences of liver cancer recorded by the Naples CR in the male and female populations were 34.8 and 10.2 cases/100,000 residents, respectively, whereas the corresponding values recorded in the nearby Salerno CR were 14.6 and 6.2 cases/100,000 residents, respectively [32, 33]. A moderate North to South downward gradient occurred in the incidence of HPV-related cancers. The incidence of Hp-related cancers was remarkably high in Central Italy regions, which confirms the observation that gained the definition of "gastric cancer belt" in Central Italian regions [34].

A statistically significant correlation ($r = 0.893$, $P < 0.001$) was detected between the estimated 2018 incidence data of HBV/HCV and Hp-related cancers in the male and female population of Northern, Central and Southern Italy, as detected in the present study, and the corresponding mortality data for liver and stomach cancers for the period 2010-2014, standardized on the European population [19]. It is exceedingly difficult to relate cancer incidence to the incidence of the related infections in each region, also because these cancers have a long latency time, and the information about the geographical distribution of the corresponding infections in the past is scanty. Furthermore, many of these infections are not clinically apparent and therefore they are just detectable by implementing *ad hoc* designed screening

programs. For instance, HPV may be harbored in a latent state for 20 years or longer before manifesting as a precancerous lesion of the cervix [35], and the latent period between infection with hepatotropic viruses and primary hepatocellular carcinoma is in the order of decades [36].

Assessing the incidence of infection-related cancers has two intrinsic limitations. The first critical point is that we had to extrapolate incidence data to the whole population. The second one is that, for each infection-related cancer, AFs may vary depending on the regional area and may not necessarily be uniform over the whole national territory, depending on several local variables.

Conclusions

In conclusion, our estimates suggest that cancers of infectious origin contributed to the overall burden of cancer in Italy with more than 27,000 new cases, which represent the 7.3% of all incident cancer cases in 2018. This figure is comparable to the fraction of new cancer cases diagnosed in Europe in 2012 that was ascribed to infections, which accounted for the 7.2% of all cancer cases [7].

There were differences highlighting a higher incidence of these cancers in males, with the exception of HPV-related cancers. Regional variations and geographical clusters of cancer cases were evident, depending on the type of cancer and on the gender. Nevertheless, the overall figures were rather similar, the infection-related cancers accounting for the 7.2, 7.6, and 7.1% of all cancers in Northern, Central, and Southern Italy, respectively.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SDF: study conception, design, and writing of the manuscript; SLM: data analysis and interpretation and statistical analysis; EC: interpretation of data and manuscript review; LM: contribution to the design of the study; FB: statistical analysis; FS: interpretation of data and manu-

script review; CB: collection of data, estimate of incidence and interpretation.

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Tab. S1. Estimated incidence (new cases/100,000 residents) of cancers attributable to infectious agents in Northern Italy regions in 2018.

		Gender	Emilia Romagna	Friuli Venezia Giulia	Liguria	Lombardia	Piemonte	Trentino Alto Adige	Valle d'Aosta	Veneto	All Northern regions
Resident population as to January 2018		M	2,162,684	589,785	743,755	4,907,685	2,123,610	525,523	61,695	2,395,801	13,510,538
		F	2,289,945	625,753	813,226	5,128,573	2,252,255	542,125	64,507	2,509,236	14,225,620
		M+F	4,452,629	1,215,538	1,556,981	10,036,258	4,375,865	1,067,648	126,202	4,905,037	27,746,158
Population covered by Cancer Registries (%)		M+F	80	100	55	92	30	100	100	53	71
Cancer site (ICD-10)	Infectious agent										
Non-cardia stomach (C16.1-C16.9)	Hp	M	30.6	35.8	25.9	28.2	27.1	19.7	26.0	20.2	26.7
		F	19.6	17.8	14.3	15.1	14.0	13.0	12.4	10.9	14.6
		M+F	50.3	53.6	40.2	43.3	41.1	32.7	38.4	31.1	41.3
MALT (C88.4)	Hp	M	0.4	0.0	0.4	0.5	0.4	1.1	0.0	0.4	0.4
		F	0.5	0.0	0.3	0.3	0.2	0.3	0.0	0.2	0.2
		M+F	0.9	0.0	0.7	0.8	0.6	1.4	0.0	0.6	0.6
Total Hp-associated cancers	Hp	M	31.0	35.8	26.3	28.6	27.5	20.8	26.0	20.6	27.1
		F	20.1	17.8	14.6	15.3	14.2	13.2	12.4	11.1	14.9
		M+F	51.1	53.6	40.9	43.9	41.7	34.0	38.4	31.7	42.0
Liver (C22)	HBV (± HDV) + HCV	M	18.8	22.5	24.0	24.5	24.6	20.8	29.8	22.3	23.4
		F	7.8	7.5	10.1	9.5	9.3	4.9	5.3	7.8	7.8
		M+F	26.6	30.0	34.1	34.0	33.9	25.7	35.1	30.1	31.2
Uterine cervix (C53)	HPV	M	-	-	-	-	-	-	-	-	-
		F	7.6	9.1	10.7	8.7	9.4	5.5	9.3	7.5	8.5
		M+F	7.6	9.1	10.7	8.7	9.4	5.5	9.3	7.5	8.5
Vulva (C51)	HPV	M	-	-	-	-	-	-	-	-	-
		F	1.2	1.4	1.1	1.0	1.0	0.8	0.8	1.1	1.0
		M+F	1.2	1.4	1.1	1.0	1.0	0.8	0.8	1.1	1.0
Vagina (C52)	HPV	M	-	-	-	-	-	-	-	-	-
		F	0.7	0.8	0.8	0.7	0.7	1.0	0.0	0.7	0.7
		M+F	0.7	0.8	0.8	0.7	0.7	1.0	0.0	0.7	0.7
Penis (C60)	HPV	M	0.8	0.8	1.3	0.8	1.0	0.7	0.8	0.8	0.9
		F	-	-	-	-	-	-	-	-	-
		M+F	0.8	0.8	1.3	0.8	1.0	0.7	0.8	0.8	0.9
Oral cavity (C00-C08)	HPV	M	0.4	0.6	0.4	0.4	0.5	0.5	0.5	0.5	0.5
		F	0.3	0.3	0.3	0.2	0.3	0.2	0.3	0.3	0.3
		M+F	0.7	0.9	0.7	0.6	0.7	0.7	0.8	0.8	0.8
Oropharynx (C09-C10, C12-C14)	HPV	M	1.4	3.2	1.6	1.7	1.8	2.4	2.0	1.6	1.9
		F	0.4	0.8	0.4	0.5	0.4	0.4	0.7	0.4	0.5
		M+F	1.8	4.0	2.0	2.2	2.2	2.8	2.7	2.0	2.4
Larynx (C32)	HPV	M	0.6	1.0	0.8	0.7	0.7	0.5	1.1	0.8	0.8
		F	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1
		M+F	0.7	1.1	0.9	0.8	0.8	0.6	1.3	0.9	0.9
Total HPV-associated cancers	HPV	M	3.3	5.6	4.2	3.6	3.9	4.0	4.3	3.6	4.1
		F	10.2	12.5	13.5	11.1	11.9	8.1	11.3	10.0	11.1
		M+F	13.5	18.1	17.7	14.7	15.8	12.2	15.6	13.6	15.2
Nasopharynx (C11)	EBV (HHV4)	M	1.2	0.5	1.2	1.2	1.3	0.8	1.3	0.8	1.0
		F	0.4	0.5	0.4	0.4	0.4	0.4	0.0	0.4	0.4
		M+F	1.6	1.0	1.6	1.6	1.7	1.2	1.3	1.2	1.4
Burkitt's lymphoma (C83.7)	EBV (HHV4) ± Pf	M	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
		F	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0
		M+F	0.1	0.2	0.1	0.1	0.2	0.0	0.0	0.1	0.1
Hodgkin's lymphoma (C81)	EBV (HHV4)	M	1.6	1.3	1.8	1.4	1.4	1.2	0.0	1.6	1.3
		F	1.1	1.2	0.8	1.2	1.2	1.0	0.6	1.4	1.1
		M+F	2.7	2.5	2.6	2.6	2.6	2.2	0.6	3.0	2.4
Total EBV-associated cancers	EBV	M	2.9	2.0	3.1	2.8	2.8	1.9	1.3	2.5	2.4
		F	1.5	1.8	1.2	1.6	1.6	1.4	0.6	1.8	1.4
		M+F	4.4	3.8	4.3	4.4	4.4	3.3	1.9	4.3	3.8
Kaposi's sarcoma (C46)	KSHV (HHV8)	M	2.2	1.4	1.6	2.2	2.6	1.0	1.6	1.3	1.7
		F	0.8	0.0	1.1	0.8	0.9	0.6	0.0	0.2	0.6
		M+F	3.0	1.4	2.7	3.0	3.5	1.6	1.6	1.5	2.3

Adult T cell lymphoma/ leukemia (C91.5)	HTLV1	M	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		M+F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
All the above cancers		M	58.2	67.1	59.0	61.6	61.4	48.5	63.0	50.2	58.7
		F	40.4	39.6	30.3	38.3	37.9	28.3	29.5	31.0	35.7
		M+F	98.6	106.7	89.3	99.9	99.3	76.8	92.5	81.2	94.4

Hp: *Helicobacter pylori*; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus (Delta agent); HPV: human papillomavirus; EBV: Epstein-Barr virus; HHV4: human herpesvirus 4; PF: *Plasmodium falciparum*; KSKV: Kaposi's sarcoma virus; HHV8: human herpesvirus 8; HTLV: human T-lymphotropic virus; M: males; F: females.

Tab. SII. Estimated incidence (new cases/100,000 residents) of cancers attributable to infectious agents in Central Italy regions in 2018.

		Gender	Lazio	Marche	Toscana	Umbria	All Central regions
Resident population as to January 2018		M	2,848,727	743,645	1,803,203	425,547	5,821,122
		F	3,047,966	788,108	1,933,765	459,093	6,228,932
		M+F	5,896,693	1,531,753	3,736,968	884,640	12,050,054
Population covered by Cancer Registries (%)		M+F	15	0	33	100	25
Cancer site (ICD-10)	Infectious agent						
Non-cardia stomach (C16.1-C16.9)	Hp	M	24.0	34.1	34.3	37.2	32.4
		F	14.4	20.9	20.9	21.9	19.6
		M+F	38.4	55.0	55.2	59.1	52.0
MALT (C88.4)	Hp	M	0.4	0.6	0.6	0.5	0.6
		F	0.3	0.4	0.3	0.3	0.3
		M+F	0.7	1.0	0.9	0.8	0.9
Total Hp-associated cancers	Hp	M	24.4	34.7	34.9	37.8	33.0
		F	14.7	21.3	21.3	22.2	19.9
		M+F	39.1	56.0	56.2	60.0	52.9
Liver (C22)	HBV (± HDV) +HCV	M	18.8	16.4	15.1	18.4	17.2
		F	7.9	6.9	6.4	7.6	7.2
		M+F	26.7	23.3	21.5	26.0	24.4
Uterine cervix (C53)	HPV	M	-	-	-	-	-
		F	7.6	8.1	8.8	8.7	8.3
		M+F	7.6	8.1	8.8	8.7	8.3
Vulva (C51)	HPV	M	-	-	-	-	-
		F	1.0	1.2	1.1	1.3	1.2
		M+F	1.0	1.2	1.1	1.3	1.2
Vagina (C52)	HPV	M	-	-	-	-	-
		F	0.6	0.6	0.5	0.7	0.6
		M+F	0.6	0.6	0.5	0.7	0.6
Penis (C60)	HPV	M	0.9	1.2	1.1	1.3	1.1
		F	-	-	-	-	-
		M+F	0.9	1.2	1.1	1.3	1.1
Oral cavity (C00-C08)	HPV	M	0.4	0.4	0.4	0.5	0.4
		F	0.2	0.2	0.2	0.2	0.2
		M+F	0.6	0.6	0.6	0.7	0.6
Oropharynx (C09-C10, C12-C14)	HPV	M	1.2	0.9	1.0	0.9	1.0
		F	0.3	0.2	0.2	0.3	0.3
		M+F	1.5	1.1	1.2	1.2	1.3
Larynx (C32)	HPV	M	0.7	0.6	0.7	0.6	0.7
		F	0.1	0.1	0.1	0.1	0.1
		M+F	0.8	0.7	0.8	0.7	0.8
Total HPV-associated cancers	HPV	M	3.1	3.2	3.2	3.3	3.2
		F	9.7	10.4	11.0	11.3	10.6
		M+F	12.8	13.6	14.2	14.6	13.8
Nasopharynx (C11)	EBV (HHV4)	M	1.2	0.9	1.0	0.8	1.0
		F	0.4	0.5	0.4	0.7	0.5
		M+F	1.6	1.4	1.4	1.5	1.5
Burkitt's lymphoma (C83.7)	EBV (HHV4) ± Pf	M	0.1	0.1	0.0	0.1	0.1
		F	0.0	0.1	0.1	0.0	0.1
		M+F	0.1	0.2	0.1	0.1	0.2
Hodgkin's lymphoma (C81)	EBV (HHV4)	M	1.6	1.8	1.9	1.7	1.7
		F	1.2	1.2	1.0	1.4	1.2
		M+F	2.8	3.0	2.9	3.1	2.9
Total EBV-associated cancers	EBV	M	2.8	2.7	2.9	2.5	2.7
		F	1.5	1.8	1.4	2.2	1.7
		M+F	4.31	4.5	4.3	4.7	4.4
Kaposi's sarcoma (C46)	KSHV (HHV8)	M	2.0	1.1	1.6	0.7	1.3
		F	0.8	0.3	0.2	0.2	0.4
		M+F	2.8	1.4	1.8	0.9	1.7
Adult T cell lymphoma/leukemia (C91.5)	HTLV1	M	0.0	0.1	0.2	0.2	0.1
		F	0.0	0.0	0.1	0.0	0.0
		M+F	0.0	0.1	0.3	0.2	0.1

All the above cancers	M	51.3	58.2	57.8	62.8	57.5
	F	34.6	40.6	40.4	43.4	39.7
	M+F	85.9	98.8	98.2	106.2	97.2

Hp: *Helicobacter pylori*; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus (Delta agent); HPV: human papillomavirus; EBV: Epstein-Barr virus; HHV4: human herpesvirus 4; PF: *Plasmodium falciparum*; KSKV: Kaposi's sarcoma virus; HHV8: human herpesvirus 8; HTLV: human T-lymphotropic virus; M: males; F: females.

Tab. III. Estimated incidence (new cases/100,000 residents) of cancers attributable to infectious agents in Southern Italy regions in 2018.

		Gender	Abruzzo	Basilicata	Calabria	Campania	Molise	Puglia	Sardegna	Sicilia	All Southern regions
Resident population as to January 2018		M	641,185	278,882	959,437	2,841,049	152,228	1,967,751	810,072	2,445,343	10,095,947
		F	674,011	288,236	997,250	2,985,811	156,265	838,104	2,581,646	10,601,814	
		M+F	1,315,196	567,118	1,956,687	5,826,860	308,493	4,048,242	1,648,176	5,026,929	20,697,761
Population covered by Cancer Registries (%)		M+F	0	100	64	71	0	54	42	91	65
Cancer site (ICD-10)	Infectious agent										
Non-cardia stomach (C16.1-C16.9)	Hp	M	20.0	30.0	24.4	19.9	20.5	17.6	17.8	16.1	20.8
		F	13.1	17.9	12.5	12.8	13.7	11.9	11.8	10.2	13.0
		M+F	33.1	47.9	36.9	32.7	34.2	29.5	29.6	26.3	33.8
MALT (C88.4)	Hp	M	0.4	0.00	0.2	0.3	0.5	0.5	0.7	0.3	0.4
		F	0.2	0.5	0.4	0.2	0.0	0.3	0.4	0.2	0.3
		M+F	0.6	0.5	0.6	0.5	0.5	0.8	1.1	0.5	0.7
Total Hp-associated cancers	Hp	M	20.3	30.0	24.6	20.2	21.0	18.1	18.5	16.4≤	21.1
		F	13.3	18.4	12.9	13.0	13.7	12.1	12.1	10.3	13.2
		M+F	33.6	48.4	37.5	33.2	34.7	30.2	30.6	26.7	34.3
Liver (C22)	HBV (± HDV) + HCV	M	20.8	21.5	20.4	22.2	21.0	19.4	22.5	14.3	20.3
		F	10.7	9.9	10.1	10.8	11.3	9.2	10.7	7.5	10.0
		M+F	31.5	31.4	30.5	33.0	32.3	28.6	33.2	21.8	30.3
Uterine cervix (C53)	HPV	M	-	-	-	-	-	-	-	-	-
		F	7.1	8.0	7.4	6.8	7.0	6.9	7.0	6.9	7.1
		M+F	7.1	7.98	7.42	6.80	7.04	6.87	7.04	6.86	7.14
Vulva (C51)	HPV	M	-	-	-	-	-	-	-	-	-
		F	1.0	0.9	1.1	0.9	1.1	1.1	0.8	0.9	1.0
		M+F	1.0	0.9	1.1	0.9	1.1	1.1	0.8	0.9	1.0
Vagina (C52)	HPV	M	-	-	-	-	-	-	-	-	-
		F	0.5	0.3	0.2	0.5	0.5	0.5	0.4	0.3	0.4
		M+F	0.5	0.3	0.2	0.5	0.5	0.5	0.4	0.3	0.4
Penis (C60)	HPV	M	1.2	0.7	1.2	1.0	1.3	1.0	1.0	1.1	1.1
		F	-	-	-	-	-	-	-	-	-
		M+F	1.2	0.7	1.2	1.0	1.3	1.0	1.0	1.1	1.1
Oral cavity (C00-C08)	HPV	M	0.4	0.5	0.3	0.3	0.4	0.4	0.5	0.4	0.4
		F	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
		M+F	0.6	0.6	0.5	0.5	0.6	0.6	0.6	0.6	0.6
Oropharynx (C09-C10, C12-C14)	HPV	M	0.8	1.3	0.4	0.8	0.8	0.8	1.8	0.6	0.9
		F	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
		M+F	1.00	1.4	0.6	1.0	1.0	1.0	2.0	0.8	1.01
Larynx (C32)	HPV	M	0.8	0.5	0.7	0.8	0.8	0.6	0.8	0.6	0.7
		F	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
		M+F	0.9	0.5	0.8	0.9	0.9	0.7	0.9	0.7	0.8
Total HPV-associated cancers	HPV	M	3.2	3.0	2.6	2.9	3.3	2.8	4.1	2.6	3.0
		F	9.0	9.3	9.1	8.6	9.1	8.9	8.7	8.4	8.9
		M+F	12.2	12.3	11.7	11.5	12.4	11.7	12.8	11.0	11.9
Nasopharynx (C11)	EBV (HHV4)	M	1.6	2.3	1.5	1.2	1.6	1.3	1.2	2.0	1.6
		F	0.5	0.6	0.2	0.4	0.5	0.4	0.3	0.6	0.4
		M+F	2.1	2.9	1.7	1.6	2.1	1.7	1.5	2.6	2.0
Burkitt's lymphoma (C83.7)	EBV (HHV4) ± Pf	M	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.1	0.1
		F	0.00	0.0	0.00	0.0	0.0	0.0	0.0	0.0	0.0
		M+F	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.1	0.1
Hodgkin's lymphoma (C81)	EBV (HHV4)	M	1.4	1.0	1.4	1.5	1.4	1.3	1.6	1.5	1.4
		F	1.1	1.6	1.6	1.2	1.2	1.3	1.3	1.0	1.3
		M+F	2.5	2.6	3.0	2.7	2.6	2.6	2.9	2.5	2.7
Total EBV-associated cancers	EBV	M	3.1	3.4	3.0	2.7	3.0	2.8	2.9	3.5	3.0
		F	1.5	2.2	1.8	1.6	1.7	1.7	1.6	1.6	1.7
		M+F	4.6	5.6	4.8	4.3	4.7	4.5	4.5	5.1	4.7
Kaposi's sarcoma (C46)	KSHV (HHV8)	M	3.0	3.6	3.0	2.4	2.6	4.3	3.2	2.0	3.0
		F	1.3	1.0	0.8	1.1	1.3	2.2	1.4	0.7	1.2
		M+F	4.3	4.6	3.8	3.5	3.9	6.4	4.6	2.7	4.2

Adult T cell lymphoma/leukemia (C91.5)	HTLV1	M	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0
		F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		M+F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
All the above cancers		M	50.3	61.4	53.5	50.3	50.8	47.4	51.4	38.8	50.5
		F	35.9	40.9	34.6	35.0	37.0	34.0	34.6	28.5	35.1
		M+F	86.2	102.3	88.1	85.4	87.8	81.4	86.0	67.3	85.6

Hp: Helicobacter pylori; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus (Delta agent); HPV: human papillomavirus; EBV: Epstein-Barr virus; HHV4: human herpesvirus 4; Pf: Plasmodium falciparum; KSKV: Kaposi's sarcoma virus; HHV8: human herpesvirus 8; HTLV: human T-lymphotropic virus; M: males; F: females.

Tab. SIV. Estimates of total incident cancer cases and proportion of incident cancer cases attributable to the main cancer-associated infections in Italian regions in 2018.

Region	Gender	Total incident cases ^a	Infection-related cases ^b
Northern Italy			
Emilia Romagna	M	15,550	1,270 (8.2%)
	F	15,350	943 (6.1%)
Friuli Venezia Giulia	M	4,750	399 (8.4%)
	F	4,300	253 (5.9%)
Liguria	M	6,150	441 (7.2%)
	F	5,800	336 (5.8%)
Lombardia	M	33,550	3,050 (9.1%)
	F	30,650	2,001 (6.5%)
Piemonte	M	16,300	1,216 (8.1%)
	F	14,550	870 (6.0%)
Trentino Alto Adige	M	3,100	257 (8.3%)
	F	2,800	156 (5.6%)
Valle d'Aosta	M	450	40 (8.9%)
	F	350	20 (5.7%)
Veneto	M	16,759	1,215 (7.3%)
	F	15,100	789 (5.2%)
All Northern regions	M	96,600	7,987 (8.3%)
	F	88,900	5,369 (6.0%)
Central Italy			
Lazio	M	17,150	1,472 (8.6%)
	F	16,700	1,074 (6.4%)
Marche	M	5,000	437 (8.7%)
	F	4,800	325 (6.8%)
Toscana	M	12,900	1,053 (8.2%)
	F	12,000	796 (6.6%)
Umbria	M	3,050	270 (8.9%)
	F	2,900	202 (7.0%)
All Central regions	M	38,100	3,233 (8.5%)
	F	36,400	2,397 (6.6%)
Southern Italy and Islands			
Abruzzo	M	4,200	324 (7.7%)
	F	3,800	245 (6.4%)
Basilicata	M	1,850	174 (9.4%)
	F	1,400	118 (8.4%)
Calabria	M	5,850	514 (8.8%)
	F	4,500	346 (7.7%)
Campania	M	16,350	1,420 (8.7%)
	F	13,700	1,056 (7.7%)
Molise	M	1,000	77 (7.7%)
	F	900	59 (6.6%)
Puglia	M	10,850	936 (7.9%)
	F	10,750	716 (6.7%)
Sardegna	M	5,200	417 (8.0%)
	F	4,800	292 (6.1%)
Sicilia	M	13,900	956 (6.9%)
	F	13,250	746 (5.6%)
All Southern Italy and Islands	M	60,200	4,418 (8.0%)
	F	53,100	3,577 (6.7%)
All Italian regions	M	194,900	16,038 (8.2%)
	F	178,400	11,223 (6.4%)
	M+F	373,300	27,381 (7.3%)

^a From AIOM/AIRTUM [19]. ^b From Tables SI-SIII.

Fig. S1. Geographical distribution of the 20 Italian regions.

