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Report

Trends in cutaneous melanoma mortality in Italy from 1982 to 2016

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Abstract

Background In Italy, comprehensive national studies, about mortality rates for cutaneous melanoma, are missing. The aim of this study was to analyze the trend of cutaneous melanoma mortality in Italy from 1982 to 2016.

Methods Data on death certificates were obtained from Italian National Institute of Statistics (ISTAT: Istituto nazionale di STATistica, Indagine sulle cause di morte). Mortality rates were age-standardized on the European population 2013 and presented per 100,000 individuals. Age-adjusted mortality rates (AMRs) were calculated by sex, age group, and geographic areas. To identify changes in mortality rate trends, a joinpoint regression model was used, and the annual percent change (APC) was estimated.

Results In Italy, a total number of 49,312 patients (44.0% women) died for cutaneous melanoma from 1982 to 2016. Melanoma mortality rates significantly increased in the study period in both sexes, with higher AMR values and a steeper increase in men (from 2.71 to 4.02; APC: 1.43; 95% CI 1.26–1.61) than women (from 1.94–2.10; APC: 0.23; 95% CI 0.00–0.46). The largest difference between men and women was observed in patients aged ≥65 years with APC of 2.17 in men (95% CI 1.97–2.37) and 0.37 in women (95% CI 0.08–0.66).

Conclusion In conclusion, the melanoma mortality rate in Italy progressively increased especially in elderly men. Several hypotheses might explain the observed age and geographic differences such as sun exposure habits or different strategies of prevention campaigns.

Introduction

Cutaneous melanoma is one of the deadliest skin tumors, and its incidence is steadily increasing. In Europe, the estimated age-adjusted incidence rates of melanoma in 2018 were 15.8 and 14.6 per 100,000 in men and women, respectively.[1]

The estimated age-standardized incidence rate in Italy in 2020 is 21.8 in men and 16.5 in women, and the estimated age-standardized mortality rate in Italy in 2020 is 4.5 in men and 2.1 in women.[2] Northern European countries registered the highest incidence rates, with Norway and Sweden in the first positions, followed by Germany, United Kingdom, and Switzerland.[3] Despite the higher level of sun irradiation, Southern countries had lower melanoma incidence rates. This is probably because of the presence of darker-skinned inhabitants as well as a minor tendency to sunburn. Sunburn is considered as a surrogate for intermittent pattern exposure, which is more frequent among fair-skinned people from high latitudes spending short periods of vacation in warmer countries.[4] However, melanoma mortality has been almost stable since 1980 in Northern Europe, in contrast to Southern countries where incidence and mortality have both been increasing.[5] Spanish data on melanoma mortality from 1982 to 2016 showed an increasing trend from 0.9 to 1.8 deaths per 100,000 in men and from 0.64 to 1.11 per 100,000 in women.[6]

In Italy, comprehensive national studies reporting the trend of melanoma mortality are missing. The current evidence is fragmentary and mostly based on regional reports.[7–9] The aim of this study was to analyze the trend of cutaneous melanoma mortality rates in Italy from 1982 to 2016, according to sex, age, and geographic areas.

Material and methods

Data on death certificates and mid-year population per year were obtained by the Italian National Institute of Statistics (ISTAT: Istituto nazionale di STATistica, Indagine sulle cause di morte). All deaths caused by cutaneous melanoma (International Classification of Diseases [ICD] codes: ICD-9172 and ICD-10 C43) from January 1, 1982, to December 31, 2016, were included. Mortality data were stratified by sex, age groups (≤19,

20–44, 45–64 and ≥65 years), and geographic areas: Northwest (Valle D'Aosta, Piemonte, Liguria and Lombardia regions), Northeast (Emilia Romagna, Veneto, Trentino Alto Adige and Friuli Venezia Giulia), Center (Toscana, Lazio, Umbria, Marche), South (Campania, Abruzzo, Molise, Basilicata, Puglia, Calabria), and islands (Sicily and Sardinia). Mortality rates were age-standardized on the European population 2013 and presented per 100,000 individuals. Age-adjusted mortality rates (AMRs) were calculated by sex, age group, and geographic areas. All analysis was reported for the whole study period and for specific time intervals: 1982–1990, 1991–2000, 2001–2010, and 2011–2016. Statistical analyses were performed using Stata version 13.0 (College Station, Texas, USA).

To identify changes in mortality rate trends, joinpoint regression was estimated for each sex within each age group and geographic area, using the Joinpoint Regression Program, Version 4.5.0.1 (Statistical Research and Applications Branch, National Cancer Institute). Using mortality rates as inputs, this method identifies the year(s) when a trend change is produced and estimates the annual percent change (APC) for each trend by fitting a regression line to the natural logarithm of the mortality rates. The number of maximum joinpoints allowed in the analysis was five.

The study was conducted in accordance with the Declaration of Helsinki. Ethical committee approval was waived because the data were provided by a third party.

Results

Study population

A total number of 49,312 deaths for cutaneous melanoma (56.0% men and 44.0% women) were retrieved from the ISTAT database from 1982 to 2016, corresponding to a mean number of 1409 deaths per year. Most of the deceased patients were aged more than 44 years (43,520, 88.3%) and 57.1% (28,156) more than 64 years.

Concerning the geographical distribution, a higher proportion of deaths was observed in the Northwest area (n: 15,296, 31.0%), while no differences were observed in the other areas. In Table 1, the absolute number of deaths is reported for the first three decades (1982–2010) and the last quinquennium (2011–2016) of our study period. The absolute number of deaths progressively increased over time, both in the overall population and in subgroups. However, a slighter increase was observed in women, in patients aged <65 years, and in Northern regions, leading to decreasing mortality ratios in these subgroups and conversely to increasing ratios in men, in patients aged ≥65 years, and in Central and Southern areas.

Adjusted mortality rates and joint point analysis

Considering the whole 35-year study period, AMR values were 3.42 in men and 2.06 in women (Table 2).

Table 1 Number of deaths for melanoma from 1982 to 2016 in the overall population and according to sex, age groups, and geographic areas

	1982–1990	1991–2000	2001–2010	2011–2016	Overall (1982–2016)
Overall	8,984	12,873	15,858	11,597	49,312
Sex					
M	4,719	6,915	9,095	6,875	27,604
	52.5%	53.7%	57.4%	59.3%	56.0%
F	4,265	5,958	6,763	4,722	21,708
	47.5%	46.3%	42.6%	40.7%	44.0%
Age groups					
≤19 years	32	42	19	9	102
	0.4%	0.3%	0.1%	0.1%	0.2%
20–44 years	1,334	1,617	1,813	926	5,690
	14.8%	12.6%	11.4%	8.0%	11.5%
45–64 years	3,401	4,342	4,605	3,016	15,364
	37.9%	33.7%	29.0%	26.0%	31.2%
≥65 years	4,217	6,872	9,421	7,646	28,156
	46.9%	53.4%	59.4%	65.9%	57.1%
Geographic areas					
Northwest	3,030	4,062	4,672	3,532	15,296
	33.7%	31.6%	29.5%	30.5%	31.0%
Northeast	2,168	2,827	3,486	2,506	10,987
	24.1%	22.0%	22.0%	21.6%	22.3%
Center	1,886	2,845	3,563	2,560	10,854
	21.0%	22.1%	22.5%	22.1%	22.0%
South and islands	1,900	3,139	4,137	2,999	12,175
	21.1%	24.4%	26.1%	25.9%	24.7%

Table 2 Number of deaths and age-adjusted mortality rates for melanoma in males and females and stratified for age groups and geographic area (pop. Std EU 2013)

		1982–1990		1991–2000		2001–2010		2011–2016		Overall (1982–2016)	
		Deaths	**AMR**	**Deaths**	**AMR**	**Deaths**	**AMR**	**Deaths**	**AMR**	**Deaths**	**AMR**
Males	Overall	4,719	2.71	6,915	3.13	9,095	3.62	6,875	4.02	27,604	3.42
	Age groups										
	≤19 years	17	0.00	21	0.01	9	0.00	5	0.00	52	0.00
	20–44 years	722	0.29	863	0.28	938	0.29	504	0.27	3,027	0.28
	45–64 years	1,998	0.90	2,636	1.02	2,821	1.03	1,878	1.03	9,333	1.00
	≥65 years	1,982	1.51	3,395	1.82	5,327	2.29	4,488	2.72	15,192	2.14
	Geographic areas										
	Northwest	1,604	3.33	2,181	3.65	2,719	3.98	2,094	4.47	8,598	3.91
	Northeast	1,129	3.31	1,513	3.50	1,983	3.99	1,464	4.32	6,089	3.84
	Center	1,003	2.74	1,538	3.35	2,013	3.94	1,540	4.40	6,094	3.69
	South and islands	983	1.78	1,683	2.32	2,380	2.87	1,777	3.19	6,823	2.58
Females	Overall	4,265	1.94	5,958	2.10	6,763	2.06	4,722	2.10	21,708	2.06
	Age groups										
	≤19 years	15	0.00	21	0.01	10	0.00	4	0.00	50	0.00
	20–44 years	612	0.24	754	0.25	875	0.27	422	0.22	2,663	0.25
	45–64 years	1,403	0.58	1,706	0.62	1,784	0.62	1,138	0.59	6,031	0.60
	≥65 years	2,235	1.11	3,477	1.23	4,094	1.17	3,158	1.29	12,964	1.20
	Geographic areas										
	Northwest	1,426	2.22	1,881	2.33	1,953	2.13	1,438	2.30	6,698	2.24
	Northeast	1,039	2.34	1,314	2.30	1,503	2.27	1,042	2.28	4,898	2.31
	Center	883	1.96	1,307	2.25	1,550	2.32	1,020	2.19	4,760	2.21
	South and islands	917	1.38	1,456	1.65	1,757	1.70	1,222	1.75	5,352	1.62

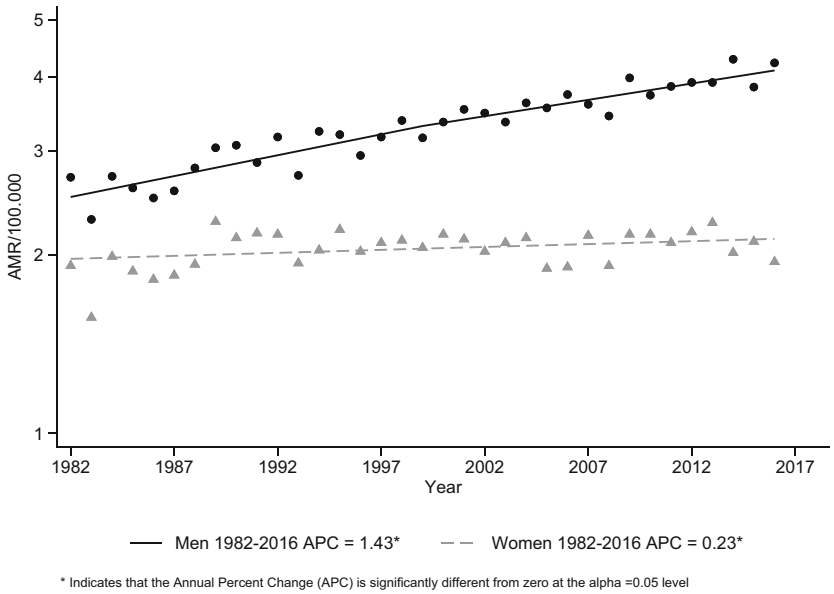
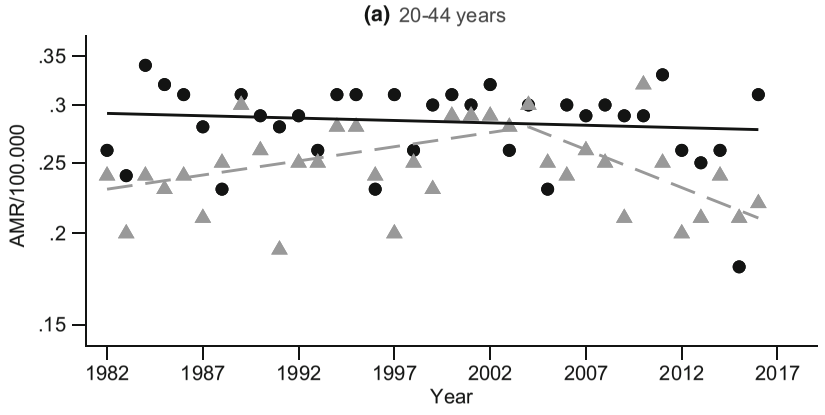


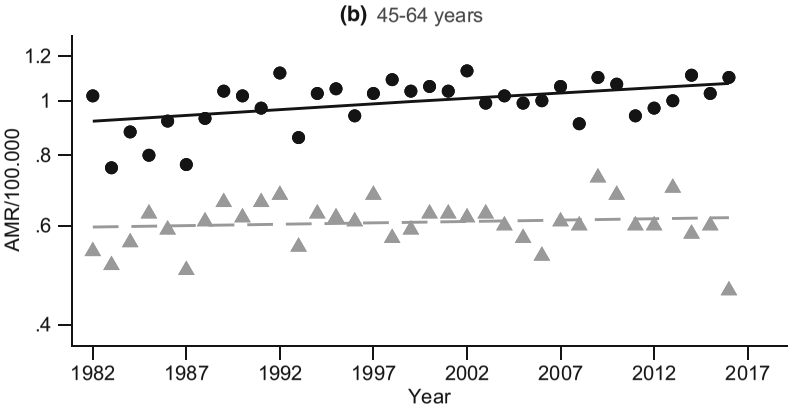
Figure 1 Melanoma age-adjusted mortality rate trend from 1982 to 2016 in men and women. Joinpoint analysis. APC, Annual Percent Change

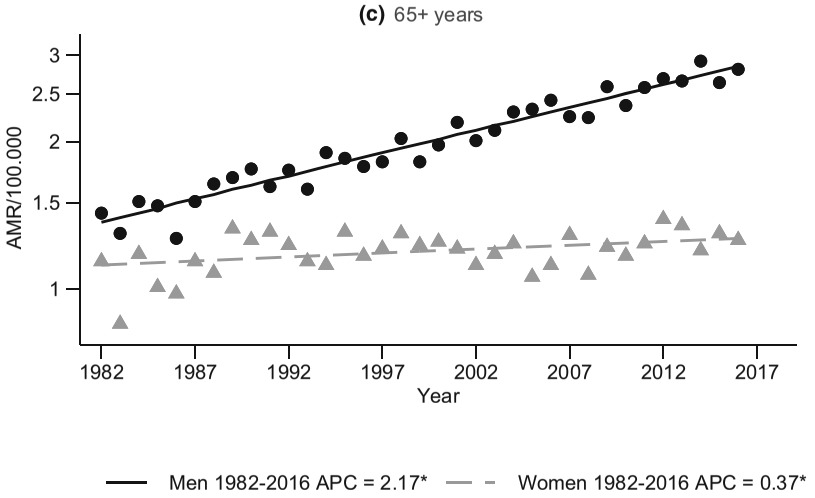
Among men, we registered a progressive increase of AMR from 1982 to 2016, with a value of 2.71 in the 80s, 3.13 in the 90s, 3.62 in the first decade of 2000, and 4.02 in the last quinquennium (2011–2016).

The mortality trend significantly and progressively increased during the whole study period (APC: 1.43; 95% CI 1.26–1.61).

In women, however, the AMR ranged from 1.94 (1982–1990) to 2.10 (2011–2016), with an APC of 0.23 (95% CI 0.00–0.46) (Fig. 1).







* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha =0.05 level

Figure 2 Age groups stratification (a: 20–44 years; b: 45–64 years; c: ≥65 years). Melanoma age-adjusted mortality rate trend from 1982 to 2016 in men and women. Joinpoint analysis. APC, Annual Percent Change

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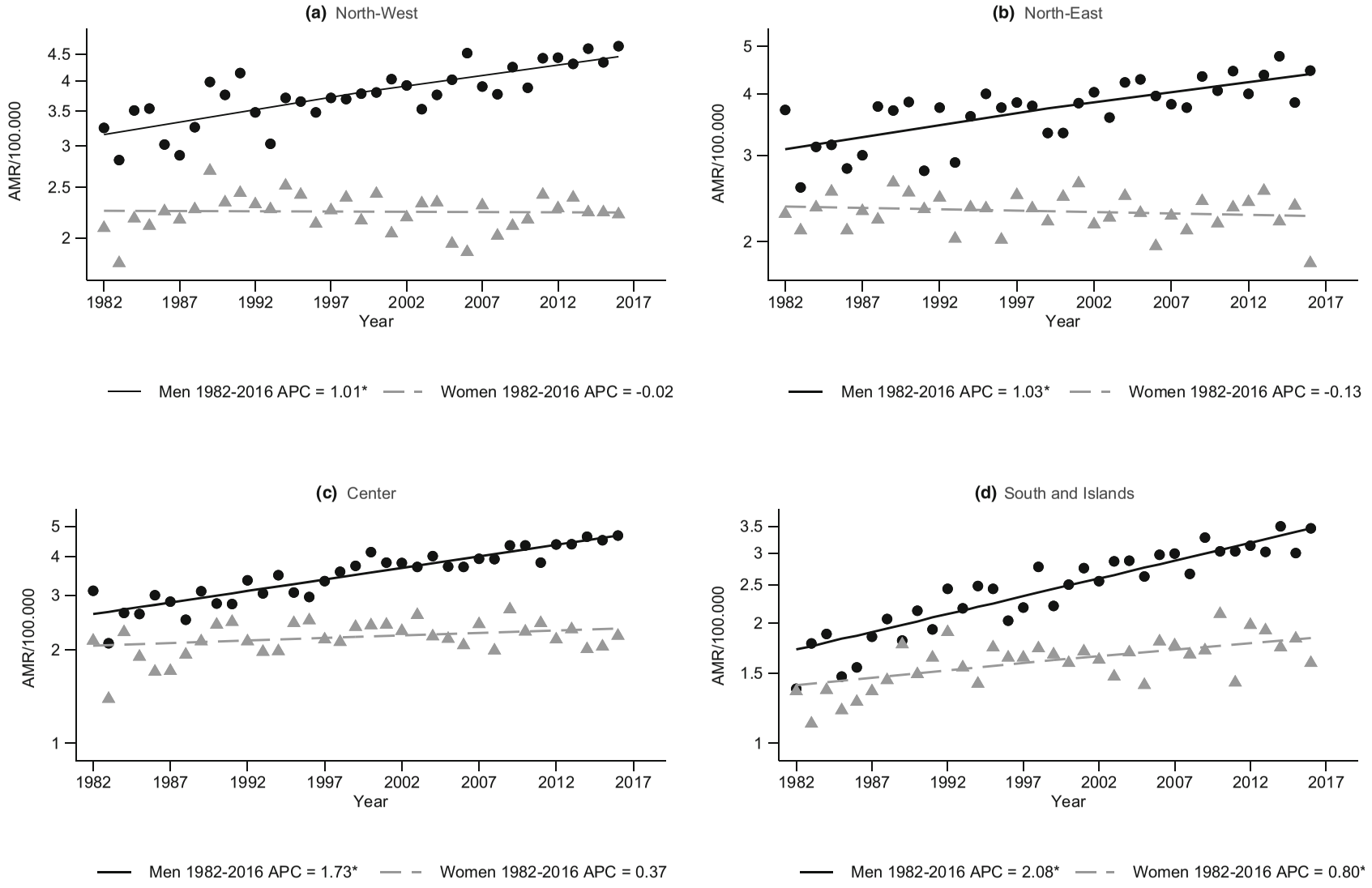

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha =0.05 level

Figure 3 Geographic areas stratification (a: Northwest; b: Northeast; c: Center; s: South and islands). Melanoma age-adjusted mortality rate trend from 1982 to 2016 in men and women. Joinpoint analysis. APC, Annual Percent Change

Sex-specific trend by age groups

When exploring how AMR varied across age categories, we found a progressive increase of mortality rate with older age in both sexes, with women showing lower rates in all age categories (Fig. 2).

As a result of the paucity of melanoma deaths, AMRs were almost always zero in patients ≤19 years.

In patients aged from 20 to 44 years, men had an almost flat mortality rate ranging from 0.27 to 0.29; women had lower AMR values than men, but we observed a joint point in 2004 with a significant increase from 1982 to 2004 (from 0.24 to 0.27; APC: 0.94; 95% CI 0.13–1.76) and a significant decrease from 2004 to 2016 (from 0.27 to 0.22; APC: −2.14; 95% CI −4.08 to −0.17) (Fig. 2a).

Concerning patients aged from 45 to 64 years, we found a constant trend in women (ranging from 0.58 in 1982–1990 to 0.59 in 2011–2016), while men showed a progressive low increase in the whole study period, from 0.90 to 1.03 (APC: 0.45; 95% CI 0.16−0.74) (Fig. 2b).

The largest difference between men and women was observed in patients aged ≥65 years, with women showing a significant but low increase in AMR from 1.11 to 1.29 from 1982 to 2016 (APC: 0.37; 95% CI 0.08−0.66), while mortality rate in men steeply increased from 1.51 to 2.72 (APC: 2.17; 95% CI 1.97−2.37) (Fig. 2c).

Sex-specific trends by geographic areas

When examining how AMR varied across Italy, we found a North–South gradient with higher mortality rates in the Northern regions for both men and women (Fig. 3).

Furthermore, AMRs significantly and constantly increased in men, with no joint points in all of the geographic areas, with a steeper increase in Southern regions (APC: 1.01, 95% CI 0.75−1.26 in Northwest; 1.03, 95% CI 0.71−1.36 in Northeast; 1.73, 95% CI 1.47−1.98 in the Center; 2.08, 95% CI 1.76−2.40 in the South and Islands).

In women, the mortality trend was instead flatter and lower than men's, with the only exception of Southern regions where the women's mortality rate progressively and significantly increased from 1.38 to 1.75 with no joint points (APC: 0.80 95% CI 0.41−1.19, $P < 0.001$).

Sub-analysis: Sex-specific trends by age groups and geographic areas

We finally evaluated the trend of AMR stratifying for both age groups and geographic regions.

In patients aged 20–44 years, we demonstrated decreasing mortality trends in both sexes in Northern regions. In Central regions, a significant decrease was also reported for both men and women starting from 2006 with an APC of −3.31 (95% CI −6.67 to 0.17), while AMR progressively increased from 1982 to 2006 (APC: 0.93 95% CI −0.02 to 1.89). In Southern regions and Islands, however, we found a constant increase in the mortality rate for both men and women (APC: 1.10, 95% CI 0.55−1.65) (Figure S1).

In patients aged from 45 to 64 years, we calculated a stable trend in the whole study period in Northern regions, a significant but very low increase in Central regions in both sexes (APC: 0.34 95% CI 0.00−0.68) and a steeper increase in AMR in the South of Italy, especially from 1982 to 1992 (APC: 4.12 95% CI 1.60−6.71) (Figure S2).

Finally, in patients aged ≥65 years, men registered a steeper increase in mortality rates than women in all of the geographic areas (Figure S3).

Discussion

In this study, we reported how melanoma mortality varied in Italy from 1982 to 2016. Thanks to the ISTAT collaboration, we were able to retrieve comprehensive Italian national data on melanoma mortality. We found that AMR was higher in men than women in the whole study period; mortality progressively increased, with no joint points, in both sexes, but with a steeper slope in men, making the difference with women wider over time.

An increase in melanoma mortality in recent decades has also been reported for other countries, located at different latitudes and with different population characteristics than Italy.[10–13] This suggests that factors other than the level of ultraviolet radiation and the prevalence of fair-skinned inhabitants may contribute to melanoma mortality, such as sun-exposure habits, healthcare efficiency, and adherence to prevention campaigns.[4–14]

Data from other countries[10–13] also highlighted higher mortality rates for melanoma in men than women, as well as the same sex-mortality gap we observed in our study. Recently, a study reporting melanoma mortality trends in 31 countries (including Italy) from the World Health Organization (WHO) database found that all countries, except the Czech Republic, had melanoma mortality increased in men over the considered period, with the largest increases seen in the Republic of Korea (+535.3%), Ireland (+115.5%), and Croatia (+91.2%).[12] Mortality in women, however, was stable or decreased over the observed period, with Israel, the Czech Republic, and Australia reporting the greatest reductions (−23.4%, −15.5%, and −10.3%, respectively). Other studies exploring melanoma mortality in single countries, reported similar results in Australia and New Zeland,[10] the United States of America,[11] Spain,[6] and Germany.[3]

Several hypotheses might contribute to explain these findings, first of all the lower attention of men to sun protection and self-skin examination.[13] A study about awareness, attitude, and adherence to preventive measures in 185 patients at high risk for melanoma showed that even people with a good level of knowledge about melanoma risk factors and photoprotection measures may not recognize the importance of

self-examination.[14] Furthermore, men are less likely to adhere to prevention campaigns and more frequently have outdoor occupations.[15,16]

Women seem to pay more attention to prevention campaign and sun protection, despite the higher propensity to intentional sun-tanning.[17–19] It has been reported that women aged between 18 and 35 years, with fair hair and skin phototype (I-II) and a suitable level of knowledge about risk factors are more prone to correctly using sunscreens and avoiding sun exposure.[14]

Another cause of lower mortality in women is related to the location of the disease. It is already known the higher frequency of presentation of melanomas in the legs in women.[20] It may favor an early detection for two main reasons. First, location and clothing-style behaviors lead women to see a new or changing lesion on the legs, whereas the back, a frequent location in men, is not an accessible site, and men living alone have a later stage at diagnosis.[13] The second reason is the higher attention of women than men to self-skin examination.[14] Previous studies have already shown a correlation between self-examinations and earlier melanoma diagnosis.[21]

Biological factors might also contribute to explain survival differences observed among sexes, such as differences in the immunological response activated against the tumor.[22,23]

The same trend in mortality rates as the overall population was observed in our study when stratifying for a geographic area, with a North–South gradient characterized by higher AMRs in the North of Italy in the 80s; however, Northern regions underwent a slower increase in melanoma mortality than the Central and the Southern. The latest AMRs were indeed similar for men and women independently from the geographic area. To summarize, we found that although melanoma mortality increased over the whole study period, geographic differences became thinner, since the North of Italy registered a slower increase than the South. Regional disparities in prevention campaigns and healthcare system efficiency might be mainly responsible for the observed geographic differences.[24]

We further stratified our population into four age groups and found that only patients aged ≥65 years, accounting for the majority of deaths, had a similar trend as the overall population, with mortality trends progressively increasing, especially in men.

In patients aged 20–44 years, AMRs underwent a tiny decrease in the whole study period, with a progressive reduction in men and a double increasing-decreasing trend in women. Interestingly, in this age group, Northern and Southern regions had inverse mortality trends, with a progressive decrease and increase, respectively, but with similar AMR values in the latest quinquennium (2011–2016). A similar trend was also observed in patients aged 45–64 years, but the AMRs were more stable over time and the curves were flatter in this age group.

The same trend toward increasing mortality in older individuals and stable or decreasing rates in younger people has also been reported in many other countries, especially in fair-skinned populations.[12,25]

The observed differences in mortality among age groups should be interpreted in light of melanoma incidence trends. The AIRTUM (Associazione Italiana Registro TUMori) data, available from 2003 to 2014, reported melanoma incidence age-adjusted rates increasing from 14 to 21 per 100,000 in men and from 12 to 16 per 100,000 in women. It is well known that early diagnosis has largely contributed to the increase of melanoma incidence; in particular, the use of dermoscopy played a critical role in increasing the proportion of superficial melanomas.[26]

AIRTUM data reported similar trends of melanoma incidence among age groups, which is apparently in contrast with the lower increase of mortality rates of younger individuals as compared to the elderly. This might be mainly explained by the higher proportion of slow-growing superficial melanomas diagnosed in younger people, as well as by the longer survival of a younger individual, dying at an older age than in the past thanks to the use of novel therapies, whose effects will become more evident in future updates of our data.

One of the main limitations of this retrospective study is regarding the use of the ICD coding classification to retrieve melanoma deaths. Indeed, the long study period, geographic differences, and the switch from ICD-9 to ICD-10 classification could have affected the coding accuracy. Other limitations regard the retrospective design, which does not allow defining the causal role of factors potentially influencing melanoma mortality, and the lack of comprehensive data on melanoma staging. In the end, AIRTUM does not contain data on the whole national territory but only the real data recorded in the areas of the country covered by an accredited cancer registry and estimates for the others. It could influence the correlations with mortality data.

In conclusion, we found that in the last three decades, the melanoma mortality rate in Italy progressively increased in the elderly, especially in men. The increasing mortality was faster in Southern regions that, consequently, showed progressively similar rates to that of the Northern regions, thus leading to a more uniform National framework. In young and adults, where melanoma incidence usually peaks, a tendency toward higher uniformity of AMRs on the entire national territory was also observed. However, this was the result of a decreasing trend in the North and an increasing trend in the South of Italy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Age groups 20–44 years: geographic areas stratification (a: Northwest; b: Northeast; c: Center; s: South and islands). Melanoma age-adjusted mortality rate trend from 1982 to 2016 in men and women. Joinpoint analysis. APC, Annual Percent Change.

Figure S2. Age groups 45–64 years: geographic areas stratification (a: Northwest; b: Northeast; c: Center; s: South and islands). Melanoma age-adjusted mortality rate trend from 1982 to 2016 in men and women. Joinpoint analysis. APC, Annual Percent Change.

Figure S3. Age groups 20–44 years: geographic areas stratification (a: Northwest; b: Northeast; c: Center; s: South and islands). Melanoma age-adjusted mortality rate trend from 1982 to 2016 in men and women. Joinpoint analysis. APC, Annual Percent Change.

