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Authors Contribution Statement

- Dr. Ortiz-Álvarez has contributed to the conception and design of the manuscript, data collection, data analysis and interpretation and redaction, revision and approval of the manuscript.
- Dr. Duran-Romero has contributed to the conception and design of the manuscript, data collection, data analysis and interpretation and redaction, revision and approval of the manuscript.
- Dr. Hernández-Rodríguez has contributed to data collection and redaction, revision and approval of the manuscript.
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- Dr. Conejo-Mir has contributed to the redaction, revision and approval of the manuscript.

- Dr. Pereyra-Rodriguez has contributed to the conception and design of the manuscript, data collection, data analysis and interpretation and redaction, revision and approval of the manuscript.

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- Dr. Ortiz-Álvarez has nothing to disclose.
- Dr. Duran-Romero has nothing to disclose.
- Dr. Hernández-Rodríguez has nothing to disclose.
- Dr. Sendin-Martin has nothing to disclose.
- Dr. Conejo-Mir has nothing to disclose.
- Dr. Pereyra-Rodriguez has nothing to disclose.

The data that support the findings of this study are available from Instituto Nacional de Estadística.. Restrictions apply to the availability of these data, which were used under license for this study. Data are available www.ine.es with the permission of Instituto Nacional de Estadística.

ABSTRACT

Background and objectives: malignant melanoma accounts for 80% of deaths due to skin cancer. Its incidence is globally increasing. However, melanoma mortality seems to be decreasing. The aim of this study was to analyse mortality rates due to melanoma in Andalusia between 1979 and 2018.

Material and methods: deaths due to melanoma and mid-year population in Andalusia were collected from the National Institute of Statistics. Age-adjusted mortality rates were calculated for overall population and for each sex and age group. Regression models were used to calculate significant points of change. Sex-ratio and the independent effects of age, period and cohort were also analysed.

Results: age-adjusted mortality due to melanoma rose from 0,61 to 1,94 deaths per 100.000 from 1979 to 2018 for the overall population. A significant change of trends was detected around 1994 when, after a steady rise from 1979, mortality rates stabilized up to the end of the period studied. The cited increase was more pronounced in >64 yo males. From the end of the 2000s there was a decrease in mortality rates to date in all population groups, producing a period effect.

Conclusions: A stabilization in melanoma mortality rates was observed in Andalusia from 1994 with a decrease in some groups at the beginning of the 21st century. Trends observed in Andalusia don't differ substantially from those in Spain. The development of new therapies and an earlier diagnosis may have an influence in those changes. Studies that compare differences between Spanish regions are needed to define better prevention strategies.

BACKGROUND

The incidence of malignant melanoma, unlike other malignant neoplasms, is increasing, with global incidence rates of 11.5 and 11.3 per 100,000 persons-years in men and women respectively (1). Multiple meta-analyses have established key risk factors, among which are intermittent sun exposure and history of sunburn (especially in early ages), skin phototype or family history (2).

Although it accounts for 80% of skin cancer deaths (3), its previously feared death rates appear to be trending downward according to recent studies. This decrease may be due to various factors. In this way, multiple primary and secondary prevention strategies seem to have a positive effect in younger cohorts. The aim is to detect earlier stages, thereby increasing survival (4,5).

However, the great paradigm shift in the approach to melanoma is given by the emergence at the end of the 2000s of the so-called immunotherapy, a new therapy directed against regulators of the immune response. The appearance of drugs against cytotoxic T lymphocytes antigen 4 (CTLA-4: Ipilimumab, funded since 2012) (6,7) followed by therapies against programmed death receptor type 1 (PD-1: Pembrolizumab and Nivolumab, funded since 2016) have led to a considerable increase in survival in patients with locally advanced or metastatic melanoma (7–9). Also in this decade, therapies aimed at proteins of the MAP kinase pathway expressed by the tumor emerged, such as B-RAF (Vemurafenib and Dabrafenib, funded since 2012 and 2013 respectively) and MEK (Cobimetinib and Trametinib, funded since 2016) (7).

With regard to melanoma mortality trends in Spanish territory, a decrease in age-adjusted mortality rates has been observed in last years, especially in the younger subgroups (22-44 years). On the other hand, the mortality rate in people over 65 seems to increase in the latest reports published up to 2016 in both sexes (4).

Nevertheless, to date there are no published data on the trends in mortality rates of malignant melanoma in Andalusia. This is a region of Spain with particular characteristics such as high insolation with a significant part of the population dedicated to activities carried out in the open air such as livestock, fishing or agriculture. Therefore, with this study we seek to evaluate the evolution of mortality from this neoplasm in Andalusia in the period 1979-2018, observing the possible changes in trends in relation to the arrival of new therapies. To our knowledge, this is first study to analyse melanoma mortality in Andalusia for such a long period, and it may be useful to compare the differences in mortality between regions of Spain and Europe in subsequent studies.

MATERIAL AND METHOD

Following the methodology established in previous studies on melanoma mortality, such as those carried out by Cayuela et al. or (10–12), more recently, by Gutiérrez-González et al. (4), death certificates and population data in the middle of the year were obtained for the period 1979-2018 through the National Institute of Statistics (INE) of Spain (http://www.ine.es). These data, obtained by a third party (code ES0002 / 2020), are provided free of charge and its use authorised for the realization of this study with a commitment to cite the source. Through microdata provided from the Death Certificates, all those who died between 1979 and 2018 in Andalusia due to malignant melanoma were selected (codes ICD 8 and ICD9: 172; ICD 10: C43). The mortality rate by age was computed, establishing five-year age groups. Age-adjusted mortality rates were calculated using the direct method for the entire country and stratifying by sex and age group (<35, 35-64 and> 64 years of age), as well as the sex ratio, defined as the proportion of male mortality in relation to female. These results were expressed as deaths per 100.00 persons-year using the new European standard population of 2013 as a reference, in order to facilitate comparisons with other recent European-focused studies (13). To manage and obtain these data, the Epidat3.1®, Microsof® Excel and SPSS Statistics 25® programs were used.

Using regression models, both the significant trend change points for mortality rates by sex and age group were calculated, as well as the Annual Average Percentage Change (AAPC). For this, the Joint regression program developed by the Surveillance Research Program of the National Cancer Institute of the United States was used (14), defining the maximum number of joint points at 5.

Finally, the independent effects of age, period, and cohort (APC effects) on mortality rates were calculated using the penalty functions proposed by Decarli and La

Vecchia, using the GLIM macros provided by the authors for R® software (15). This proposal is based on the Osmond and Gardner models (16), estimating the APC models using Poisson regression. The data were divided into periods of 5 years and five years of age and the goodness of fit of the possible APC models was also compared.

RESULTS

The global mortality due to melanoma in Andalusia for the first period studied (1979-1983) was 0.61 cases per 100,000 (0.34; 0.87 95% CI), reaching a value of 1.94 cases per 100,000 (1.63; 2.25 95% CI) in the last five years (2014-2018). Stratifying by sex, mortality rose from 0.661 to 2.707 cases per 100,000 in men in these intervals, while in women the increase was less pronounced, going from 0.347 to 1.336 cases per 100,000 (Table 1).

In the regression analysis for the total population, a statistically significant change in trend was observed, defining two stages. The first of them, from 1979 to 1994 (AAPC 7.7 with a 95% CI of 5.5-9.9), is characterized by a progressive rise in mortality, followed by a stabilization of it from 1994 to 2018 (AAPC 0.2 with a CI 95% of -0.5-0.9). In this same analysis stratified by sex, a single junction point is seen in both groups that defines two periods of the same duration as in the global analysis. In both groups, the first period is characterized by a progressive ascent. However, while in men an ascent of attenuated slope was appreciated, in women there was a decrease that is maintained until the present time (Table 1).

Respecting the age and sex-adjusted analysis, in the subgroup under 34 years of age, a downward trend can be seen globally without appreciating any change in trend both for the analysis of the subgroup as a whole and for men (Figure 1a). On the other hand, in the 35-64 year-old subgroup, an upward trend is observed at the beginning that affects both sexes, producing a point of trend change around 1996-1998, when there was a decrease in mortality rates. Later, mortality rates rose again in the early 2010s in men and if we take into account both sexes (Figure 1b). In women aged 35-64 years, the downward trend continues to this day. Contrary to what happens in the youngest subgroup, in those over 65 years of age, a globally upward trend was observed, in which, both taking into account both sexes and women separately, there was a marked rise in the period 1979-1994, subsequently producing an attenuation of said slope (Figure 1c).

With regard to the sex ratio, the change observed in the intermediate age subgroup is especially relevant (Figure 2). In that group, the study period begins with fairly equal rates, and at the end of it we can appreciate a male predominance. With respect to the other subgroups, in the youngest one a male predominance can be seen during the 90s, returning to a more equal ratio at the end of the period. In the oldest subgroup, the sex-ratio remains relatively constant throughout the period without major changes.

Analysing the age-cohort-period effect, a progressive increase in mortality rates was observed according to age (Figure 3). On the other hand, with respect to the birth cohort, the mortality rates in both women and in both sexes rose in all cohorts up to those born in the 1960s, when a decrease can be appreciated in them. Nonetheless, the male cohorts showed a progressive ascent that continues to this day. With respect to the period effect, both in the general population and stratifying by sex, mortality rates rose progressively until the 2000s, when a significantly marked decline is seen in women (Figure 3). The goodness of fit was calculated for each possible regression model to calculate the APC effects. It can be seen that a three-factor model fits better than one that includes only two, since it has a lower AIC and a smaller deviation (Table 2).

DISCUSSION

After experiencing a worrying increment in melanoma mortality from the 1970s to the 1990s in Spain, we are recently experiencing an encouraging downward trend that is expected to continue in the coming years (4,6,9), mainly because of the introduction of directed therapies. Inn older age groups mortality had been reported to be still rising (4); however, recent studies have shown a decrease even in this subgroup (17).

The north-south disparity in Europe in terms of figures related to melanoma is a well-known fact, with higher incidence rates at higher latitudes but without reducing the incidence/mortality ratio (18). Although in our country we do not have national cancer registries, an increase in incidence has been observed in some partial provincial registries (19). Even though some publications point to possible differences in epidemiological parameters (19–21), no comparisons have been established in terms of incidence or mortality between the different regions.

Several factors may have contributed to the recent improvement in melanoma mortality rates. On the one hand, it is known that the survival of melanoma in early stages is more than 90% at 5 years (22) and the diagnosis of the tumor in these stages seems to be increasing (23). This can be attributed to different variables, such as the spread of dermoscopy – not only in dermatology but also in primary care, where it has shown to improve the diagnosis of melanoma (24,25). Likewise, prevention campaigns are postulated as one of the measures with the strongest impact; in Spain we must highlight the results of the Euromelanoma campaigns (26,27). Special mention should be made of the development of treatment strategies for advanced and metastatic melanoma, particularly the appearance of directed therapies and immunotherapy (6,9,28).

Recently, Durán-Romero et al. have carried out a study using the same methodology and also using the European standard population of 2013. We have observed lower figures compared to their findings (17). Andalusia has some peculiarities, such as the significant insolation received or the relevant amount of people working on the primary sector of the economy, where workers are exposed to high rates of sun radiation in activities such as agriculture or fishing (29,30). Although these are known risk factors for the development of melanoma,(2) which could lead to a higher incidence, we hypothesised some factor that could explain this lower mortality rates: population accustomed to working outdoors could have a greater awareness of the risks of sun exposure, continuous sun exposure instead of intermittent burns as a protective factor. Nevertheless, further studies are needed in order to correlate these differences.

Even so, globally, we seem to appreciate the same trends described by these authors, with higher mortality rates in men than in women and a stabilization in their growth since the mid-1990s. However, where there does seem to be a difference is in the subgroup between 35 and 64 years of age. Although in this group there was a decrease from the mid-90s to the end of the 2000s, there seems to be an upturn in mortality rates, especially in males, remaining, even so, in figures similar to those reported. Furthermore, Durán-Romero et al. have observed a change in trend since 2015, with a notable decline in mortality rates, probably attributable to the widespread use of new targeted therapies. This change of trend has not been observed in Andalusia and further studies are needed to clarify this fact. This is one of the Spanish regions with the lowest health expenditure per inhabitant according to the latest available data (31). This factor must be taken into account and may explain part of the absence of said change.

Concerning the sex ratio, the most relevant data is the change in trend observed in the 35-64 year-old subgroup. While the period begin with fairly equal values, at the end of it we observed a male preponderance. This trend, leaving aside biological components, can be explained by different factors, such as an earlier diagnosis due to greater awareness amongst the female sex (32). In this way, we can think that melanoma prevention campaigns seem to be more effective in women and young people. This makes men and the elderly potential targets for future prevention campaigns, which has already been pointed out in other studies (33). In addition, there appears to be differences between sexes in terms of response to immunotherapy, with higher risk of inmune-related adverse events amongs women, which could influence a change in trends in the future (34).

There are various factors that can explain the escalation in rates seen with increasing age, highlighting above all the diagnostic delay that occurs in these age groups, where prevention campaigns seem to have less impact (33,35). It could be hypothesized that the elderly respond worse or, at least, differently to new therapies.; however, recent studies seem to refute this theory (36).

We refer to a cohort effect when there is a change in rates due to one or more factors that affect a generation as a whole. This study showed a cohort effect with a rise in mortality rates up to the cohorts born in the 1980s, especially in women but also if we take into account the entire sample. Although it is necessary to determine the exact cause of this fact, we can hypothesize that the rise in sun exposure for recreational purposes together with the lower awareness regarding photoprotection in these cohorts could have influenced a more aggressive photoexposure. We must highlight the differences with the study of Durán-Romero et al.(17), where this cohort effect is much more remarkable. We suggest that these differences account for the perpetuation in Andalusia of some of the factors that affect incidence or greater late diagnosis.

On the other hand, we speak of the period effect when we find one or more factors that affect the population as a whole regardless of the birth cohort. In our study we can see a clear period effect with a manifest decrease in rates starting in the 2000s. The cause of this diminishment could be found in events such as the increasingly widespread use of dermoscopy or the appearance of new therapeutic alternatives for more advanced melanomas (6,8).

One of the main limitations of this study is the use of indirect and collected data obtained through certificates, due to possible omissions at the time of its completion. Even though that, mortality records are postulated as much more reliable than incidence records, especially in Spain, where the available data is only partial (20). Plus, there is a need of studies for a better understanding of the correlation between melanoma mortality and its incidence.

CONCLUSIONS

Melanoma mortality rates in Andalusia have increased gradually since 1979. However, the figures seem to be stabilizing in recent years, with hopeful decreases in subgroups such as the youngest or middle-aged women. Although these trends seem to be parallel to those reported so far for the rest of the Spanish territory, better comparisons should be established between the different regions of the country.

Early diagnosis and the development of new therapies seem to be behind these encouraging data. Nonetheless, we cannot ignore prevention campaigns, focusing on those subgroups in which they seem to be having less effect.

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LEGENDS

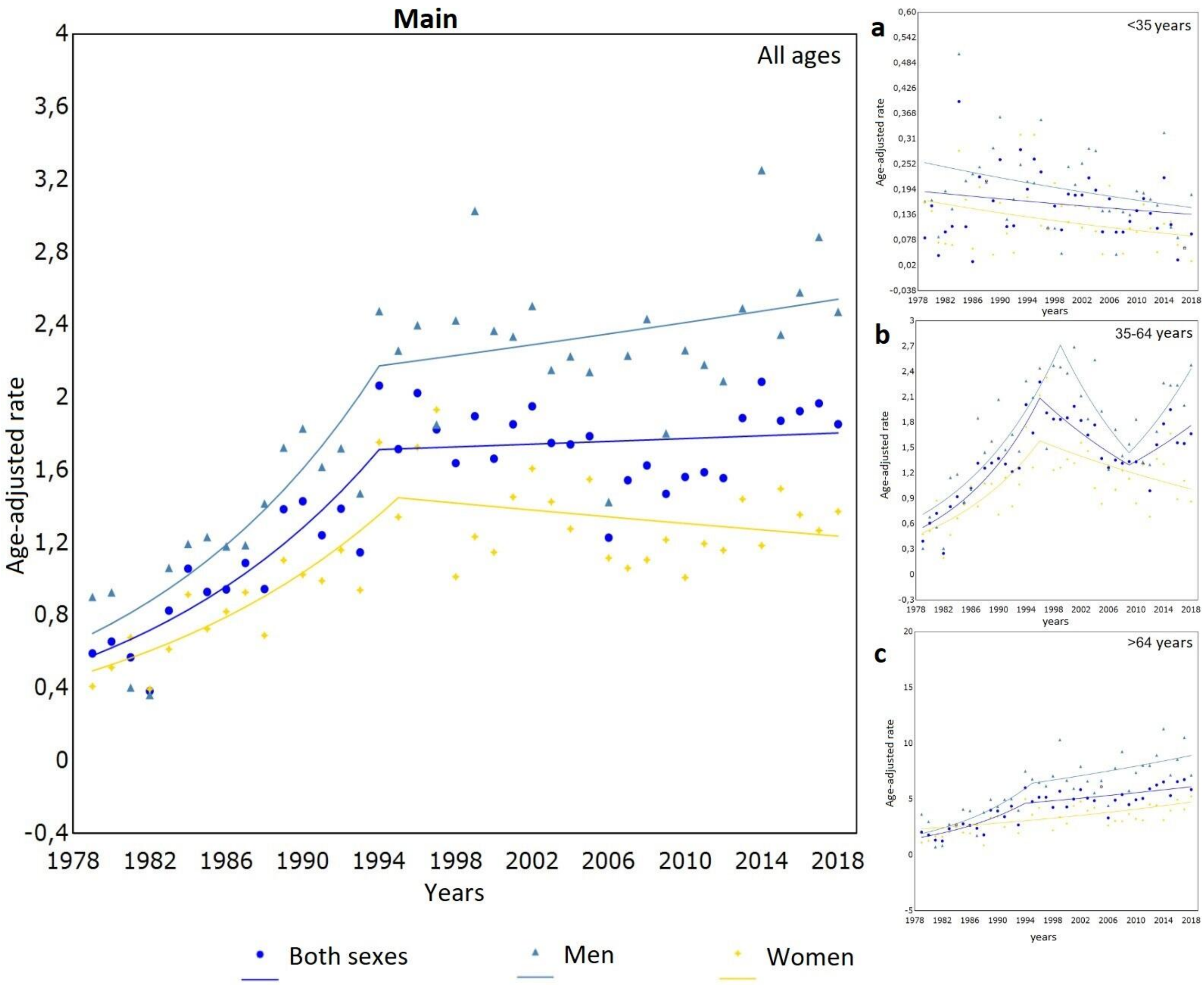
Table 1. Trend análisis on anual average percentage change (AAPC) global and stratified by age and sex.

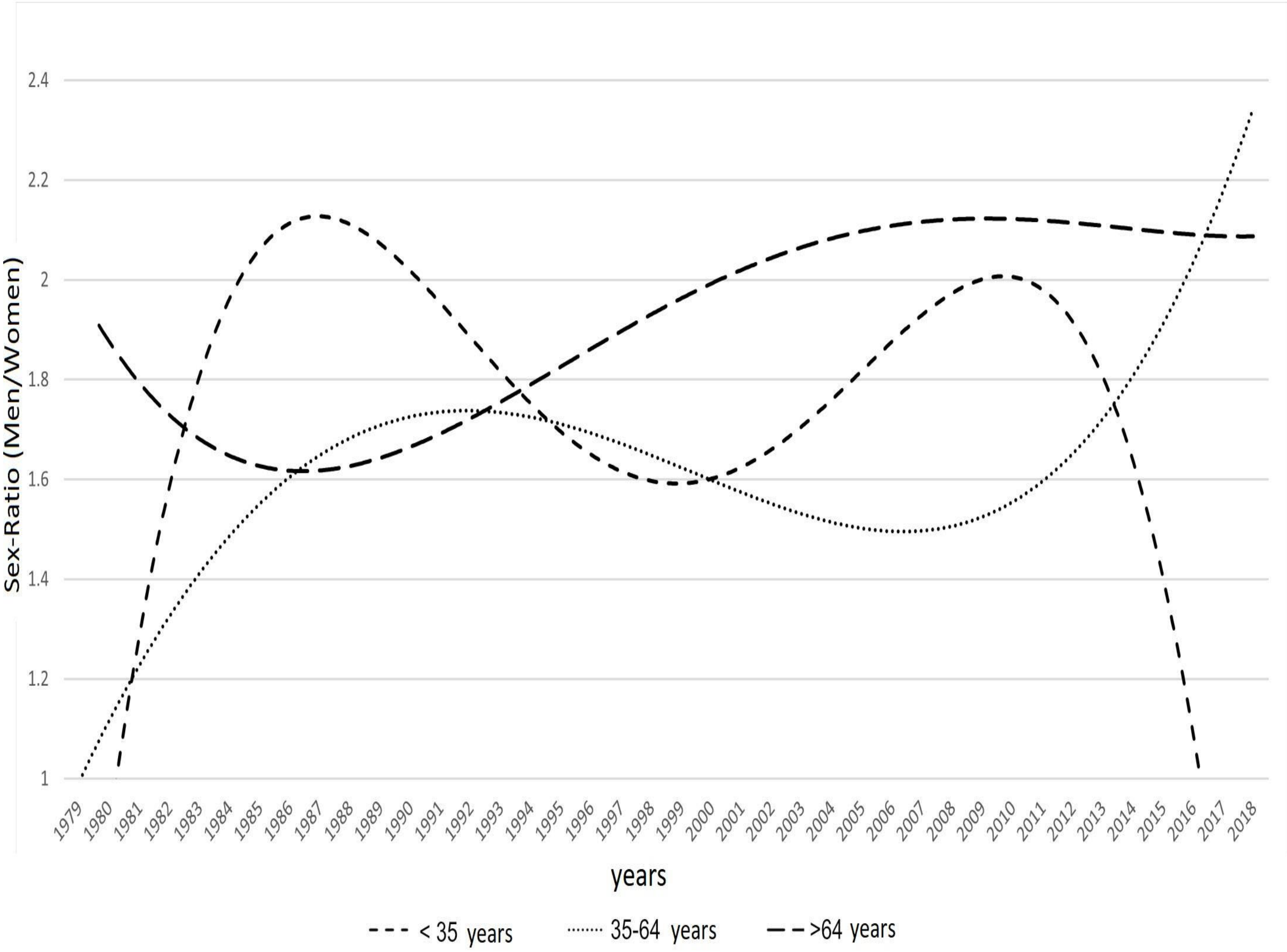
Table 2. Goodness-of-fit test for different age, period and cohort specific models of cutaneous malignant melanoma in Andalusia, 1979–2018

Figure 1. Global and age and sex-adjusted mortality rates

Figure 2. Sex-ratio adjusted by age groups.

Figure 3. Age-period-cohort effect for the whole population and adjusted by sex


Main
All ages
Age-adjusted rate
Years
Both sexes
Men
Women
a
<35 years
b
35-64 years
c
>64 years
years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Sex-Ratio (Men/Women)
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< 35 years
35-64 years
>64 years

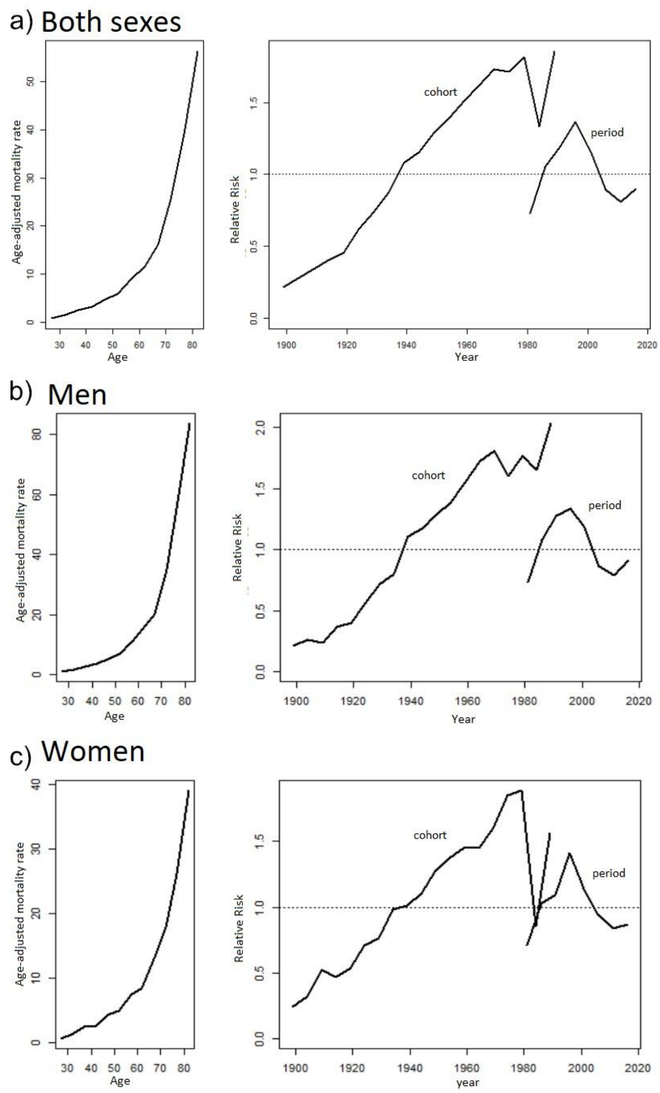
a) Both sexes
Age-adjusted mortality rate
Age
Relative Risk
Year
cohort
period
b) Men
Age-adjusted mortality rate
Age
Relative Risk
Year
cohort
period
c) Women
Age-adjusted mortality rate
Age
Relative Risk
year
cohort
period

TABLE 1 Trend análisis on annual average percentage change (AAPC) global and stratified by age and sex

	Both sexes				Men				Women			
	1979-1983 ASMR (95% CI)	**2014-2018 ASMR (95% CI)**	**JP**	**Period(s) years: AAPC (95% CI)**	**1979-1983 ASMR (95% CI)**	**2014-2018 ASMR (95% CI)**	**JP**	**Period(s) years: AAPC (95% CI)**	**1979-1983 ASMR (95% CI)**	**2014-2018 ASMR (95% CI)**	**JP**	**Period(s) years: AAPC (95% CI)**
All	0.61 (0.34;0.87)	1.94 (1.63;2.25)	1	1979-1994: 7.7* (5.5;9.9) 1994-2018: 0.2 (-0.5;0.9)	0.73 (0.26-1.21)	2.71 (2.14-3.27)	1	1979-1994: 8* (5.1-11) 1994-2018: 0.6 (-0.3-1.5)	0.52 (0.21-0.84)	1.34 (0.99-1.68)	1	1979-1994: 7.9* (5.3-10.5) 1994-2018: -0.6 (-1.4-0.3)
<35 years	0.10 (0.01;0.33)	0.10 (0.02;0.30)	0	1979-2018: -0.8* (-2.3;0.7)	0.15 (0.01;0.57)	0.14 (0.02;0.41)	0	1979-2018: -1.3* (-2.7-0.1)	0.04 (0;020)	0.07 (0;0.32)	0	1979-2018: -1.7* (-1.7-0)
35-64 years	0.56 (0.28;1.01)	1.70 (1.30;2.21)	2	1979-1996: 8.1* (5.9;10.3) 1996-2009: -3.6* (-5.9;-1.2) 2009-2018: 6.9 (4.6;9.3)	0.60 (0.23;1.37)	2.25 (1.61;3.08)	2	1979-1999: 6.9* (4.6-9.3) 1996-2009: -6.1* (-11.2;-0.8) 2009-2018: 6* (1-11.2)	0.51 (0.17;1.18)	1.16 (0.73;1.81)	1	1979-1996: 7.1* (3.6;10.6) 1996-2018: -2* (-3.5;-0.4)
>64 years	1.75 (0.79;3.61)	6.21 (4.96;7.70)	1	1979-1994: 7.4* (4.1;10.8) 1994-2018: 1.2* (0.3;2)	2.19 (0.64;7.23)	8.94 (6.65;11.99)	1	1979-1994: 7.9* (3.4-12.5) 1994-2018: 1.4* (0.1-2.8)	1.53 (0.51;3.95)	4.27 (2.98;5.98)	0	1979-2018: 1.8* (0.9-2.7)

Abbreviations: AAPC (95% CI), annual average percentage change and 95% confidence interval; ASMR, age standardized mortality rate; JP, jointpoint.

* = p<0.05

TABLE 2 Goodness-of-fit test for different age-, period- and cohort-specific models of cutaneous malignant melanoma in Andalusia, 1979 to 2018

Model	**df**	Deviance	**p**	**AIC**
Both sexes				
Age model	84	330.13452	**<0.001**	842.4383
Age-drift model	83	192.07657	**<0.001**	706.3803
Age-period model	77	94.48422	**<0.001**	620.7880
Age-cohort model				
Age-period-cohort model	60	51.22173	**<0.001**	611.5255
Men				
Both sexes	84	233.15429	**<0.001**	1292.6945
Age model	83	141.13486	**<0.001**	826.9273
Age-drift model	77	83.14841	**<0.001**	820.2742
Age-period model				
Age-cohort model	60	46.15752	0.6908	760.0682
Women				
Both sexes	84	147.52663	**<0.001**	575.3663
Age model	83	106.55987	**<0.001**	536.3996
Age-drift model	77	81.32948	**<0.001**	545.1692
Age-period model				
Age-cohort model	60	46.93657	**<0.001**	522.7763

Abbreviations: AIC, Akaike information criteria; df, degrees of freedom.
Bold values indicate statistical significance.