Journal of the European Academy of Dermatology and Venereology (JEADV) (2021): abril 2021

DOI: https://doi.org/10.1111/jdv.16983

Title Page

Title: Cutaneous malignant melanoma mortality in Spain from 1979 to 2018. Trends and new perspectives in the immunotherapy era.

Running head: MELANOMA MORTALITY IN SPAIN

Manuscript words: 28933~~36~~; Tables: 2; Figures: 4

Authors:
A.J. Durán-Romero[1]
M. Sendín-Martin[1]
J. Conejo-Mir[1]
J.J. Pereyra-Rodriguez[1]

[1] Dermatology Department. Hospital Universitario Virgen del Rocío. Sevilla. España.

Corresponding autor:
José Juan Pereyra Rodriguez
H.U. Virgen del Rocio. Centro de Diagnostico, 3ª planta
Avda. Manuel Siurot S/N. 41013 - Sevilla
Email: pe3reyra@gmail.com

Financial aid: This work has not received any financial assistance for its realization

Conflict of interests:
Dr. Duran-Romero 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.

SUMMARY

Background: Recent studies suggest that cutaneous melanoma mortality rates in Spain are stabilizing and even decreasing in younger cohorts.

Objectives: To analyse mortality rates of melanoma from the last 40 years, focusing on changes related with the development of new therapeutic approaches.

Methods: Death records and mid-year population data were collected from the National Statistics Institute. By using the direct method, age-standardized mortality rates were calculated for overall population and for each sex and age group. Significant changes in mortality trends were identified by Joinpoint regressions. The independent effects of age, period and cohort (APC) and Potential Years of Life Lost (PYLL) due to melanoma were also analysed.

Results: Age-standardized melanoma mortality rates rose in Spain from 0.78 to 2.13 deaths per 100.000 from the first to the last quinquennium of the study (1979-83 to 2014-18) for the overall population. After a marked increase until 1995, mortality rates levelled off. Following this stabilization, from 2015 to 2018 there was a decrease in mortality rates for the overall population (Average Annual Percent Change (AAPC): -4.3, not significant), more accused in males over 64 years old (yo). A period effect was observed from the beginning of 21st century, with mortality rates dropping to date.

Conclusions: There is a decrease in melanoma mortality rates from 2015 in all age groups, that confirms previous trends in mortality in younger cohorts. Improvement in diagnosis and development of new therapies for advanced melanoma may have a crucial role in this event. Close monitoring of melanoma mortality rates is necessary to confirm these trends.

BACKGROUND

Although cutaneous malignant melanoma represents only a minority of all skin cancer cases, it causes most deaths from skin cancer, being responsible for 1.4% of all cancer deaths registered in Europe in 2018.[1–3] Unlike other malignancies, global incidence of melanoma continues rising, with globally age-standardized incidence rates of 11.5 cases per 100,000 person-years (P-Y) in males and 11.3 cases per 100,000 P-Y infemales.[2] Nevertheless, melanoma mortality rates are levelling off according to recent studies, and across certain regions and age groups they show a downward trend.[1,2,4]

When diagnosed at initial stages, more than 90 % 5-year survival is expected in patients with melanoma. Therefore, early diagnosis is essential to reduce morbidity and mortality associated with this malignancy.[1] Multiple primary and secondary prevention strategies have been promoted by public health systems in recent decades, and may be responsible for the slight mortality rate decrease in younger cohorts.[4,5]

Development of new ~~targeted~~ therapies against immune response checkpoints, known as immunotherapy, has led to a considerable survival increase in patients with locally advanced or metastatic melanoma. First studies using anti "cytotoxic T lymphocyte associated antigen" 4 (CTLA-4) drugs for the treatment of melanoma were published in 2007.[6] In 2011, Ipilimumab was approved for this indication in Spain, and from 2012 it is financed by the National Health System for widespread use.[7,8] Meanwhile, ~~targeted therapies~~ immune checkpoint inhibitors that block ~~against~~ the programmed deathreceptor 1 (PD-1) ~~for melanoma~~ were later authorized in Spain for melanoma: Nivolumab and Pembrolizumab (financed from 2016). Anti PD-1 drugs have shown better survival rates and lower toxicity compared to anti-CTLA-4 drugs,[9] and the first reports about their benefits in patients with melanoma appeared in 2013.[10] Apart from immunotherapy, ~~other~~ targeted therapies~~, directed~~ to specific proteins involved in cell proliferation signaling pathways, have been developed for the treatment of melanomas with mutations in these molecular pathways. These therapies include 2 different drugs: those that inhibit B-Raf (a serine/threonine kinase enzyme encoded by the human gene BRAF), such as Vemurafenib and Dabrafenib (available in Spain from 2013 and 2014 respectively) or Encorafenib (2019); and those that inhibit MEK (another kinase enzyme of the MAPK signaling pathway), among which are Trametinib and Cobimetinib, financed for use in Spain from 2016, and Binimetinib (2019).[8] Several combinations of anti-BRAF and anti-MEK drugs have been approved for advanced melanoma, showing better results than monotherapy (Vemurafenib-Cobimetinib in 2016, Dabrafenib-Trametinib and Encorafenib- Binimetinib in 2019). Finally, immune checkpoint inhibitor drugs have been added to BRAF and MEK inhibitors with promising results[8].

In Spain, recent studies have observed a decrease in melanoma age-standardized mortality rates in the 20-44 yo age group in both sexes since the mid-90s. Similar trends have been seen in 44-64 yo male group, while mortality rate in females in this age group has shown a levelling off. Despite these hopeful trends, a mortality rate increase in older groups (>65 yo) in both sexes, that remains until at least 2016, has been also reported.[4]

The objective of this study is to assess the evolution of malignant melanoma mortality in Spain in the period 1979-2018, focusing on possible trend changes related to the arrival of new treatment alternatives for this malignancy. To the best of our

knowledge, there are no reports about trends in melanoma mortality rates in Spain since 2016.

MATERIAL AND METHOD

Data on mid-year population and death certificates for the period 1979-2018 were obtained from the Spanish National Statistics Institute (http://www.ine.es), in accordance with the methodology set out in previous epidemiological studies on melanoma mortality such as those carried out by Cayuela et al.[11–13] and, more recently, by Gutiérrez-González et al.[4] Death certificates in developed countries provide a very reliable source of mortality information. All death records, obtained in microdata files, which included cutaneous malignant melanoma (International Classification of Diseases (ICD): ICD-8/9: 172; ICD-10: C-43) as the cause of the death were included in the study. Age-specific mortality rates by 5-year age groups were computed. Annual age-adjusted mortality rates were calculated using the direct method for the whole country and stratifying by sex and age groups (<35, 35-64 and > 64 yo). The new European standard population of 2013 was taken as reference.[14] These results were expressed as deaths per 100,000 P-Y, and Epidat3.1®, Microsoft® Excel and SPSS Statistics 25® softwares were employed to obtain them. Likewise, sex ratio was computed as the proportion of male mortality rate divided by female mortality rate for each year.

Points of significant trend changes in mortality rates by sex and age group were assessed using Jointpoint regression models. The Average Annual Percent Change (AAPC) was also computed by this method. For this purpose, the Joinpoint software developed by the Surveillance Research Program of the US National Cancer Institute was employed.[15] A maximum of 5 Joinpoints were allowed in the analysis. The minimum number of years until the extremes of the observation periods was established at 2 years for both the beginning and the end of the periods.

Independent effects of age, period and cohort factors (Age-Period-Cohort effects (APC)) on mortality rates were also computed using the penalty functions proposed by Decarli and La Vecchia.[16] In this proposal, based on the Osmond and Garnermodels,[17] APC models are estimated by the Poisson regression, and the authors provide some GLIM macros (APC package: Age-Period-Cohort Analysis version 1.3 for R®) to perform the calculation using the R® software. Data were divided into 5-year periods and age quinquenniums to carry out these estimates. The goodness-of-fit of possible APC models was also compared.

Finally, to quantify premature mortality due to melanoma in the population, Potential Years of Life Lost (PYLL) were computed. Crude and standardized by age and sex PYLL were obtained, using again the 2013 European standard population as reference.

RESULTS

Global melanoma age-standardized mortality rates in Spain for the first studied period (1979-83) were 0.78 cases per 100,000 P-Y (95% CI 0.70-0.87), and they reached the value of 2.13 cases per 100,000 P-Y (95% CI 2.05-2.21) in the last five years (2014-18). Male mortality rates rose from 0.87 to 2.75 cases per 100,000 P-Y in the quoted interval, while in females the rise was less pronounced, going from 0.70 to 1.65 cases per 100,000 P-Y (Table 1).

The studied period showed 3 trend changes for the entire population, giving rise to 4 stages (Figure 1a). First, a significant mortality increase from 1979 to 1984 (AAPC = 16.8) was observed. Although less sharply, this trend continued from 1984 to 1995 (AAPC = 5.2). From 1995 to 2015 a stabilization (AAPC = 0.5) in mortality rates was found. Finally, there was a marked drop in mortality rates from 2015 until the end of the study in 2018 (AAPC = -4.3). Stratifying by sex, 2 significant trend changes were observed in males. The first one in 1992 when mortality rate slowed down its ascent rate. The second appeared in 2014, when mortality rate began a dropping phase until the end of the period (Figure 1a). Otherwise, only one trend change in females was found. It was observed in 1994 when mortality rate levelled off to this day after an initial rise (Figure 1a).

Age group analysis showed that mortality rates in < 35 yo population rose until 1982 in males and 1993 in females, with a subsequent progressive fall up to 2018 (Figure 1b). In the 35-64 yo group there were no significant differences between sexes, with a mortality rates rise seen until the mid-90s, when a gradual decrease was observed until the end of the study (Figure 1c). At last, mortality rate in males over 64 yo increased until 2014, when they showed a marked drop. Female mortality rates, however, grew to peak in 1992, when a plateau phase began and remained to nowadays (Figure 1d).

Sex ratio tended to decrease in people under 35 yo in our study, underwent a progressive decrease in those over 64 yo in recent years and remained stable, with oscillations, in the middle age groups (Figure 2). Despite this, male mortality remained higher than female mortality for all age groups throughout the study period, with one punctual exception in the group of <35 yo in the mid-90s.

Concerning the effect of age, a progressive increase in mortality rates with age was observed. Secondly, regarding the effect of birth cohort, mortality rates rose in all birth cohorts in both sexes from the beginning of the study until those born in the 60s, when they tended to level off. Successive male cohorts showed a significant drop since the late 80s, while female cohorts experienced an increase (Figure 3a-b). For the period effect, in the overall population and stratifying by sex, there was a progressive growth in mortality rates until the beginning of 21st century, more marked in males. Thenceforth, mortality rate trend has reversed and a reduction is seen, maintained up to date (Figure

3abc). The degree of goodness for each possible regression model has been computed for the calculation of the APC effects. For the overall population and for each gender separately the 3 factors model adjusted better than those which included only two, since it had a lower AIC and narrower deviation (Table 2). Focusing on two-factor models, the age-cohort model in males and the age-period model in females were the best fitting ones.

A similar increase in both sexes until the beginning of 21st century was appreciated in PYLL (Figure 4). At this point, they levelled off and showed a progressive fall to 2018. A summary of total deaths, crude and age-standardized mortality rates and PYLL is available as supplementary material for each year of the study.

DISCUSSION

Age-adjusted melanoma mortality rates in Spain rose worryingly from 70s to 90s. At that point they tended to level off and started to decline especially in younger cohorts. Mortality rates in older age groups, however, continued rising until the end of 2016.[4,11–13,18] These trends displayed in previous studies would make us expect a decrease in mortality rates the following years.

Our study showed and overall and sex-stratified mortality slightly higher than previous similar posts, this may be explained by the reference population used to standardise, which was different between studies (world standard population, European population from 1976, and we used the European population from 2013).[4,11,14] The new European population was selected for this study to facilitate comparisons with recent and future research works in Europe. Nevertheless, trends followed similar patterns, already described above.

A very interesting finding from this research was the trend change observed in males >64 yo in 2014, when the mortality rates of this group started dropping until 2018. This fall secondarily affected the global mortality rates at the same point, which suffered a more slightly reduction (Figure 1). The aforementioned mortality decrease confirmed previous trends, that showed stable decline in mortality rates in young and middle age people and their respective cohorts. Throughout last years, European countries with population-based national registries have reported an incidence increase, particularly in elderly groups.[19] In Spain, 14 regional cancer registries are available, grouped into the Spanish Cancer Registry Network (REDECAN), which have also shown an increase in melanoma incidence in recent years.[20] Nonetheless, there has been also an improvement in melanoma survival rates in Europe.[21,22] On the one hand, this event could be explained, in part, by primary and secondary prevention campaigns, most of them started in 80s and the beginning of 21st century and had more impact in those generations. We can cite as example, the Euromelanoma plan.[23–27] On the other hand, new ~~targeted~~ therapies for the treatment of advanced melanoma may have contributed to this mortality decline in the oldest group of males. These treatments are generally well tolerated and have less adverse effects than classical chemotherapy. Hence, those groups of patients could benefit from them.[28,29] However, female >64 yo group showed a mortality rate plateau, with no downward curve in that period. Although some studies suggested that women could undergo more immumo-mediated adverse effects than men,[30] which could partially explain this finding, other research works reported similar response despite sex condition.[31] The trend change exposed wasn`t statistically significant, perhaps because mortality rates from the following years are needed to confirm this change. The study developed by Berk-Krauss et al on melanoma mortality in the white population of the United States (US) reported similar results to our research. A large increase in melanoma mortality was also found in the US from 1986 to 2013, when a pronounced mortality drop started and remained until 2016.[32] Given the association between new systemic therapies for melanoma and the decrease in mortality shown by ~~this~~ that study, the delay in the approval of this therapies in Spain compared to the US could explain the subsequent decrease in mortality in Spain compared to the US. The cited study did not analyse mortality by age groups.

Con formato: Color de fuente: Rojo, Tachado

Con formato: Color de fuente: Rojo

Although they don't offer mortality data by age group either, there are recent reports analysing melanoma mortality trends in many countries. According to Yang et al publication assessing mortality trends in 31 countries,[33] all the countries analysed but the Czech Republic showed an increase in age-standardized death rates in males over 1985-2015. Besides, most countries exhibited a decline or stabilization in melanoma mortality rates in females. The arrival of new treatments may modify these trends in the next years.

Concerning sex ratio, the most striking finding was the decline observed in >64 yo group, consistent with the reduction of male mortality rate in this age group. As known, despite higher melanoma incidence in women, higher mortality rates were found in men.[11] Ignoring biological differences, this has been attributed to early diagnosis in women due to tumour location and higher skin cancer awareness.[34,35] However, the sex ratio gap is disappearing in younger population (Figure 2). Similar sensitivity to skin cancer prevention campaigns between men and women in younger age groups, as well as a greater awareness of preventive measures in young men may explain these trends.

It is well known the North / South melanoma mortality rate gap in Europe. North countries have higher incidence rates and, contrary to what might be expected, they also have a higher incidence/mortality ratio probably due to surveillance campaigns and subsequent early diagnosis. [36,37] Recent reports suggest that mortality rates are levelling off in most South-Eastern countries, decreasing the gap.[38] Spain has one of the lowest mortality rate in Europe,[18] which could be explained by skin phototype or continuous sun exposure as protective factors. In addition, other factors such as the greater Spanish global life expectancy or the wide public health coverage may explain these findings. This study proves that Spain remains as an exception in South Europe.

Older population showed higher mortality rates than younger people. In addition to well-known factors such as higher incidence, delay in diagnosis or comorbidities,[26,35] for this age-effect may contribute cumulative DNA damage from sun exposure and oxidative stress and decreasing immune surveillance mechanisms (immunosenescence). We refer to a cohort effect, when one or many factors mark a generation over time, establishing changes of different magnitude in the following age groups. In this study we identified a cohort effect. Mortality rate rises until 60s born cohort and from this point it tends to level off. Male cohorts born from 80s had decreasing mortality rates, while female cohorts experienced a slight rise if compared with previous decades. It would be necessary to find out the reasons of this event. Unlike a cohort effect, a period effect refersto factors that take place in a specific moment and induce changes in rates for all age groups at the same time. All age groups mortality rates rose until the beginning of 21st century, when they started to decline until 2018. We hypothesized that the introduction of new treatment options with higher survival rates, combined with the widespread useof dermoscopy, that allows the diagnosis of thinner melanomas, were two determining factors to explain this period effect. In fact, recent studies have shown an increase of "in situ" and thin (Breslow < 1mm) melanomas in our country over the total number of melanomas diagnosed.[39,40]

The decline in mortality rates in all age groups, but especially in younger people, have consolidated lower premature mortality, reflected in PYLL data.

Main limitations of this study were collected data, which are subject to possible omissions at the time of completing death certificates. Besides, another limitation was the intrinsic problem of APC analysis models, which can overrate cohort or period effect depending on the model.

CONCLUSIONS

Melanoma mortality rates in the overall population and, for the first time, in older age groups, decreased from 2015 to date. This fact supports previous descending trends observed in younger cohorts. Improvement in diagnosis and development of new therapies for advance melanoma may have a leading role in this event. Maintaining primary prevention strategies becomes a crucial challenge for next years.

As a consequence of the higher drop seen in male mortality relative to females, mortality gap between sexes was reduced in the studied period. PYLL downward curve illustrates from another perspective how efforts in prevention, diagnosis and treatment of melanoma reverberate in the population life. Future study of quality-adjusted life years lost by this disease could add valuable information.

Although the exposed results anticipate a continued downward trend, close monitoring of melanoma mortality rates is necessary to confirm these findings. The creation of a national cancer registry would help for this purpose.

REFERENCES

1 Cancer.org [Internet]. Atlanta GACS c2020 [cited 2020 A 23]. A from: https://www. cancer. org/es/cancer/cancer-de-piel-tipo-melanoma/acerca/estadisticas-clave. html.

2 Global Cancer Observatory [Internet]. Lyon FIA for R on CWHO c2018-20 [cited 2020 A 23]. A from: 2. http://gco. iarc. fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=900.

3 Ferlay J, Colombet M, Soerjomataram I, *et al.* Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018; **103**:356–87.

4 Gutiérrez-González E, López-Abente G, Aragonés N, *et al.* Trends in mortality from cutaneous malignant melanoma in Spain (1982–2016): sex-specific age-cohort-period effects. *J Eur Acad Dermatology Venereol* 2019; **33**:1522–8.

5 Erdmann F, Lortet-Tieulent J, Schüz J, *et al.* International trends in the incidence of malignant melanoma 1953-2008-are recent generations at higher or lower risk? *Int J Cancer* 2013; **132**:385–400.

6 O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4). *Cancer* 2007; **110**:2614–27.

7 Agencia Española de Medicamentos y Productos Sanitarios [Internet]. Madrid S c2017 [cited 2020/08/08]. A from: https://cima. aemps. es/cima/publico/home. htm.

8 BIFIMED: Buscador de la Información sobre la situación de financiación de los medicamentos. Ministerio de Sanidad, Consumo y Bienestar Social [Internet]. [cited 2020/08/08]. A from: https://www.mscbs.gob.es/profesionales/medicamentos.do?

9 Robert C, Schachter J, Long G V., *et al.* Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; **372**:2521–32.

10 Robert C, Soria J-C, Eggermont AMM. Drug of the year: Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies. *Eur J Cancer* 2013; **49**:2968–71.

11 Cayuela A, Rodriguez-Dominguez S, Lapetra-Peralta J, Conejo-Mir JS. Has mortality from malignant melanoma stopped rising in Spain? Analysis of trends between 1975 and 2001. *Br J Dermatol* 2005; **152**:997–1000.

12 Cayuela A, Rodríguez-Domínguez S, Vigil E, Conejo-Mir JS. Effect of age, birth cohort and period of death on skin melanoma mortality in Spain, 1975 through 2004. *Int J Cancer* 2008; **122**:905–8.

13 Cayuela A, Cayuela L, Rodríguez-Domínguez S, *et al.* Is melanoma mortality declining in Spain? Analysis of trends from 1975 to 2016. *Br J Dermatol* 2018; **179**:991–2.

14 Pace M, Cayotte E AL et al. Revision of the European Standard Population: report of Eurostat's task force : 2013 edition. [Internet]. Publications Office,

Luxembourg, 2013. [cited 2018 May 7]. URL http://dx.publications.europa.eu/10.2785/11470. doi:10.2785/11470.

15 National Cancer Institute. Joinpoint Regression Program, Version 4.2.0.2, Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute 2015. No Title. .

16 Decarli A, Vecchia C La, Malvezzi M, Micciolo R. An R package for fitting age, period and cohort models. *Epidemiol Biostat Public Heal* 2014; **11**:e 9 9 7 7-1-12.

17 Osmond C, Gardner MJ. Age, period and cohort models applied to cancer mortality rates. *Stat Med* 1982; **1**:245–59.

18 Sáenz S, Conejo-Mir J, Cayuela A. Epidemiología del melanoma en España. *Actas Dermosifiliogr* 2005; **96**:411–8.

19 Arnold M, Holterhues C, Hollestein LM, *et al.* Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *J Eur Acad Dermatology Venereol* 2014; **28**:1170–8.

20 Tejera-Vaquerizo A, Descalzo-Gallego MA, Otero-Rivas MM, *et al.* Cancer Incidence and Mortality in Spain: A Systematic Review and Meta-Analysis. *Actas Dermosifiliogr* 2016; **107**:318–28.

21 Crocetti E, Mallone S, Robsahm TE, *et al.* Survival of patients with skin melanoma in Europe increases further: Results of the EUROCARE-5 study. *Eur J Cancer* 2015; **51**:2179–90.

22 Galceran J, Uhry Z, Marcos-Gragera R, Borràs J. Trends in net survival from skin malignant melanoma in six European Latin countries. *Eur J Cancer Prev* 2017; **26**:S77–84.

23 Sánchez Conejo-Mir J. Campañas de prevención del melanoma. *Piel* 2002; **17**:457–65.

24 Conejo-Mir J, Bravo J, Díaz-Pérez JL, *et al.* Euromelanoma day. Results of the 2000, 2001 and 2002 campaigns in Spain. *Actas Dermosifiliogr* 2005. doi:10.1016/S0001-7310(05)73073-8.

25 MacKie RM, Bray CA, Hole DJ, *et al.* Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. *Lancet* 2002; **360**:587–91.

26 Giblin A-V, Thomas JM. Incidence, mortality and survival in cutaneous melanoma. *J Plast Reconstr Aesthetic Surg* 2007; **60**:32–40.

27 Aceituno-Madera P, Buendía-Eisman A, Arias-Santiago S, Serrano-Ortega S. Changes in the Incidence of Skin Cancer Between 1978 and 2002. *Actas Dermo-Sifiliográficas (English Ed* 2010; **101**:39–46.

28 Sattar J, Kartolo A, Hopman WM, *et al.* The efficacy and toxicity of immune checkpoint inhibitors in a real-world older patient population. *J Geriatr Oncol* 2019; **10**:411–4.

29 Joshi K, Atwal D, Ravilla R, *et al.* Immunotherapy Outcomes in Advanced Melanoma in Relation to Age. *Perm J* 2020; **24**. doi:10.7812/tpp/19.093.

30 Duma N, Abdel-Ghani A, Yadav S, *et al.* Sex Differences in Tolerability to Anti-Programmed Cell Death Protein 1 Therapy in Patients with Metastatic Melanoma and Non-Small Cell Lung Cancer: Are We All Equal? *Oncologist* 2019; **24**. doi:10.1634/theoncologist.2019-0094.

31 Wallis CJD, Butaney M, Satkunasivam R, *et al.* Association of Patient Sex With Efficacy of Immune Checkpoint Inhibitors and Overall Survival in Advanced Cancers. *JAMA Oncol* 2019; **5**:529.

32 Berk-Krauss J, Stein JA, Weber J, *et al.* New Systematic Therapies and Trends in Cutaneous Melanoma Deaths Among US Whites, 1986–2016. *Am J Public Health* 2020; **110**:731–3.

33 Yang DD, Salciccioli JD, Marshall DC, *et al.* Trends in malignant melanoma mortality in 31 countries from 1985 to 2015. *Br J Dermatol* 2020; :bjd.19010.

34 Ríos L, Nagore E, López JL, *et al.* Melanoma Characteristics at Diagnosis From The Spanish National Cutaneous Melanoma Registry: 15 Years of Experience. *Actas Dermo-Sifiliográficas (English Ed* 2013; **104**:789–99.

35 Marcoval J, Moreno A, Torras A, *et al.* Changes in Incidence of Malignant Melanoma in the Last 19 Years in a Tertiary Hospital on the Mediterranean Coast. *Actas Dermo-Sifiliográficas (English Ed* 2008; **99**:464–8.

36 de Vries E, Willem Coebergh J. Cutaneous malignant melanoma in Europe. *Eur J Cancer* 2004; **40**:2355–66.

37 Simon AE, Forbes LJL, Boniface D, *et al.* An international measure of awareness and beliefs about cancer: development and testing of the ABC. *BMJ Open* 2012; **2**:e001758.

38 Barbaric J, Sekerija M, Agius D, *et al.* Disparities in melanoma incidence and mortality in South-Eastern Europe: Increasing incidence and divergent mortality patterns. Is progress around the corner? *Eur J Cancer* 2016; **55**:47–55.

39 Tejera-vaquerizo A, Mendiola-fernández M, Fernández-orland A, Herrera-ceballos E. Thick melanoma: The problem continues. *J Eur Acad Dermatology Venereol* 2008; **22**:575–9.

40 Sacchetto L, Zanetti R, Comber H, *et al.* Trends in incidence of thick, thin and in situ melanoma in Europe. *Eur J Cancer* 2018; **92**:108–18.

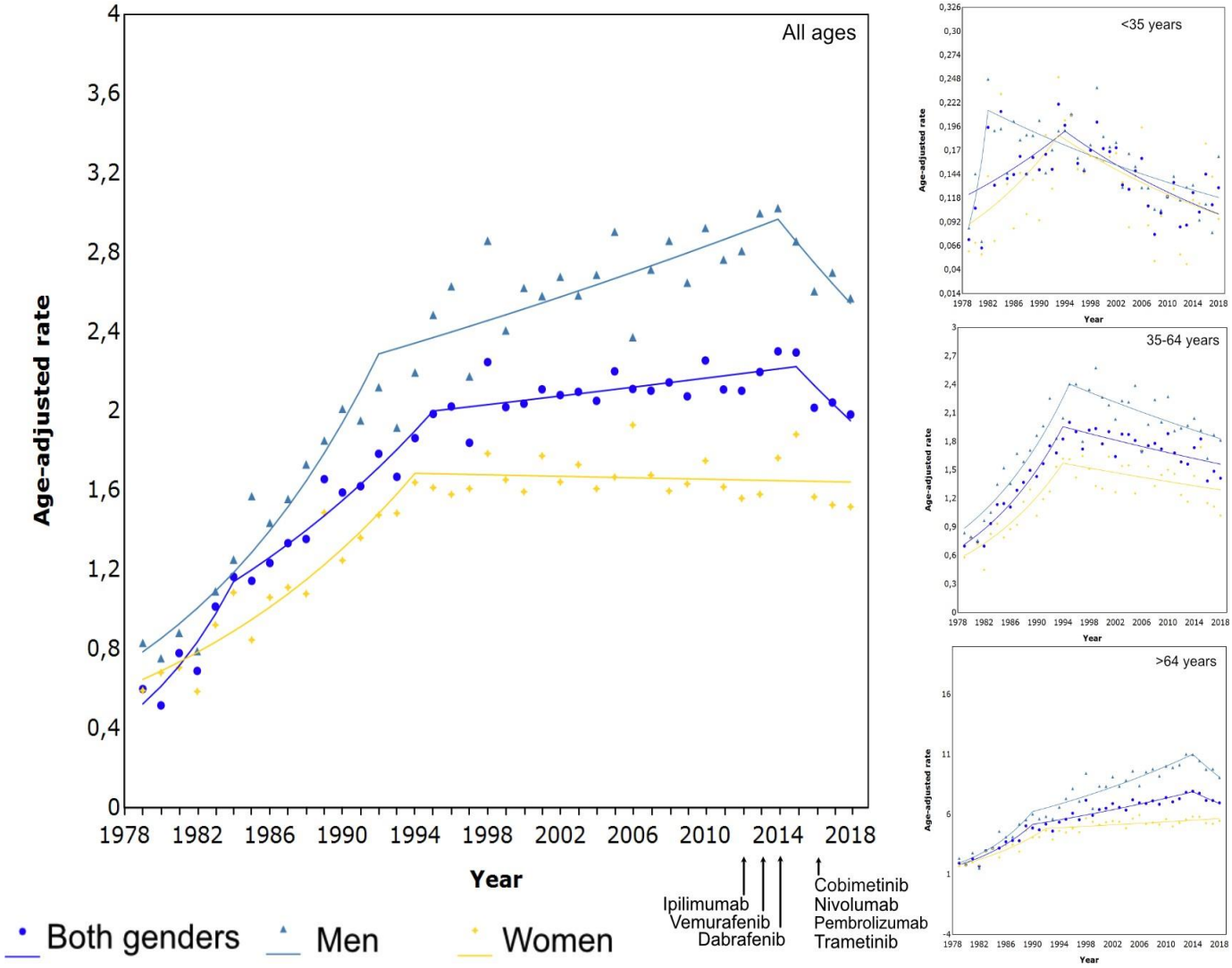
LEGENDS

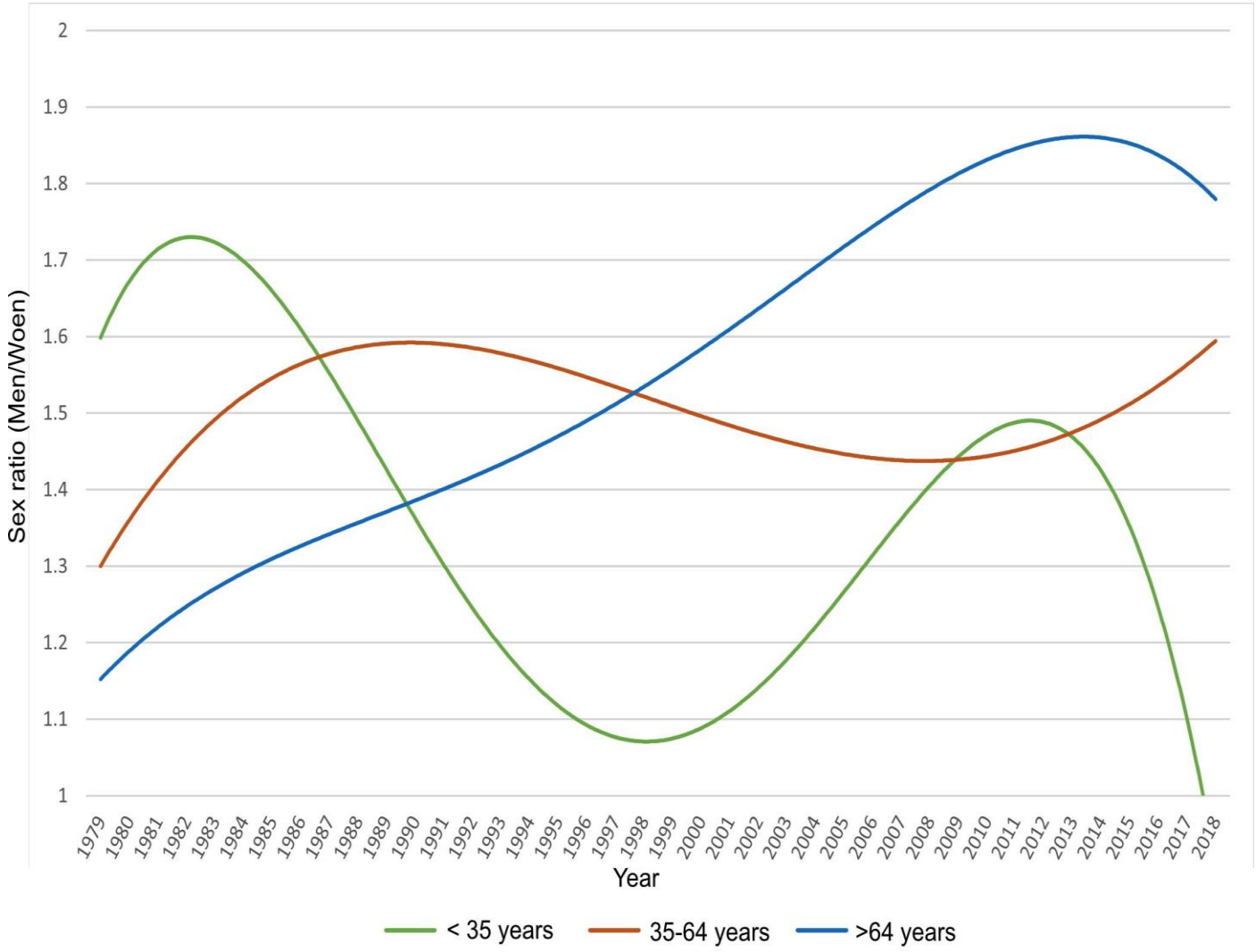
Fig 1. Joint point regression analysis (years 1979-2018) of the entire population (a), under 35 years (b), between 35 and 64 years (c) and over 65 years (d).

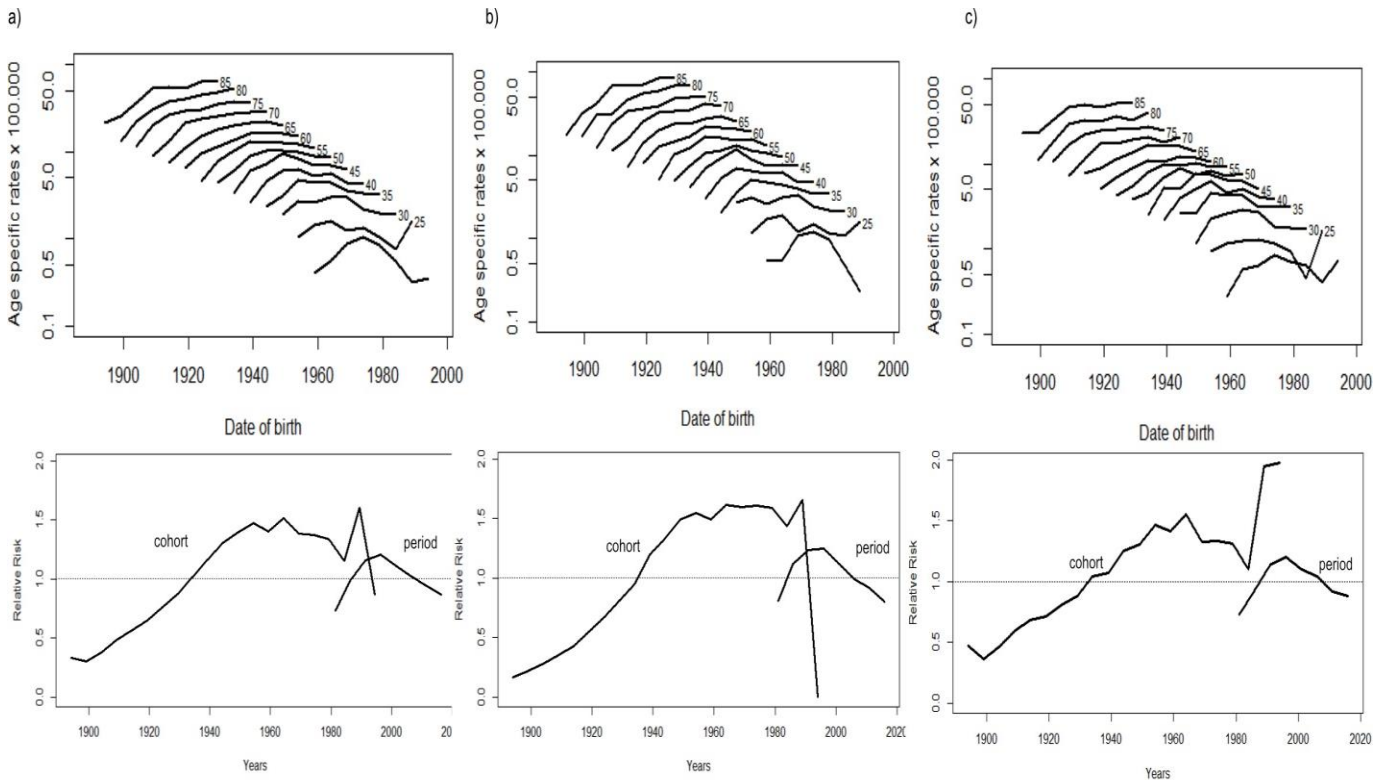
Fig 2. Trend in the sex ratio (men / women) over the years 1979-2018 by age group

Fig 3. Analysis of the age-cohort period effect for both sexes (a), men (b) and women (c). The upper graph shows the mortality rates for each five-year age; the lower graph shows the variation of the relative risk for the different cohorts and period

Fig 4. Rates of potential years lost per 100,000 persons-year


All ages
Age-adjusted rate
Year
Both genders
Men
Women
Ipilimumab
Vemurafenib
Dabrafenib
Cobimetinib
Nivolumab
Pembrolizumab
Trametinib
<35 years
35-64 years
>64 years


Sex ratio (Men/Woen)
2
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018
Year
< 35 years
35-64 years
>64 years


a)
b)
c)
Age specific rates x 100.000
Date of birth
Relative Risk
cohort
period
Years

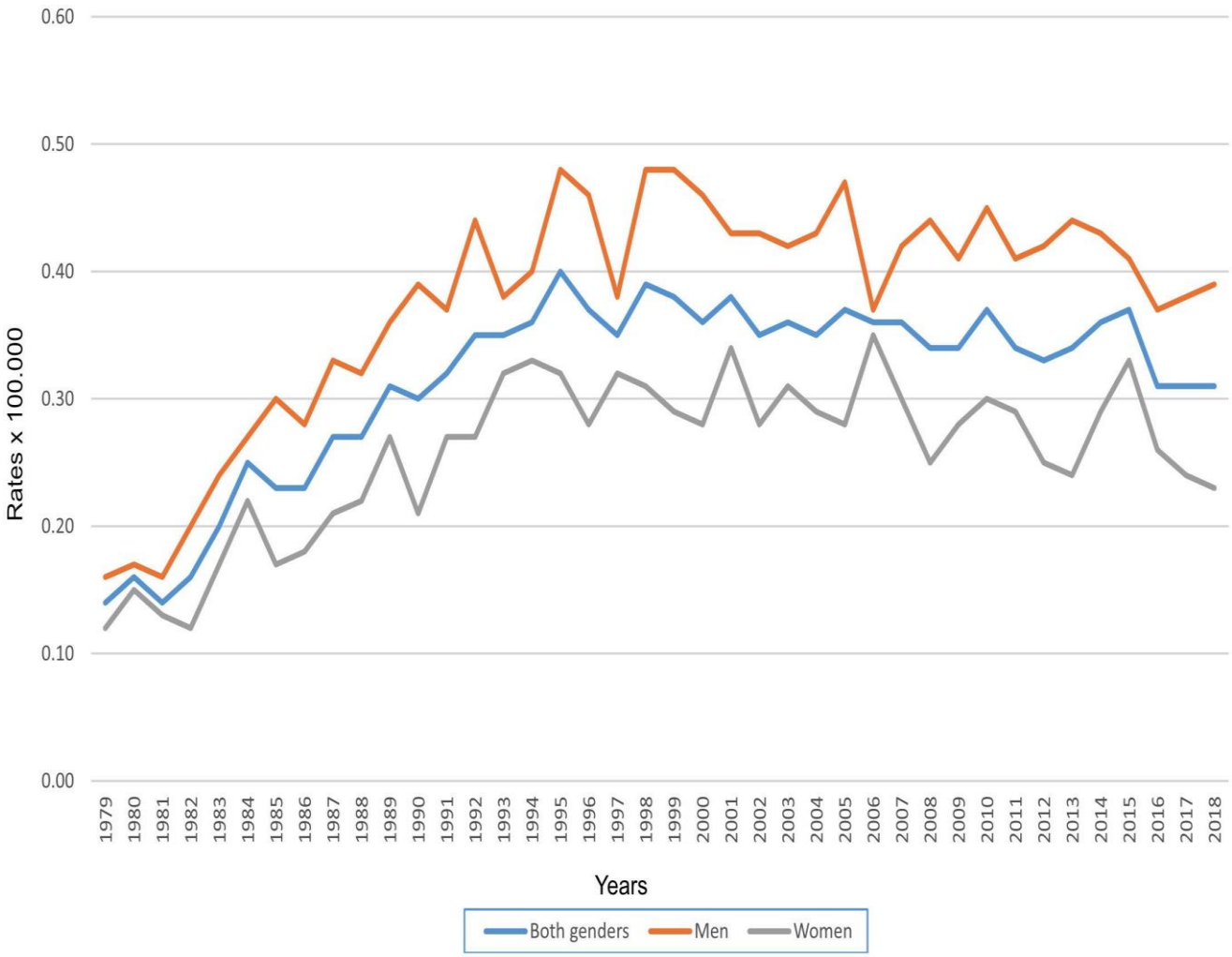

0.60
0.50
0.40
0.30
0.20
0.10
0.00
Rates x 100.000
1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018
Years
Both genders
Men
Women

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

All ages	JP	1979-1983 ASMR (95% CI)	Period 1		Period 2		Period 3		Period 4		2014-2018 ASMR (95% CI)
			years	AAPC (95% CI)	years	AAPC (95% CI)	years	AAPC (95% CI)	years	AAPC (95% CI)	
All	3	**0.78 (0.70;0.87)**	1979-1984	16.82* (9,45;24,68)	1984-1995	5.24* (3.74;6.76)	1995-2015	0.53* (0.15;0.92)	2015-2018	-4.26 (-9.71;1.5)	**2.13 (2.05;2.21)**
Men	2	**0.87** (**0.77**;**0.99**)	1979-1992	8.6* (6.6;10.5)	1992-2014	1.2* (0.7;1.7)	2014-2018	-3.8 (-8.5;1.2)	-	-	**2.75** (**2.63**;**2.88**)
Women	1	**0.70 (0.64;0.84)**	1979-1994	6.6* (5.1;8.1)	1994-2018	-0.1 (-0.5; 0.3)	-	-	-	-	**1.65 (1.55;1.75)**

<35 yo	JP	1979-1983 ASMR (95% CI)	Period 1		Period 2		2014-2018 ASMR (95% CI)
			years	AAPC (95% CI)	years	AAPC (95% CI)	
All	1	0.11 (0.05;0.19)	1979-1994	3* (0.2;5.9)	1994-2018	-2.6* (-3.9;-1.4)	0.12 (0.05;0.19)
Men	1	0.15 (0.05;0.19)	1979-1982	35.1 (-10.2;103.4)	1982-2018	-1.6* (-2.2;-1.0)	0.12 (0.05;0.19)
Women	1	0.08 (0.00;0.14)	1979-1993	5.4* (0.1;10.9)	1993-2018	-2.5* (-4.2; -0.7)	0.13 (0.05;0.19)

35 – 64 yo	JP	1979-1983 ASMR (95% CI)	Period 1		Period 2		2014-2018 ASMR (95% CI)
			years	AAPC (95% CI)	years	AAPC (95% CI)	
All	1	0.77 (0.69;0.87)	1979-1994	6.9* (5.7;8.1)	1994-2018	-0.9* (-1.3;-0.5)	1.57 (1.48;1.67)
Men	1	0.88 (0.78;0.99)	1979-1995	6.4* (4.9;8)	1995-2018	-1.2* (-1.8;-0.6)	1.85 (1.74;2.00)
Women	1	0.67 (0.57;0.81)	1979-1994	6.6* (4.5;8.9)	1994-2018	-0.8* (-1.6; -0.1)	1.29 (1.18;1.39)

>64 yo	JP	1979-1983 ASMR (95% CI)	Period 1		Period 2		Period 3		2014-2018 ASMR (95% CI)
			years	AAPC (95% CI)	years	AAPC (95% CI)	years	AAPC (95% CI)	
All	2	2.17 (1.97;2.42)	1979-1990	10.1* (7.4;12.8)	1990-2014	1.8* (1.3;2.2)	2014-2018	-3.3 (-7.6;1.3)	7.41 (7.14;7.65)
Men	2	2.34 (1.99;2.78)	1979-1990	11.1* (7.4;15)	1990-2014	2.4* (1.8;3)	2014-2018	-4.6 (-9.9;1)	10.01 (9.54;10.52)
Women	1	2.05 (1.81;2.36)	1979-1992	7.9* (5.7;10.2)	1992-2018	0.6* (0.2;1)	-	-	5.53 (5.25;5.80)

ASMR: Age standardized mortality rate; AAPC (95% CI): Anual Average percentage change and 95% confidence interval. * = $p<0.05$

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

Model	df	Deviance	p	AIC
Both genders				
Age-Model	98	1746.5620	**<0.001**	2541.251
Age-Drift Model	97	888.2833	**<0.001**	1684.972
Age-Period Model	91	410.5998	**<0.001**	1219.288
Age-Period-Cohort Model	72	65.1944	0.7019	911.883
Age-Cohort Model	78	407.2959	**<0.001**	1241.984
Men				
Age-Model	98	1162.56349	**<0.001**	1886.0677
Age-Drift Model	97	631.51762	**<0.001**	1357.0219
Age-Period Model	91	357.89507	**<0.001**	1095.3993
Age-Period-Cohort Model	72	64.21765	**0.7315**	839.7219
Age-Cohort Model	78	250.87459	**<0.001**	1014.3788
Women				
Age-Model	98	653.14882	**<0.001**	1357.8926
Age-Drift Model	97	367.19955	**<0.001**	1073.9434
Age-Period Model	91	149.23259	**<0.001**	867.9764
Age-Period-Cohort Model	72	51.21566	**0.9697**	807.9595
Age-Cohort Model	78	210.12922	**<0.001**	954.8730

Df: degrees of freedom; AIC: Akaike information criteria