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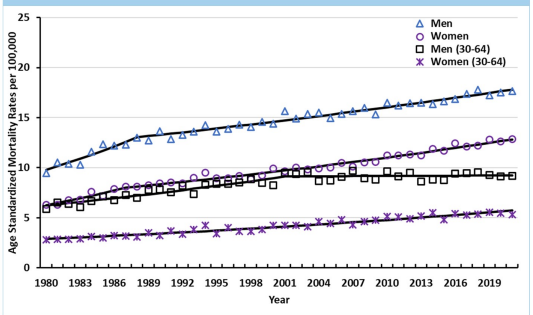
Conclusions: The upward trend in pancreatic cancer mortality in some ACs seems to have slowed (in both sexes in Madrid), stabilized (in men in Galicia and Navarre) or turned around (in men aged 30-64 in Navarre).



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Has the trend in pancreatic cancer mortality in Spain started to slow down?

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Authors Contributions: All authors contributed to the conception and design of the work; the acquisition, analysis, and interpretation of data; drafting the work and revising it critically for important intellectual content; approved the version to be published; and are responsible for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are properly investigated and resolved.

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Ethics Statement: As the data extracted from the National Institute of Statistics were anonymous, following the principles of good clinical practice and the Declaration of Helsinki, no participants were identified and no personal information was accessed, this study did not require patient consent or ethics committee approval.

Abstract

Introduction: the aim of this study was to describe the trends of pancreatic cancer mortality by autonomous communities (ACs) and gender in Spain (1980-2021).

Methods: We conducted an ecological trend study (with aggregated data obtained from the National Institute of Statistics). Age-standardized mortality rates (ASMRs) for pancreatic cancer (per 100,000) were estimated by direct standardization, using the European standard population. Trends in ASMR (all ages and truncated 35-64 years) were analysed by sex in each AC using a joinpoint regression model. The annual percent changes (APC) and average annual percentage of change (AAPC) were computed for trends using the joinpoint regression analysis.

Results: In both sexes ASMRs (all ages) increase significantly ($p<0.05$) during the study period (AAPC: 1.5% in men and 1.8% in women). The joinpoint analysis identifies a turning point in the trends in the late 1980s which delineates two periods: an initial period of significant increase followed by a period of slowing of the increase (APC: 0.9% and 1.4% in males and females respectively; $p<0.05$). In both sexes, a significant increase in ASMR (all ages) is observed in all ACs, except in Navarre where the rates remain stable in men. In men, three ACs (Galicia, Madrid and Navarre) show a point of inflexion in the time trend around the year 2000 (1999, 2000 and 2001 respectively) when rates, after a period of significant increase (ACs: 2.6%, 2.4%, and 2.4% respectively, $p<0.05$), stabilise (Galicia and Navarre) or slow down their increase (Madrid). In women, only Madrid shows a point of inflection in

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1992 when, after a significant increase, rates slow down (1992-2021; APC:1.5%, p<0.05).

Conclusions: The upward trend in pancreatic cancer mortality in some ACs seems to have slowed (in both sexes in Madrid), stabilised (in men in Galicia and Navarre) or turned around (in men aged 30-64 in Navarre).

Keywords: Pancreatic cancer. Trends. Incidence. Mortality. Spain. Risk factors

INTRODUCTION

According to the latest data available, pancreatic cancer (PC) is recognized as the twelfth most frequently diagnosed cancer (2.6%) and ranks as the seventh highest contributor to cancer-related deaths (4.7%) on a global scale in 2020[1].

Recently, many countries have experienced a sharp increase in PC incidence and mortality rates[2,3], especially women and the over 50s[4,5]. However, PC mortality rates in Canada and Mexico have continued to decline in both sexes[6]. In the European Union, age-standardised rates are expected to remain stable (incidence) or increase slightly (mortality)[3]. By 2025, it is projected to be the third leading cause of cancer-related deaths in Europe[7].

In Spain, time trends in PC mortality and/or its geographical distribution have long been analysed[8–11]. Time trend studies have shown that PC mortality rates have steadily increased since the 1950s. However, since the late 1980s, there has been a deceleration of the upward trend in both sexes. In addition, downward trends have been observed in men aged 35-44 years since the 1990s. These trends were attributed to the decline in smoking prevalence in both sexes[10,12]. Despite this, studies on the evolution of PC mortality at a regional level are scarce[9,10] and there is a lack of information beyond 2013.

Surveillance of PC mortality trends by the autonomous community (AC) can be a useful tool, both from an epidemiological and public health point of view. It could help in the design and

evaluation of public health interventions on potentially modifiable risk factors for PC (eg, it should help us to evaluate the effectiveness of programmes to control smoking, obesity, etc.), as well as to assess the effectiveness of treatments. Therefore, our proposal aims to analyse and depict the trends in PC mortality spanning the years 1980 to 2021. Additionally, we seek to provide updated mortality rates for PC in Spain during the aforementioned time frame, broken down by sex and AC.

Material and Methods

We performed an ecological trend study of PC mortality in Spain during the period 1980-2021.

Data source:

The data on the population on 1 July and on the mortality of the PC come from the National Institute of Statistics[13]. The code used for the period 1980-1998 was 157 (9th Revision of the International Classification of Diseases [ICD9]) and the code for the period 1999-2021 was C25 [ICD10]).

Statistical analysis:

Age-standardized mortality rates (ASMRs), overall and truncated 30-64 years, were reported as rates per 100,000 persons. They were calculated using the direct method (European standard population) [14].

For calculating rates and conducting trend analysis, we employed Joinpoint regression software, specifically version 4.9.1.0, utilizing its default values[15]. The annual percentage change (APC) for each segment was estimated by fitting a regression line to the natural logarithm of the rate, using the calendar year as an independent variable. To quantify the trend over the entire period, we computed the average annual per cent change (AAPC) as a geometrically weighted average of the various APCs from the joinpoint regression analysis, with weights equivalent to the length of each segment during the specified time interval.

If there were no observed deaths in certain years, it would not be possible to perform joint-point regression analysis.

Results

Figure 1 shows the ASMR for all ages and truncated rates (30-64 years) and trends estimated by joinpoint analysis for PC in Spain over the period 1980-2021. In both sexes, ASMRs (all ages) increase significantly during the study period (AAPC: 1.5% in men and 1.8% in women). The joinpoint analysis identifies a turning point in the trends in the late 1980s (1988 in males and 1987 in females) which delineates two periods: an initial period of significant increase (APC: 3.6%; $p<0.05$ in both sexes) followed by a period of slowing of the increase (APC: 0.9% and 1.4% in males and females respectively; $p<0.05$).

Truncated ASMRs increased significantly during the study period in both sexes (AAPC: 1% in men and 1.7% in women, $p<0.05$). The joinpoint analysis detects a trend inflexion point in men in 2001 with a first period of significant increase (1980-2001; AAPC: 1.8, $p<0.05$) followed by a period of stabilisation of rates (2001-2021; 0.1%, not significant). In women, no inflexion point in the trend can be detected.

In both sexes (table 1-2), a significant increase in ASMR (all ages) is observed in all ACs, except in men in Navarre where the rates remain stable. In men, three ACs (Galicia, Madrid and Navarre) show a point of inflexion in the time trend (1999, 2000 and 2001 respectively) when rates, after a period of significant increase (ACs: 2.6%, 2.4%, and 2.4% respectively), stabilise (Galicia and Navarre) or slow down their increase (Madrid). In women, only Madrid shows a point of inflexion in 1992 when, after a significant increase, rates slow down (1992-2021; APC:1.5%, $p<0.05$).

In men (table 3), 11 ACs show a significant increase in ASMR (30-64 years) during the study period. Asturias, Balearic Islands, Canary Islands, Cantabria, Navarre and La Rioja maintain a stable trend. The joinpoint analysis detected 3 ACs (Galicia, Madrid and Navarre) where there was a change in trend (the years 1999, 2000 and 2006 respectively) in which after a period of significant increase the rates stabilised (Galicia and Madrid) or decreased significantly (Navarre).

In women (table 4), truncated ASMRs increased during the study period in all AC except in Asturias, where the rates remained stable. The joinpoint analysis did not detect any change in trend in any of the ACs. In Navarre and La Rioja, as no deaths were observed in some years, no joinpoint analysis was available.

Discussion

This study represents a complete and updated analysis of the time trends in PC mortality in Spain, considering the main differences by sex, age and AC of residence.

Regional sex and age differences in PC mortality rates and time trends may reflect factors related to the incidence and/or survival of PC in the population and possibly other unknown factors[16,17]. Modifiable risk factors that can increase the incidence of PC include smoking[18],

overweight[19], alcohol consumption[20], type 2 diabetes[21] and metabolic syndrome[22]. Despite this, there is evidence that greater adherence to the Mediterranean Diet[23,24] and dietary fibre intake[25] are associated with a lower risk of PC. Similarly, the risk of PC decreases rapidly in a few years after quitting smoking, but it takes about 20 years to reach the risk of never smokers[26].

In Spain, although more men smoke than women (figure 2), the gap has narrowed: in 1987, the prevalence of male smokers was 2.4 times higher than that of female smokers (54.7% vs 22.9%), but the latest National Health Survey in 2020 showed smaller differences in prevalence between the sexes (23.3% in men and 16.4% in women)[27]. Among men, smoking prevalence in Spain decreased by -57.4% in the period 1987-2020 (ranging from -43% in Extremadura to -63.1% in Cantabria). In women, although it also decreased, it did so to a lesser extent (-28.2%) and the decrease ranged from -3.5% in Castile-La Mancha to -56.0% in the Basque Country).

The slowdown in the rate of decline in both sexes in ASMR (all ages) at the national level (consistent with a recent study)[28], and Madrid, together with the stagnation in men in Galicia and Navarre, may reflect the role of decreasing smoking prevalence.

In the period 1987-2020, smoking prevalence in men decreased by -61.9%, -60.1%, and -61.4% in Galicia, Madrid, and Navarre ranking among the five communities with the largest decreases observed in men. The sharp decline in truncated ASMRs observed in men in Navarra or their stabilisation in Galicia and Madrid would reflect the decline in smoking prevalence decades earlier than that observed in women. Therefore, a continued decline in smoking prevalence among women may be plausible for reversing the unfavourable trend observed in PC ASMRs among women, as seems to be occurring in men. The slowdown in

ASMR (all ages) observed in women in Madrid may reflect the fact that the prevalence of smoking has declined markedly in women (-49% during the period 1987-2020, making it the third community with the largest decline in prevalence after the Basque Country, -56% and Aragon, -55.2%). Despite the positive effect of this decrease, it is not enough to reverse the trend of PC mortality, as other risk factors are increasing at the same time[29]. Thus, the reported prevalence of diabetes in the adult population increased from 4.1% in 1993 to 7.5% in 2020. All ACs show an increase in the prevalence of diabetes in both men and women, although in women Asturias, Baleares and Cantabria showed a slight decrease. A similar pattern is also observed for the prevalence of obesity. In the period 1993-2020, an increase in the prevalence of obesity in Spain is observed (81% in men and 67% in women). In men, all ACs show an increase in the prevalence of obesity. In women, all ACs show an increase in the prevalence of obesity (except Castilla-La Mancha and Extremadura, which show a slight decrease of -15% and -13%, respectively).

Our study has some strengths and some limitations. Due to the lack of incidence data, we have used mortality data, the only data source that meets the requirements of continuity and completeness[30]. Moreover, despite the limitations of epidemiological mortality studies, it remains a fundamental approach to understanding the burden of disease and its determinants. Mortality data can be considered a reliable indicator of the incidence of PC given its low survival (despite diagnostic and therapeutic advances, PC remains highly lethal and less than 5% of patients survive more than five years after diagnosis)[31] and the reliability of death certificates in our country[32].

Although two different classification systems, ICD-9 and ICD-10, were used during the study period, the trend in the leading causes of mortality was not affected by this change[33].

Given the descriptive nature of mortality trend analyses, we can only suggest possible aetiologies; otherwise, we could fall into the so-called ecological fallacy[34].

In women aged 30-64 years in Navarra and La Rioja, joinpoint analysis could not be performed because in some years there were no deaths from PC.

Our results are strengthened by the use of the latest available mortality data and using appropriate statistical methods for detecting changes in mortality trends over a long period (42 years). This analysis made it possible to identify the points in time at which trends changed in the different ACs, allowing hypotheses to be generated as to why changes occurred at that particular point in time and helping policymakers to identify and act on the factors that contributed to these trends.

Conclusions: The upward trend in PC mortality in some ACs seems to have slowed (in both sexes in Madrid), stabilised (in men in Galicia and Navarre) or turned around (in men aged 30-64 in Navarre).

Healthcare professionals and policymakers need to promote public awareness measures on tobacco use both in practice and in public health policy.

References

1. Cancer Today. Accessed March 1, 2023. https://gco.iarc.fr/today/fact-sheets-populations
2. Abboud Y, Samaan JS, Oh J, et al. Increasing Pancreatic Cancer Incidence in Young Women in the US: A Population-Based Time-Trend Analysis, 2001-2018. *Gastroenterology*. Published online February 2023. doi:10.1053/J.GASTRO.2023.01.022
3. Yu J, Yang X, He W, Ye W. Burden of pancreatic cancer along with attributable risk factors in Europe between 1990 and 2019, and projections until 2039. *Int J Cancer*. 2021;149(5):993-1001. doi:10.1002/IJC.33617
4. Ilic I, Ilic M. International patterns in incidence and mortality trends of pancreatic cancer in the last three decades: A joinpoint regression analysis. *World J Gastroenterol*. 2022;28(32):4698-4715. doi:10.3748/WJG.V28.I32.4698
5. Huang J, Lok V, Ngai CH, et al. Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer. *Gastroenterology*. 2021;160(3):744-754. doi:10.1053/J.GASTRO.2020.10.007
6. Lucas AL, Malvezzi M, Carioli G, et al. Global Trends in Pancreatic Cancer Mortality From 1980 Through 2013 and Predictions for 2017. *Clin Gastroenterol Hepatol*. 2016;14(10):1452-1462.e4. doi:10.1016/J.CGH.2016.05.034
7. Hu JX, Lin YY, Zhao CF, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. *World J Gastroenterol*. 2021;27(27):4298. doi:10.3748/WJG.V27.I27.4298
8. Cayuela A, Vioque J, Rodríguez-Arce Á, Rojas M, Jiménez-Mengíbar C. [Geographic differences in mortality from digestive tumors in Spain, 1980-1984]. *Gac Sanit*. 1991;5(23):72-81. doi:10.1016/S0213-9111(91)71050-9
9. Etxeberria J, Goicoa T, López-Abente G, Riebler A, Ugarte MD. Spatial gender-age-period-cohort analysis of pancreatic cancer mortality in Spain (1990-2013). *PLoS One*. 2017;12(2). doi:10.1371/JOURNAL.PONE.0169751
10. Seoane-Mato D, Nuñez O, Fernández-de-Larrea N, et al. Long-term trends in pancreatic cancer mortality in Spain (1952-2012). *BMC Cancer*. 2018;18(1). doi:10.1186/s12885-018-4494-3
11. Cortés Vizcaíno C, Sabater Pons A, González Arráez JI, Felipe González N. Cáncer del páncreas: evolución de la mortalidad en España y estudio descriptivo de los principales factores de riesgo. *Rev Esp Enferm Apar Dig*. 1988;74(1):5-9.
12. Marra-López Valenciano C. Factors associated with pancreatic cancer in Spain. What can we learn from epidemiological studies? *Rev Esp Enferm Dig*. 2022;114(8):445-447. doi:10.17235/reed.2022.8927/2022

13. INEbase / Sociedad /Salud /Estadística de defunciones según la causa de muerte / Últimos datos. Accessed February 12, 2023. https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176780&menu=ultiDatos&idp=1254735573175

14. 2013 edition Revision of the European Standard Population Report of Eurostat's task force. doi:10.2785/11470

15. Download Joinpoint Desktop Software. Accessed February 17, 2023. https://surveillance.cancer.gov/joinpoint/download

16. Ben QW, Liu J, Sun YW, Wang LF, Zou DW, Yuan YZ. Cigarette Smoking and Mortality in Patients With Pancreatic Cancer: A Systematic Review and Meta-analysis. *Pancreas*. 2019;48(8):985-995. doi:10.1097/MPA.0000000000001383

17. Hunger R, Seliger B, Ogino S, Mantke R. Mortality factors in pancreatic surgery: A systematic review. How important is the hospital volume? *Int J Surg*. 2022;101. doi:10.1016/J.IJSU.2022.106640

18. Jiang W, Xiang C, Du Y, Li X, Zhou W. The Global, Regional and National Burden of Pancreatic Cancer Attributable to Smoking, 1990 to 2019: A Systematic Analysis from the Global Burden of Disease Study 2019. *Int J Environ Res Public Health*. 2023;20(2):1552. doi:10.3390/IJERPH20021552

19. Sun M, Fritz J, Häggström C, et al. Metabolically (un)healthy obesity and risk of obesity-related cancers: a pooled study. *J Natl Cancer Inst*. Published online January 17, 2023. doi:10.1093/JNCI/DJAD008

20. Okita Y, Sobue T, Zha L, et al. Association Between Alcohol Consumption and Risk of Pancreatic Cancer: The Japan Public Health Center-Based Prospective Study. *Cancer Epidemiol Biomarkers Prev*. 2022;31(11):2011-2019. doi:10.1158/1055-9965.EPI-22-0216

21. Ling S, Brown K, Miksza JK, et al. Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts. *Nutr Metab Cardiovasc Dis*. 2021;31(1):14-22. doi:10.1016/J.NUMECD.2020.09.023

22. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35(11):2402-2411. doi:10.2337/DC12-0336

23. Nucci D, Nardi M, Cinnirella A, et al. Adherence to Mediterranean Diet and Risk of Pancreatic Cancer: Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2023;20(3). doi:10.3390/IJERPH20032403

24. Afshar N, Hodge AM, Shivappa N, et al. Dietary Inflammatory Index, Alternative Healthy Eating Index-2010, Mediterranean Diet Score and the risk of pancreatic cancer. *Cancer Epidemiol*. 2023;82. doi:10.1016/J.CANEP.2022.102295

25. Nucci D, Santangelo OE, Provenzano S, et al. Dietary Fiber Intake and Risk of Pancreatic Cancer: Systematic Review and Meta-Analysis of Observational Studies. *Int J Environ Res*

Public Health. 2021;18(21). doi:10.3390/IJERPH182111556

26. Lugo A, Peveri G, Bosetti C, et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. *Eur J Cancer*. 2018;104:117-126. doi:10.1016/J.EJCA.2018.09.007

27. Indicadores clave del Sistema Nacional de Salud. Accessed March 3, 2023. https://inclasns.sanidad.gob.es/main.html?permalink=00215a880e01835732e3f040d5387cc6

28. Gili Ortiz E. Factors influencing mortality trends of pancreatic cancer in Spain, 1955-2020. *Rev Esp Enferm Dig*. 2022;114(8):474-480. doi:10.17235/reed.2022.8559/2021

29. Indicadores clave del Sistema Nacional de Salud. Accessed February 17, 2023. https://inclasns.sanidad.gob.es/main.html?permalink=00215a880e01835732e3f040d5387cc6

30. Glasser JH. The quality and utility of death certificate data. *Am J Public Health*. 1981;71(3):231-233. doi:10.2105/AJPH.71.3.231

31. Nikšić M, Matz M, Valkov M, et al. World-wide trends in net survival from pancreatic cancer by morphological sub-type: An analysis of 1,258,329 adults diagnosed in 58 countries during 2000-2014 (CONCORD-3). *Cancer Epidemiol*. 2022;80. doi:10.1016/J.CANEP.2022.102196

32. Pérez-Gómez B, Aragonés N, Pollán M, et al. Accuracy of cancer death certificates in Spain: a summary of available information. *Gac Sanit*. 2006;20 Suppl 3(SUPPL. 3):42-51. doi:10.1157/13101089

33. Salmerón D, Cirera L, Saez M, Navarro C. Influence of the introduction of the ICD-10 on tendencies of mortality by causes (1980-2004). *Gac Sanit*. 2009;23(2):144-146. doi:10.1016/J.GACETA.2008.04.002

34. Schwartz S. The fallacy of the ecological fallacy: The potential misuse of a concept and the consequences. *Am J Public Health*. 1994;84(5):819-824. doi:10.2105/AJPH.84.5.819

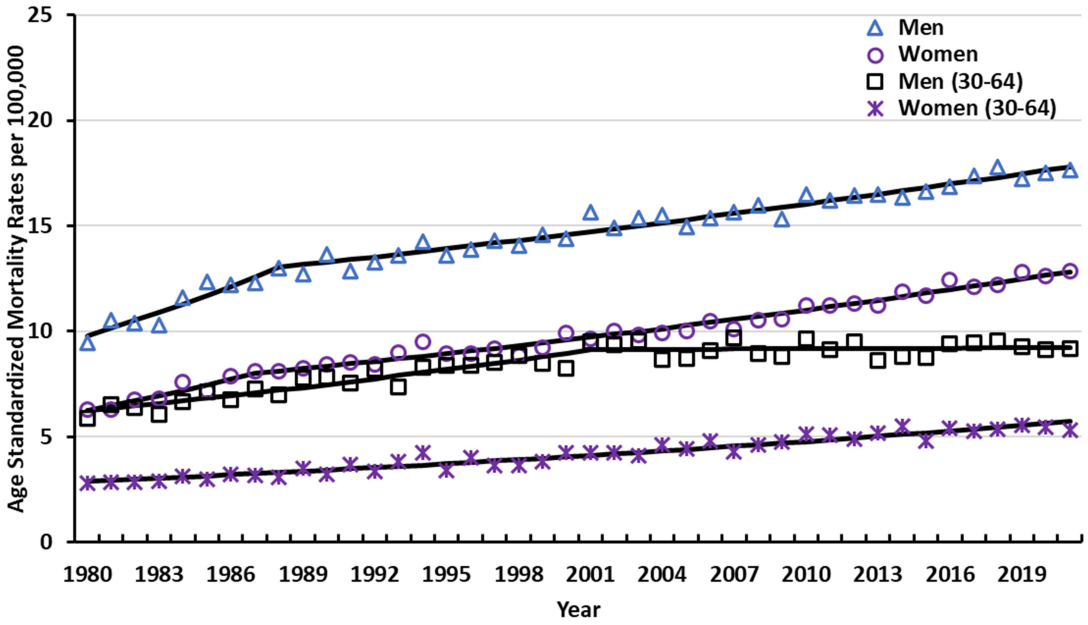

Figure 1: Age Standardised Mortality Rates (all ages and truncated 30-64 years) and trends estimated by joinpoint analysis for pancreatic cancer in Spain over the period 1980-2021 by sex.

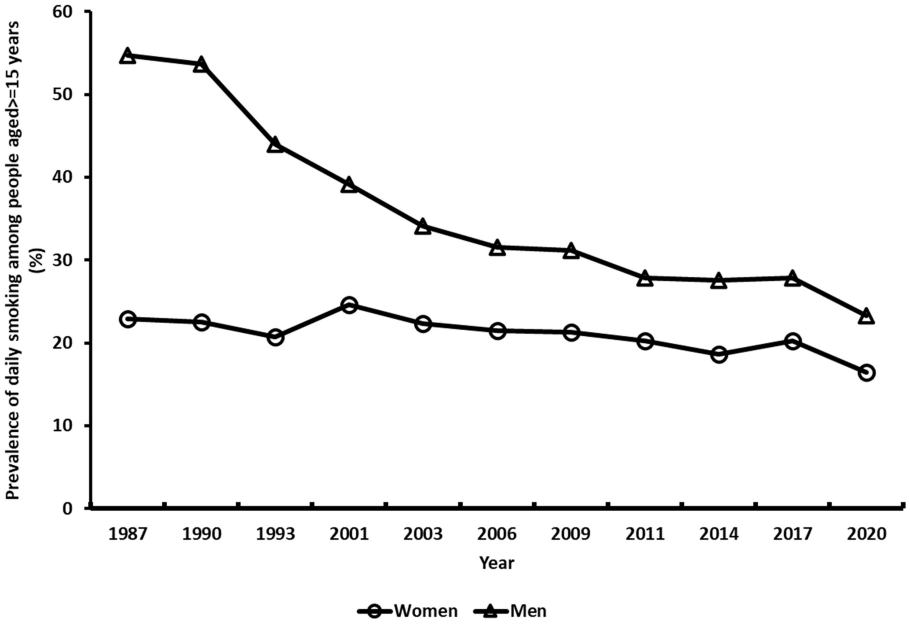

Figure 2: Prevalence (%) of daily smoking among men and women (aged ≥ 15 years old) in Spain, 1987–2020. Own elaboration from reference [27].

Table 1: Age Standardised Mortality Rates (all ages) for the years 1980 and 2021, as well as the Average Annual Percentage of Change (AAPC) for the period (1980-2021) and the results of the joinpoint analysis (period and Annual Percentage of Change, APC) in men by Autonomous Communities

Men

	ASMR		AAPC	Trend 1		Trend 2	
Autonomous Community	**1980**	**2021**	**1980-2021**	**Period**	**APC**	**Period**	**APC**
Andalusia	6.84	16.4	1.5*	1980-2021	1.5*		
Aragon	9.89	19.36	1.4*	1980-2021	1.4*		
Asturias	14.5	19.34	0.6*	1980-2021	0.6*		
Balearic Islands	10.24	14.76	0.9*	1980-2021	0.9*		
Canary Islands	15.99	16.53	0.3*	1980-2021	0.3*		
Cantabria	18.23	20.12	0.5*	1980-2021	0.5*		
Castile & León	9.02	18.39	1.1*	1980-2021	1.1*		
Castile-La Mancha	8.71	18.01	1.8*	1980-2021	1.8*		
Catalonia	9.56	17.86	0.9*	1980-2021	0.9*		
Valencia	8.99	19.26	1.3*	1980-2021	1.3*		
Extremadura	11.57	17.46	1.1*	1980-2021	1.1*		
Galicia	10.89	17.98	1.3*	1980-1999	2.6*	1999-2021	0.2
Madrid	6.3	16.47	1.4*	1980-2000	2.4*	2000-2021	0.5*
Murcia	9.35	18.25	1.6*	1980-2021	1.6*		
Navarre	7.98	14.74	0.8	1980-2001	2.4*	2001-2021	-1
Basque Country	12.39	18.27	0.8*	1980-2021	0.8*		
La Rioja	12.33	16.78	0.9*	1980-2021	0.9*		
Spain	9.47	17.66	1.5*	1980-1988	3.6*	1988-2021	0.9*

(*: $p<0.05$)

Table 2: Age Standardised Mortality Rates (all ages) for the years 1980 and 2021, as well as the Average Annual Percentage of Change (AAPC) for the period (1980-2021) and the results of the joinpoint analysis (period and Annual Percentage of Change, APC) in women by Autonomous Communities

Women

	ASMR		AAPC	Trend 1		Trend 2	
Autonomous Community	**1980**	**2021**	**1980-2021**	**Period**	**APC**	**Period**	**APC**
Andalusia	6.88	12.18	1.6*	1980-2021	1.6*		
Aragon	5.65	13.87	1.6*	1980-2021	1.6*		
Asturias	8.81	16.35	1*	1980-2021	1*		
Balearic Islands	4.2	12.04	1.3*	1980-2021	1.3*		
Canary Islands	6.15	12.13	1*	1980-2021	1*		
Cantabria	7.72	12.95	0.9*	1980-2021	0.9*		
Castile & León	6.67	12.05	1.5*	1980-2021	1.5*		
Castile-La Mancha	4.89	12.9	1.8*	1980-2021	1.8*		
Catalonia	6.04	13.04	1.4*	1980-2021	1.4*		
Valencia	5.67	13.84	1.6*	1980-2021	1.6*		
Extremadura	7.41	15.28	1.4*	1980-2021	1.4*		
Galicia	5.54	11.03	1.7*	1980-2021	1.7*		
Madrid	5.62	12.27	2.2*	1980-1992	4*	1992-2021	1.5*
Murcia	7.77	12.76	1.5*	1980-2021	1.5*		
Navarre	8.4	16.4	1.5*	1980-2021	1.5*		
Basque Country	6.58	13.66	1.2*	1980-2021	1.2*		
La Rioja	7.91	13.22	0.8*	1980-2021	0.8*		
Spain	6.28	12.88	1.8*	1980-1987	3.6*	1987-2021	1.4*

(*: $p<0.05$)

Table 3: Age Standardised Mortality Rates (truncated 30-64 years) for the years 1980 and 2021, as well as the Average Annual Percentage of Change (AAPC) for the period (1980-2021) and the results of the joinpoint analysis (period and Annual Percentage of Change, APC) in men by Autonomous Communities

Men

	ASMR (30-64 years)		**AAPC**	**Trend 1**		**Trend 2**	
Autonomous Community	**1980**	**2021**	**1980-2021**	**Period**	**APC**	**Period**	**APC**
Andalusia	5.44	10.98	1.2*	1980-2021	1.2*		
Aragon	6.8	10.31	0.9*	1980-2021	0.9*		
Asturias	9.22	12.18	0.4	1980-2021	0.4		
Balearic Islands	14.08	11.34	0.5	1980-2021	0.5		
Canary Islands	10.02	12.57	0.4	1980-2021	0.4		
Cantabria	7.27	6.45	0.2	1980-2021	0.2		
Castile & León	7.22	10.29	0.5*	1980-2021	0.5*		
Castile-La Mancha	6.31	10.7	1.5*	1980-2021	1.5*		
Catalonia	5.81	10.27	0.7*	1980-2021	0.7*		
Valencia	8.55	12.43	1.2*	1980-2021	1.2*		
Extremadura	8.84	11.38	1*	1980-2021	1*		
Galicia	7.51	12.42	0.9*	1980-1999	2.4*	1999-2021	-0.4
Madrid	3.89	8.79	1.4*	1980-2000	3.1*	2000-2021	-0.2
Murcia	7.27	9.59	1.6*	1980-2021	1.6*		
Navarre	4.56	6.92	-0.6	1980-2006	1.6*	2006-2021	-4.4*
Basque Country	6.39	8.93	0.5*	1980-2021	0.5*		
La Rioja	9.44	8.28	0.4	1980-2021	0.4		
Spain	6.78	10.64	1*	1980-2001	1.8*	2001-2021	0.1

(*: $p<0.05$)

Table 4: Age Standardised Mortality Rates (truncated 30-64 years) for the years 1980 and 2021, as well as the Average Annual Percentage of Change (AAPC) for the period (1980-2021) and the results of the joinpoint analysis (period and Annual Percentage of Change, APC) in women by Autonomous Communities

Women

	ASMR (30-64 years)		**AAPC**	**Trend 1**	
Autonomous Community	**1980**	**2021**	**1980-2021**	**Period**	**APC**
Andalusia	3.59	6.23	1.8*	1980-2021	1.8*
Aragon	1.82	7.41	1.8*	1980-2021	1.8*
Asturias	5.01	5.71	0.7	1980-2021	0.7
Balearic Islands	2.72	4.1	0.9*	1980-2021	0.9*
Canary Islands	1.83	5.57	1.4*	1980-2021	1.4*
Cantabria	3.38	5.6	0.1	1980-2021	0.1
Castile & León	3.21	5.13	1.5*	1980-2021	1.5*
Castile-La Mancha	3.63	6.81	1.6*	1980-2021	1.6*
Catalonia	3.44	6.88	1.6*	1980-2021	1.6*
Valencia	3.17	6.27	1.7*	1980-2021	1.7*
Extremadura	1.59	8.96	1.7*	1980-2021	1.7*
Galicia	3.24	5.1	1.7*	1980-2021	1.7*
Madrid	3	5.46	2.1*	1980-2021	2.1*
Murcia	3.26	6.26	1.7*	1980-2021	1.7*
Navarre	3.52	6.22	non-available		
Basque Country	2.89	6.16	1.8*	1980-2021	1.8*
La Rioja	2.07	2.31	non-available		
Spain	3.24	6.15	1.7*	1980-2021	1.7*

(*: $p<0.05$)