Rising Testicular Cancer Incidence in Spain Despite Declining Mortality: An Age-Period-Cohort Analysis

INTRODUCTION

Testicular cancer (TC), despite its relatively low overall cancer burden, disproportionately affects young and middle-aged men, posing a significant public health concern due to its impact on individual well-being and healthcare systems (1). Worryingly, TC incidence has been steadily increasing, particularly among younger age groups, amplifying these concerns (2,3). This trend is not limited to traditionally high-incidence regions like northern Europe, with concerning patterns emerging in previously less affected areas like Latin America and the Caribbean (4–6).

TC incidence in Europe is projected to rise by 21% by 2035, highlighting a significant escalation in risk independent of demographic ageing (5). Notably, some historically high-incidence regions, such as Denmark and Switzerland, show declining trends, suggesting potential changes in risk factors. In contrast, southern Europe, including Spain, presents a unique trajectory with a predicted 12% decrease in TC cases, diverging from other European regions (5).

Despite boasting one of the lowest TC rates in Southern Europe (7,8), Spain exhibits a puzzling trend. Between 1983 and 1997, it experienced a concerning rise in TC incidence, mirroring patterns observed globally. However, paradoxically, this period saw a simultaneous decline in mortality rates (1985-2004). Unfortunately, a critical data gap spanning over two decades leaves us without a clear picture of TC trends beyond 2004. This lack of updated data hinders our understanding of the current burden and evolution of this disease in Spain.

To address this critical information gap, this study leverages the power of the Global Burden of Disease (GBD) database, a comprehensive source of global TC data (9,10). Additionally, we employ the well-established age-period-cohort (A-P-C) model to disentangle the complex interplay of age, calendar period, and birth cohort influences on these trends (5–7,11–13). This multi-pronged approach aims to provide deeper insights into the drivers of TC incidence and mortality patterns in Spain, ultimately informing effective prevention and management strategies.

MATERIAL AND METHODS

This study employed an ecological trend analysis to examine TC incidence and mortality trends in Spain from 1990 to 2019.

Data source:

Age- and year-specific incidence and mortality data for TC in Spain (1990-2019) were obtained from the GBD Study online query tool (available at: https://vizhub.healthdata.org/gbd-results/).

Cases were identified using both International Classification of Diseases (ICD) versions: ICD-10 (C62-C62.9, D29.2-D29.8, and D40.1-D40.8) and ICD-9 (186-186.9, 222.0, 222.3, and 236.4).

GBD adheres to strict vetting and documentation procedures outlined in the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER), ensuring data accuracy and transparency.

Age-specific population data for Spain (1990-2019) were acquired from the Spanish National Statistics Institute (available at: https://www.ine.es/). These estimates represent the population on July 1st of each year.

Statistical analyses

We estimated age-standardized incidence rates (ASIRs) and mortality rates (ASMRs) using the direct method and the revised European Standard Population (14).

Joinpoint regression software (version 4.9.1.0, available at https://surveillance.cancer.gov/joinpoint/) was used to analyse trends and calculate turning points. Default settings were applied to identify periods with significant changes in trends and estimate the annual percentage change (APC) for each period. Additionally, the average annual percentage change (AAPC) between 1990 and 2019 was calculated, weighted by the duration of each identified period. We used the software's "Pairwise comparison" function to assess whether incidence and mortality trends were parallel. All rates are expressed per 100,000 men.

To implement the A-P-C model, we structured the dataset into six 5-year intervals, covering 1990-1994 to 2015-2019. We segmented the data into 16 5-year age brackets, spanning from 5-9 to 80-84 years. This arrangement yielded 21 birth cohorts, labelled by the central birth year, ranging from 1910 to 2010. Each age group and 5-year period underwent computation to derive age-specific rates, crucial for A-P-C model analysis.

We evaluated A-P-C effects utilizing the National Cancer Institute A-P-C tools [available at https://analysistools.nci.nih.gov/apc/](15). Key functions examined included longitudinal age-specific rates, period and cohort rate ratios, and local drifts with net drift. The longitudinal age curve provided fitted age-specific rates adjusted for period deviations. Period (or cohort) relative risk (RR) adjusted for age and non-linear cohort (or period) effects relative to the reference. Net drift illustrated the overall log-linear trend, while local drifts depicted age-specific trends. The web tool employs Wald tests, which follow a Chi-square distribution under the null hypothesis. The degrees of freedom reflect the number of estimated parameters in each test. Reported P-values indicate statistical evidence against the null hypothesis for values less than 0.05.

Informed patient consent wasn't necessary since the data were publicly accessible. Additionally, adherence to GATHER guidelines ensured the credibility and transparency of the GBD study findings.

RESULTS

Between 1990 and 2019, the incidence of TC cases doubled from 618 to 1,236, showing an annual increase of 2.5%. Similarly, the ASIR rose significantly from 3.09 to 5.40 per 100,000 men, with an annual increase of 1.9% ($p<0.05$). Joinpoint analysis identified four periods in the ASIR trend (Figure 1): a rapid increase (1990-1993, APC: 5.4%, $p<0.05$), a slowing of the increase (1993-2010, APC: 2.0%, $p<0.05$), stable rates (2010-2014, APC: -0.1, non-significant), and a further increase (2014-2019, APC: 1.3%, $p<0.05$).

In contrast, the mortality rate remained stable, ranging from 49 to 60 annually. The ASMR decreased from 0.34 to 0.26 per 100,000 population, with an average annual decrease of -0.8% ($p<0.05$). Joinpoint analysis of ASMR revealed three periods (Figure 1): stable rates (1990-1994, APC: -0.9%, not significant), followed by a marked decline (1994-1998, APC: -4.6%, $p<0.05$), and stable rates again (1998-2019, APC: -0.0%, not significant).

Figure 2 shows the net drift (annual percentage change in expected age-adjusted total rates) and local drift (age-specific rates over time) of TC incidence and mortality in Spain from 1990 to 2019. The overall net drift per year was 1.95% (95% CI, 1.7% to 2.2%) for incidence and -1.0% (95% CI, -1.7% to -0.3%) for mortality. In particular, there was an increase in local variation for incidence in all age groups from 15 to 69 years, while all other age groups remained stable. Conversely, for mortality, stability was observed in all age groups except 20-39 years, which showed a significant decrease.

Figure 3 shows the longitudinal age curves, estimated cohort relative risk (RR) trends and estimated period RR trends for TC incidence and mortality in Spain. The longitudinal trends reflecting age effects were generally consistent for both incidence and mortality. For incidence, the age effect showed an exponential increase before the age of 35 years, peaking at a rate of 7.3 cases per 100,000 man-years. After this peak, a decrease was observed up to the 50-54 age group, followed by a slight increase up to the 80-84 age group. Conversely, for mortality, the age effect showed an exponential increase before the age of 30, reaching 0.3 cases per 100,000 man-years. There was then a decrease up to the 60-64 age group, followed by a slight increase up to the 80-84 age group.

The birth cohort effect shows that, in terms of incidence, there was a period of stability in risk for people born between 1910 and 1935. However, with each successive generation, the risk has steadily increased, peaking for those born in the first decade of this century. Conversely, for mortality, a progressive decline in risk has been observed since the early 1900s, with a marked acceleration in the decline for cohorts born from the 1960s onwards.

The period effect on incidence demonstrates a consistent rise in risk over the period studied (1992-2002), contrasting with mortality rates, which initially decreased in risk before stabilizing.

Our analysis identified statistically significant trends ($P < 0.05$) in both incidence and mortality, including evidence for increasing net drifts and period effects. Additionally, a significant cohort effect was observed in incidence (Table 1).

DISCUSSION

Our findings reveal a concerning rise in TC incidence, particularly among young men in Spain, mirroring global trends (1,3,8,11,16,17). Despite improved diagnosis and treatment, the reasons for this increase remain a mystery, with few confirmed risk factors. While studies suggest a possible link between exposure to certain factors in adolescence and adulthood and the development of TC, the exact relationships are poorly understood (18).

While TC incidence has been increasing, mortality rates in Europe and the US have been steadily declining since the 1980s thanks to effective treatments. This progress is largely attributed to the introduction of cisplatin-based regimens in the late 1970s (7). Since then, further advancements in TC treatment have occurred, particularly in the 1990s, encompassing diverse therapeutic approaches like chemotherapy, surgery, radiotherapy, and even immunotherapy. These innovations have collectively contributed to a remarkable reduction in mortality rates, with 5-year survival rates exceeding 95% (19). This decline began in Northern and Western Europe, the US, and Canada in the 1970s and stabilized in these regions by the early 2000s, with very low mortality rates of around 0.2 per 100,000 (20,21). In 2008, these regions and most of northern and western Europe saw further significant declines, but some countries, including the US, have recently experienced a plateauing of death rates (21). Spain follows a similar pattern, with rates stabilizing around 0.2 per 100,000 after a decline of -4.6% per year between 1994 and 1998 (Figure 1). This is likely due to enhanced early detection, improved treatments, and a strengthened healthcare system.

Age-Effect: Despite global variations in TC incidence, our research aligns with prior observations, highlighting the age-related susceptibility pattern across diverse populations (8). This underlines the importance of age in understanding the disease. Additionally, our findings suggest a crucial role for prenatal and early life factors, with the precursor stage likely forming during the first trimester and exposures like oestrogen, maternal age, and birth weight potentially increasing risk. Furthermore, congenital malformations, maternal smoking, and individual lifestyle choices may also contribute to susceptibility, emphasizing the complex nature of TC development and the need for comprehensive risk assessment (18).

Period Effect: Recent research reveals a complex relationship between TC mortality rates and period effects (7,8,22). Our analysis, like other Spanish and international studies (7,8,12,13), confirms a strong period effect in TC mortality, primarily driven by treatment advancements. While cohort

effects have minimal impact, this analysis emphasizes the crucial role of treatment innovations in shaping mortality trends. Notably, the period effect is less pronounced for TC incidence, suggesting a more complex interplay at this level, emphasizing the dynamic nature of TC epidemiology.

Cohort Effect: Studies using A-P-C models previously suggested that TC incidence is primarily influenced by factors affecting specific birth cohorts, rather than age or period alone. This aligns with theories suggesting TC originates from pre-cancerous cells and is influenced by early-life factors. Our analysis further confirms this link, showing a significant "cohort effect" similar to other research (6,8,13,23–25).

Similar to trends observed in other European countries, Spanish men born before the 1940s have a slightly lower risk of TC (8,22,23,26). Notably, Western Europe and the US saw a sharp increase in TC incidence among men born after 1945, with earlier peak diagnosis ages (meaning they were diagnosed at a younger age) (23,27). This trend also holds in Spain, suggesting a possible link to early-life environmental exposures, such as increased prenatal oestrogen exposure. Increased prenatal oestrogen exposure is thought to disrupt foetal testicular development, potentially leading to an increased risk of TC later in life (23,28,29). Since TC typically occurs at a young age, the key influencing factors likely operate early in life, possibly even before birth (17). These findings highlight the potential role of early-life factors in shaping TC risk in Spain and underscore the need for further research to identify specific causes and develop preventive strategies.

Interestingly, a decline in TC risk was observed for men born around World War II in North America and younger generations born during the 1960s and 1970s in specific developed countries. However, this trend was not universal. Many countries, particularly those undergoing social and economic transition, witnessed a marked increase in TC rates (13). The picture across regions is far from uniform. While recent cohorts in Denmark and the UK show a plateauing risk, the US experiences a steady rise, especially for seminomas. On the other hand, Costa Rica, Croatia, and Slovakia observe a concerning increase among younger generations (6). In contrast to some European countries with stabilizing or declining rates, southern Europe, including Spain, mirrors the worrying rise seen in North America. Our data reveals a significant increase in TC risk among younger Spaniards born after 1970, aligning with these troubling trends (11).

Importantly, while incidence rates rise, mortality rates from TC are stabilizing or even declining, particularly for those born after the 1960s. This likely reflects advancements in early detection and treatment (13).

This study utilized the comprehensive GBD database and employed a robust A-P-C analysis, providing valuable insights into TC trends in Spain.

However, ecological studies like this cannot establish causal relationships and further research is needed to explore specific risk factors and mechanisms driving the observed trends.

The use of the GBD 2019 data allows for a comprehensive examination of the impact of testicular cancer in Spain, providing valuable information on its trends and patterns to inform health policies and interventions. However, this study has limitations. The GBD 2019 database relies on modelling techniques to impute missing data, which may introduce biases. In addition, the analysis is limited to the parameters available in the database, so certain aspects of the testicular cancer burden may be missed.

The study relies on secondary data and lacks details on stage distribution, treatment modalities, and potential risk factors.

Our reliance on the GBD 2019 dataset means that we lack specific details, such as histological differences, and information on incidence stages or therapeutic approaches. This limitation limits our ability to fully explore these facets of TC. Despite these limitations, our research provides valuable information on overall trends in TC in Spain, albeit without an analysis of different stages and subtypes due to a lack of data availability.

CONCLUSION

While mortality rates are encouraging, Spain reflects the global trend of escalating testicular cancer incidence. The A-P-C analysis suggests a generational influence, but the underlying causes remain elusive. Further research is crucial to understand these trends and implement effective prevention strategies to combat this growing health concern.

Table 1: Wald Chi-square test for estimable parameters in the age-period-cohort model.

Null hypothesis		Mortality		Incidence	
	df	Chi-square	P-Value	Chi-square	P-Value
NetDrift = 0	1	8.1	<.05	262.5	<.05
All Age Deviations = 0	14	236.2	<.05	2939.1	<.05
All Period Deviations = 0	4	5.4	0.248	8.0	0.090
All Cohort Deviations = 0	19	9.3	0.968	86.9	<.05
All Period RR = 1	5	13.5	0.019	265.7	<.05
All Cohort RR = 1	20	21.5	0.367	490.8	<.05
All Local Drifts = Net Drift	16	9.0	0.912	84.9	<.05

Figure 1: Testicular cancer in Spain: Age-standardized incidence and mortality rates, 1990-2019

Figure 2: Net drift and local drift of testicular cancer incidence and mortality in Spain from 1990 to 2019

Figure 3: Age-period-cohort model results for testicular cancer incidence and mortality in Spain from 1990 to 2019

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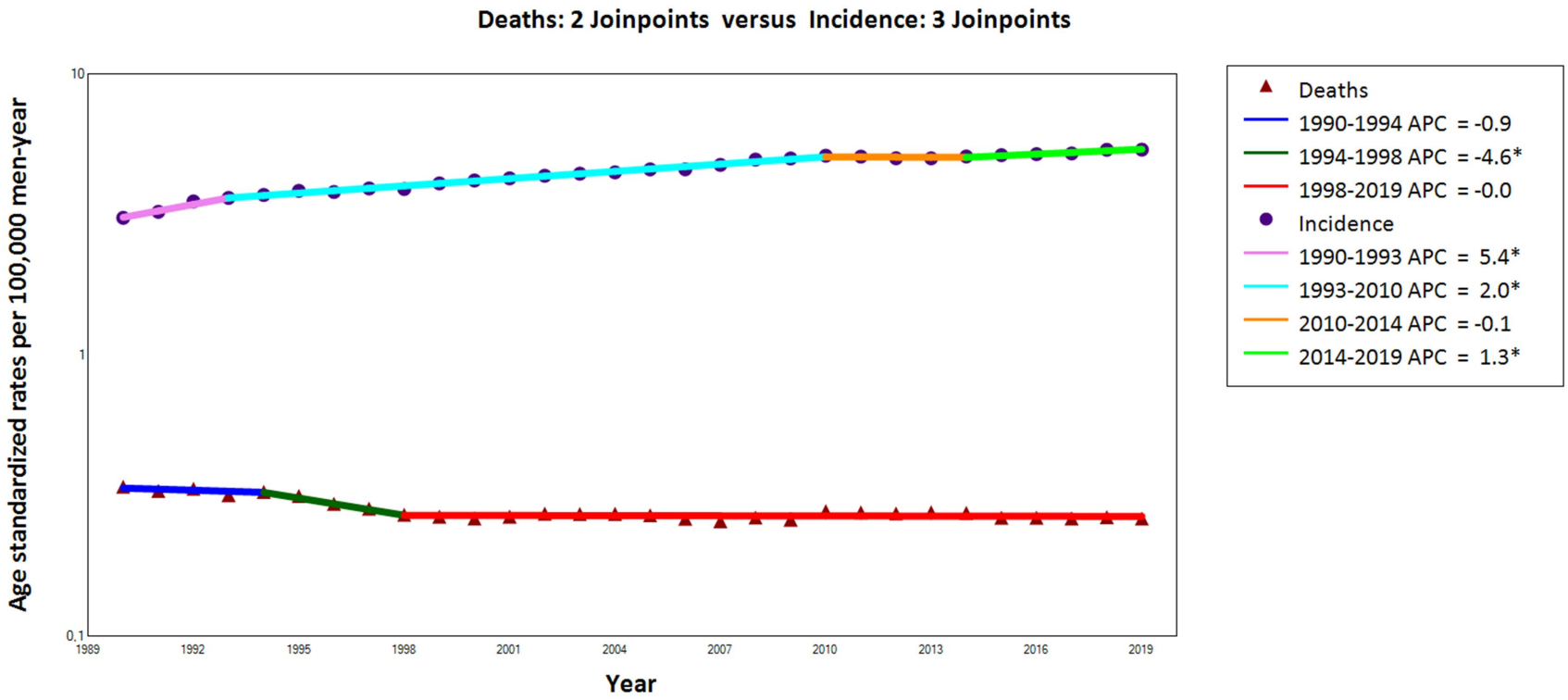
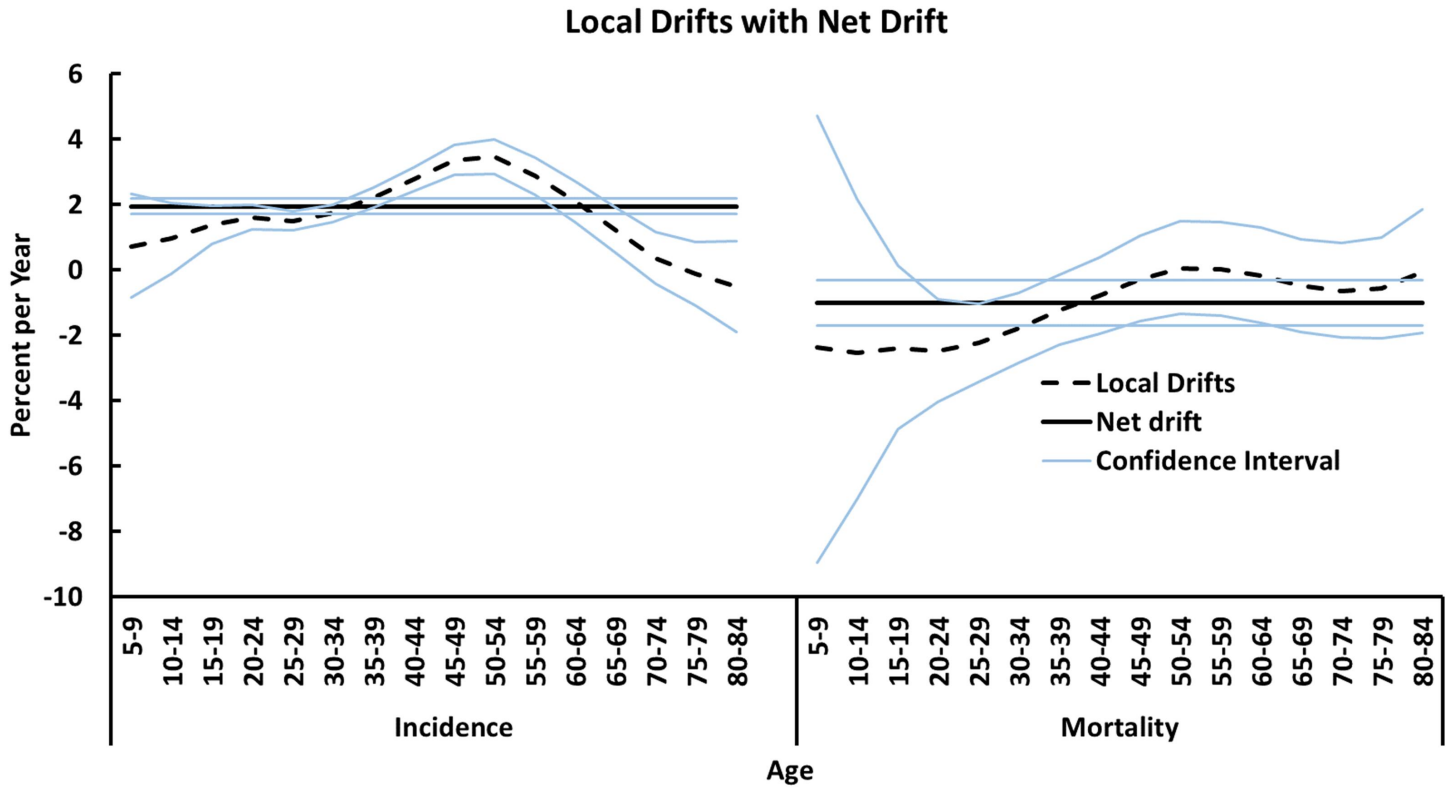
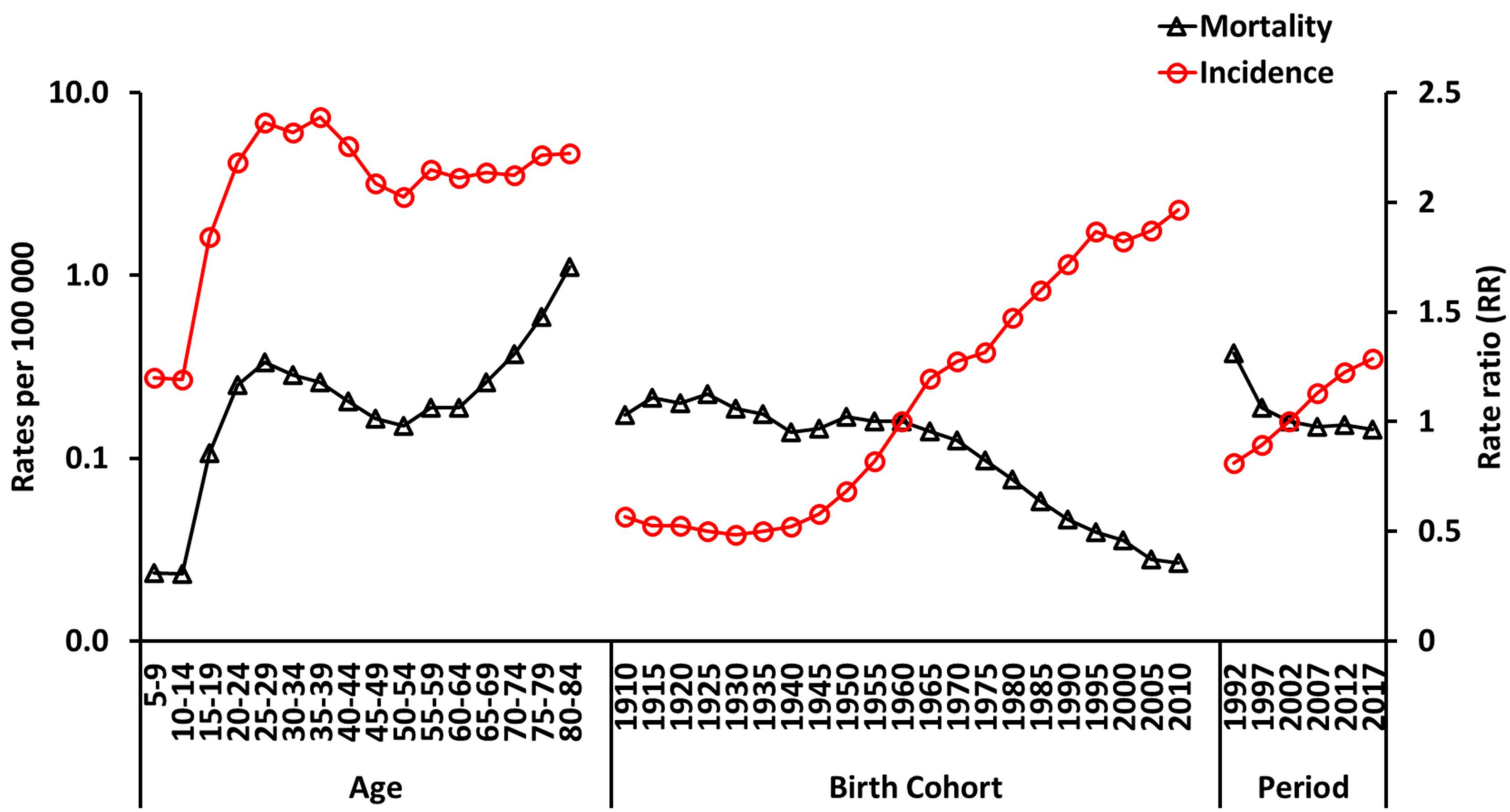


* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: Deaths - 2 Joinpoints, Incidence - 3 Joinpoints. Rejected Parallelism.


Local Drifts with Net Drift
Percent per Year
6
4
2
0
-2
-4
-6
-8
-10
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
Incidence
Mortality
Age
Local Drifts
Net drift
Confidence Interval


Mortality
Incidence
Rates per 100 000
Rate ratio (RR)
10.0
1.0
0.1
0.0
2.5
2
1.5
1
0.5
0
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
Age
1910
1915
1920
1925
1930
1935
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2005
2010
Birth Cohort
1992
1997
2002
2007
2012
2017
Period

Rising Testicular Cancer Incidence in Spain Despite Declining Mortality: An Age-Period-Cohort Analysis

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Final declarations

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Author Contributions: All authors contributed significantly to the study. Specifically, they participated in:

- Conception and design of the research
- Acquisition, analysis, and interpretation of data
- Drafting and critically revising the manuscript
- Approving the final version for publication
- Ensuring the accuracy and integrity of all aspects of the work

Ethics Statement: This study utilized anonymized data obtained from the Global Burden of Disease (GBD) study. The research adhered to the principles of good clinical practice (GCP) and the Declaration of Helsinki. As participant identification was not possible and no personal information was accessed, informed consent or ethics committee approval was not required. Additionally, the Guidelines for Accurate and Transparent Health Estimation Reporting for Population Health Research (GATHER) were followed to ensure the credibility and integrity of the findings.

Data Availability: The data for this study are publicly available through the Global Burden of Disease (GBD) Results Tool on the website of the Institute for Health Metrics and Evaluation (IHME): website link: http://ghdx.healthdata.org/gbd-resultstool. This tool allows users to explore and download GBD data, including detailed explanations of how the data were obtained: additional resources link: https://www.healthdata.org/data-tools-practices