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Evolving Patterns and Cohort-Specific Risks of Anal Cancer Mortality in Spain

Background

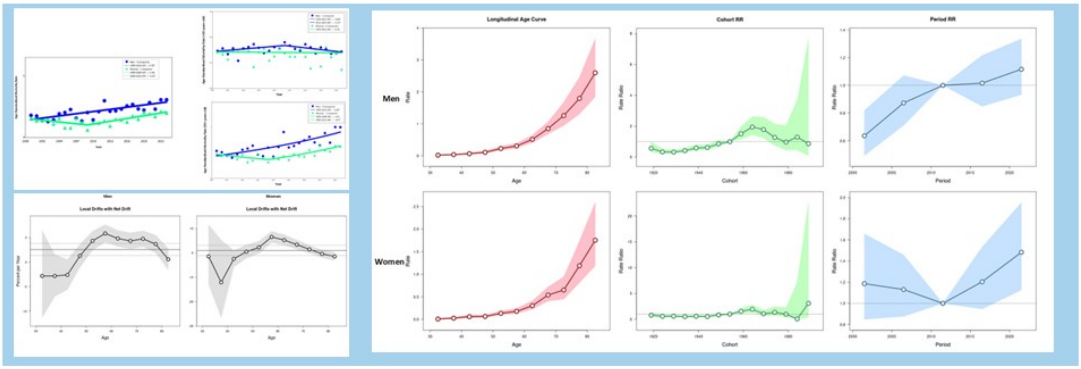
- **Anal cancer incidence and mortality are increasing in high-income countries.**

High-risk populations:
- men who have sex with men (MSM),
- people with HIV,
- transplant recipients,
- women with HPV-related gynecological cancers.

Methods

Data: Spanish National Institute of Statistics mortality records (ICD-10: C21), 1999–2023.

Analysis:
- Age-standardized mortality rates (ASMRs) per 100,000.
- Joinpoint regression for temporal trends.
- Age–period–cohort modeling for age, period, and cohort effects.



Conclusions: Anal cancer mortality in Spain is rising, especially in adults ≥50 years. Cohort effects, notably the 1964 generation, reflect higher HPV exposure. Universal HPV vaccination and targeted screening are urgently needed to curb future deaths.

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Evolving patterns and cohort-specific risks of anal cancer mortality in Spain

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Ethics Statement: All data were de-identified and publicly available, obviating the need for ethical approval. The study complies with the Declaration of Helsinki and follows STROBE reporting guideline.

Data Availability: The data for this study are publicly available through the https://www.ine.es/

Evolving Patterns and Cohort-Specific Risks of Anal Cancer Mortality in Spain

Background: Anal cancer, though rare, is rising in high-income countries, yet long-term national data from Spain remain limited. This study evaluates 25-year trends and cohort-specific mortality risks.

Methods: Anal cancer deaths from 1999–2023 were obtained from the Spanish National Institute of Statistics. Age-standardized mortality rates (ASMRs) were calculated using the 2013 European standard population. Joinpoint regression identified temporal trends, while age-period-cohort modelling disentangled age, period, and birth cohort effects.

Results: Among 2,549 deaths, overall ASMRs increased steadily in men (AAPC = 2.8%, 95% CI: 1.8;3.8). Women's rates remained lower, ranging from 0.20 to 0.25 per 100,000, with an AAPC of 1.0% (95% CI: -1.1;3.2). Women showed biphasic patterns: stable rates 1999–2009 (APC = –2.2%), then significant acceleration post-2009 (APC = 3.5%). Mortality was concentrated in adults ≥50 years, where rates increased from 0.54 to 1.01 per 100,000 in men and 0.54 to 0.63 per 100,000 in women. Rates in those <50 years remained extremely low (<0.06 per 100,000), with declining trends in men after 2012. Age-period-cohort analysis revealed strong cohort effects, with peak mortality risk in the 1964 birth cohort (RR = 1.95 in men; RR = 1.94 in women vs. 1954 cohort). Local drift analysis showed maximum annual increases at ages 55–59 years.

Conclusions: Anal cancer mortality in Spain has risen substantially, driven by birth cohort effects concentrated in adults ≥50 years. Elevated risks in post-1949 cohorts likely reflect increased HPV exposure. Urgently needed are expanded gender-neutral HPV vaccination and targeted screening for high-risk populations.

Keywords: Anal neoplasms. Mortality. Epidemiology. Time factors. Cohort studies. Human papillomavirus infections.

Lay Summary

Anal cancer is an uncommon but growing health problem. In recent years, the number of people dying from this disease has increased in many high-income countries. Most cases are linked to long-lasting infection with certain types of human papillomavirus, a very common sexually transmitted virus. Older adults, people with weakened immune systems, and some high-risk groups are particularly affected.

This study looked at all deaths from anal cancer in Spain over a 25-year period, from 1999 to 2023. Using national health records, we examined how death rates changed over time, comparing men and women and looking at different age groups. Advanced statistical methods were applied to identify long-term patterns and differences between generations.

We found that 2,549 people died from anal cancer in Spain during this period, with similar numbers in men and women. Death rates increased steadily among men, while in women they remained stable until 2009 and then began to rise quickly. The greatest risks were seen in people born after 1949, suggesting that generational changes in virus exposure and sexual behaviors are important factors.

These findings highlight that anal cancer is a growing health concern in Spain. The rise in deaths is especially marked among men, but women are also increasingly affected. Preventive measures already exist, including vaccination against human papillomavirus and screening for people at higher risk. Expanding these programs, alongside improving early diagnosis and treatment, is urgently needed to reduce future deaths.

Key points:

- Deaths from anal cancer in Spain have risen steadily from 1999 to 2023, especially among men.
- Women showed stable mortality until 2009, followed by a sharp increase in later years.
- Higher risks are seen in people born after 1949, likely due to greater exposure to HPV.

- Expanding HPV vaccination and targeted screening can prevent future deaths.

Introduction

Anal cancer, though relatively uncommon, is an emerging public health concern, with incidence and mortality rising in many high-income countries and among vulnerable populations[1–3]. Globally, an estimated 54,306 new cases were reported in 2022[4], disproportionately affecting women and high-risk groups such as people living with HIV, men who have sex with men, solid organ transplant recipients, and women with a history of HPV-related gynaecological malignancies[1,5].

Squamous cell carcinoma of the anus, the predominant histological subtype, has shown a sustained increase of 2–3% per year in the United States[6,7], with similar trends observed in Europe, Canada, and Australia[1–3,8–12]. Unlike colorectal cancer, where mortality has declined in recent decades[13,14], anal cancer mortality continues to rise[2,3,6,8–11]. This divergence probably reflects complex interactions between age, period, and cohort effects[2,6,11].

Distinct age-specific epidemiological patterns are evident, varying by sex and birth cohort. Early-onset disease (<50 years) is increasing[2,10,15], largely attributable to HPV exposure, evolving sexual behaviours, and the higher prevalence of HIV infection[2,3,15]. In contrast, late-onset disease predominates among older adults, influenced by cumulative exposures, comorbidities, and immunosenescence[7,16,17].

Despite these evolving dynamics and the demographic and healthcare transitions underway in Spain, detailed analyses of national anal cancer mortality trends have remained scarce. Most available studies have considered anal cancer only within the broader spectrum of HPV-related malignancies[3,18–20], leaving critical gaps in understanding age- and sex-specific temporal patterns and their determinants.

This study therefore aimed to investigate long-term trends in anal cancer mortality in Spain from 1999 to 2023, focusing on sex- and age-specific differences and applying age–period–cohort models to elucidate underlying drivers. Understanding these trends can inform preventive strategies such as gender-neutral HPV vaccination and targeted screening.

Methods

We analysed anal cancer mortality in Spain between 1999 and 2023 using data from the Spanish National Institute of Statistics (Instituto Nacional de Estadística, INE) mortality database, a comprehensive and reliable source of national death records[21,22]. Deaths were identified using the International Classification of Diseases, 10th Revision (ICD-10) code C21, which encompasses anal cancer. Mortality data were available by calendar year, sex, and age group. Corresponding population denominators, also obtained from INE, provided age-, sex-, and year-specific estimates to calculate mortality rates.

The central descriptive measure was the age-standardised mortality rate (ASMR) per 100,000 population, calculated using the direct standardisation method with the 2013 European standard population as the reference[23]. Analyses were conducted for the total population (all ages combined), and separately for individuals younger than 50 years and those aged 50 years or older, to account for differences in age-specific mortality patterns.

Temporal trends were examined using the Joinpoint Regression Program (version 5.2.0.0; National Cancer Institute, USA), which detects statistically significant changes in trend direction or magnitude[24]. The default settings were applied to estimate joinpoints and to obtain additional summary measures, including the annual percentage change (APC) for each segment and the average annual percentage change (AAPC) across the full study period (1999–2023). Trends were classified as “increasing” or “decreasing” if statistically significant ($p < 0.05$), and as “stable” if not.

To explore the underlying drivers of mortality trends, we conducted age–period–cohort (A-P-C) modelling using the National Cancer Institute’s statistical tools[25]. This method separates the effects of age (biological ageing processes), period (time-dependent external influences affecting all ages), and cohort (birth cohort-specific exposures) on mortality. Analyses were restricted to individuals aged 35–84 years to minimise statistical instability at the extremes of the age distribution. The additional A-P-C derived metrics included longitudinal age-specific rates, period and cohort rate ratios (RRs), local drifts (age-specific annual percentage changes), and net drift (overall annual percentage change). The central categories for age, period, and birth cohort were used as reference groups. Wald χ^2 tests were applied to assess the

significance of net drift, age deviations, period deviations, cohort deviations, and differences between local and net drifts. All results are presented with 95% confidence intervals.

Results

Between 1999 and 2023, a total of 2,549 deaths from anal cancer were recorded in Spain, comprising 1,318 in men (51.7%) and 1,231 in women (48.3%). Mortality was negligible below the age of 30, rose steadily thereafter, and peaked in those aged ≥85 years, with 514 deaths (179 in men, 335 in women). Annual deaths increased from approximately 65–70 in the early 2000s to a maximum of 172 in 2022. Although men accounted for the majority of deaths overall, women predominated at older ages and in selected years.

ASMRs displayed clear sex differences (Figure 1). In men, ASMR (all ages) rose consistently from 0.23 per 100,000 in 1999 to 0.41 in 2023, corresponding to an average annual increase of 2.8% (95% CI: 1.8–3.8). Women maintained lower rates throughout the period, ranging from 0.20 to 0.25 per 100,000, with overall trends showing relative stability until the late 2000s and subsequent increases thereafter. The male-to-female ASMR ratio generally remained above 1, peaking at 2.05 in 2012, with convergence observed only in a few years.

Marked differences were observed by age group (Figure 1). Among individuals <50 years, mortality was extremely low. In men, rates increased modestly in the early years before declining after 2012, whereas women showed persistently minimal, stable rates. In contrast, mortality in those aged ≥50 years was substantially higher and accounted for the overall increases. In men, rates rose from 0.54 per 100,000 in 1999 to 1.01 in 2023. In women, rates declined until the late 2000s before increasing to 0.63 per 100,000 in 2023.

A-P-C analyses confirmed strong age and cohort effects (Table 1, Figures 2–3). Net drift was significant in men (2.6% per year; 95% CI: 1.4–3.8; $p < 0.001$) but not in women (1.0% per year; 95% CI: –1.1 to 3.2; $p = 0.34$). Local drifts differed significantly from the net drift in both sexes ($p < 0.001$), with declines in early adulthood followed by steep increases from midlife, peaking at ages 55–59 and tapering thereafter (Figure

2). Age deviations were non-significant, consistent with a log-linear rise in mortality with advancing age (Figure 3). Period effects were not significant overall (p = 0.23 in men; p = 0.45 in women), although period relative risks increased significantly in men (p = 0.001) and showed borderline evidence in women (p = 0.05). Cohort deviations were highly significant in both sexes (p < 0.001). Earlier cohorts (1919–1944) had lower risks, whereas the 1964 birth cohort showed the highest risk (RR = 1.95 in men; 1.94 in women, reference: 1954 cohort). Elevated risks persisted in subsequent cohorts (1974–1989), although estimates were less precise due to smaller numbers.

Discussion

This study provides the first long-term, national analysis of anal cancer mortality in Spain, revealing distinct sex- and age-specific trends between 1999 and 2023. Overall mortality increased significantly, driven predominantly by men and individuals aged 50 and over. While rates among younger people remained negligible, men in this age group demonstrated a modest rise followed by a decline after 2012, whereas rates for women remained stable.

Age-period-cohort modelling revealed pronounced cohort effects. Individuals born after 1949, particularly the 1964 cohort, exhibited substantially elevated risks. This is likely a result of increased exposure to human papillomavirus (HPV) and evolving sexual behaviours[15,18–20] , a trend consistent with findings from other high-income countries like the United States, Australia, and Northern Europe[2,9,11,26].

The rising mortality in Spain mirrors international trends, with male mortality increasing steadily at 2.8% per year. This is likely driven by the higher prevalence of persistent high-risk HPV and HIV among men who have sex with men[5,6]. In contrast, female mortality followed a biphasic pattern, remaining stable until 2009 before accelerating. This temporal shift may reflect changes in sexual behaviour, HPV vaccination coverage, and improved detection of HPV-related cancers[3]. The male-to-female disparity in mortality is a common international observation[6,10]. For example, Brazilian data shows that while mortality was initially higher among women, rapid increases in men led to near-parity by 2021, with the female-to-male mortality rate ratio dropping from 1.88 (2012–2016) to 1.14 in 2021[27].

These epidemiological patterns are reflected in the clinical burden of the disease . Between 2016 and 2020, Spain recorded 3,542 hospitalisations for anal cancer. Men experienced earlier admissions, longer hospital stays, higher healthcare costs, and a higher prevalence of HIV (11%)[20], consistent with international reports linking the anal cancer burden to HPV and HIV infection[1–3,5,28]. This underscores the tangible impact on health services and confirms that men bear a disproportionate share of the clinical and economic burden[2,3,6,28].

Age-stratified analyses revealed two distinct epidemiological profiles. In adults under 50, mortality remained negligible. A post-2012 decline in men within this age group contrasts with rising early-onset incidence reported elsewhere[2,10,15], potentially reflecting improved survival, enhanced prevention strategies, or unique epidemiological dynamics within Spain.

In stark contrast, adults aged 50 and over accounted for virtually all mortality increases, with rates 15 to 30 times higher than in younger adults. This pronounced age gradient, with the highest rates observed in individuals aged 65 and older, highlights the dual aetiologies of the disease. While early-onset anal cancer is strongly linked to HPV infection and sexual behaviours, late-onset cases are likely driven by the cumulative effects of prolonged exposures, immunosenescence, and a higher burden of comorbidities[7,16].

The 2009 joinpoint observed in older women may reflect a complex interplay between epidemiological trends and external factors. This period coincided with Spain's economic crisis and subsequent healthcare reforms, which could have influenced diagnostic and treatment accessibility. Data from Brazil further supports this age-mortality relationship, where the annual percentage change for anal cancer mortality in individuals over 80 was dramatically higher in men (44% per year) compared to women (11% per year)[27].

Cohort effects were particularly pronounced, peaking amongst those born in 1964 (relative risk ~1.95 in both sexes). This generation reached adolescence during the 1980s-1990s, coinciding with HIV emergence, shifting sexual practices, and absence of HPV vaccination. Persistently elevated risks in subsequent cohorts suggest sustained exposure to risk factors, contrasting sharply with cancers where younger

cohorts benefit from prevention initiatives[3].

Period effects further illuminate dynamic epidemiological influences. Men demonstrated steadily increasing period relative risks from 1999 to 2023, potentially reflecting improved HIV survival rates delaying AIDS-related malignancies[6]. For women, temporary decline around 2009-2013 may reflect indirect benefits from cervical cancer screening programmes or enhanced HIV care protocols. However, these protective effects proved transient, with mortality rising subsequently.

These dynamic period effects highlight complex interactions between healthcare practices, risk factor prevalence, and epidemic trends. Supporting evidence from Brazil, where increased survival amongst people living with HIV and population ageing have similarly contributed to rising anal cancer mortality, reinforces this interpretation[27].

HPV represents the principal aetiological factor, detected in virtually all anal squamous cell carcinoma cases. In Spain, HPV prevalence correlates with lesion severity: 73.7% in atypical squamous cells of undetermined significance/atypical glandular cells, 67% in low-grade squamous intraepithelial lesions, and 87.1% in high-grade squamous intraepithelial lesions/adenocarcinoma in situ[29].

Population surveillance data from 2007-2022 demonstrate overall HPV prevalence of 29.2% amongst individuals with suspected infection, with HPV16 remaining the predominant genotype. Although vaccine-targeted types have declined—HPV16 prevalence decreased by 72% between 2012 and 2022—other oncogenic types (HPV58, 53, and 66) remain stable or are emerging, emphasising the importance of continued genotype surveillance and potential vaccine adaptation[29].

Our findings highlight a pressing public health concern in Spain. Anal cancer mortality continues to rise, particularly among men and older adults, in stark contrast to declining trends in other gastrointestinal cancers[13,14]. This divergence underscores the urgent need for a cohesive national strategy, as organised prevention and screening for anal cancer remain absent.

HPV vaccination is the cornerstone of prevention. Since its introduction for girls in 2007, with subsequent expansion to boys and high-risk groups, Spain has achieved substantial reductions in high-risk HPV prevalence. HPV16 prevalence alone fell by

72%, from 11.8% in 2012 to 3.3% in 2022, demonstrating robust vaccine effectiveness. Nevertheless, non-vaccine high-risk and intermediate-risk HPV types persist or are emerging, highlighting the need for ongoing genotype surveillance and potential vaccine adaptation[29].

The absence of systematic screening for anal cancer and persistent high-risk HPV infection is particularly concerning compared with international benchmarks. For example, the United States' 2024 guidelines recommend annual assessments and high-resolution anoscopy for individuals living with HIV[30] , practices yet to be implemented in Spain. Emerging evidence supports combining anal cytology with high-risk HPV testing to enhance diagnostic accuracy, providing a feasible framework for national implementation[31].

The disproportionate burden of anal cancer among men, alongside rising infection rates in less-vaccinated cohorts, demands urgent policy action. Universal gender-neutral vaccination, targeted catch-up campaigns for high-risk groups—including men who have sex with men and people living with HIV—and stratified screening are essential to reduce future incidence[28,30]. HPV vaccination prevents over 90% of HPV-related cancers[28], yet Spain's historical focus on preadolescent girls has left men and older cohorts vulnerable. The International Anal Neoplasia Society's 2024 guidelines offer evidence-based risk thresholds for screening high-risk groups, providing a robust model for adaptation within the Spanish healthcare system[32].

To address these challenges, Spain must prioritise a comprehensive national strategy. This should include universal gender-neutral vaccination, targeted catch-up campaigns for middle-aged and older adults born after 1949, and the establishment of systematic screening protocols aligned with international standards. Such measures are essential to mitigate the rising burden of anal cancer and bring Spain's public health response in line with global best practices.

Strengths and Limitations

This study's methodological strengths include the use of high-quality national mortality data spanning 25 years and the application of robust statistical methods (joinpoint regression and age-period-cohort modelling), enabling nuanced analysis of

temporal trends and sex-specific differences.

However, important limitations must be acknowledged. Reliance on mortality rather than incidence data means our findings reflect both disease occurrence and survival outcomes, potentially masking variations in treatment efficacy across time periods. Misclassification of anal cancer on death certificates, though minimized by reliable ICD-10 coding standards, cannot be completely eliminated, particularly among older age groups where multiple comorbidities may complicate cause-of-death attribution. Additionally, the absence of individual-level data on HIV status, HPV vaccination history, and treatment protocols limits direct assessment of these important risk modifiers.

Furthermore, the INE mortality data, based solely on anatomical location (ICD-10 C21), do not allow differentiation between histological subtypes such as squamous cell carcinoma and adenocarcinoma, which may have distinct etiological factors (e.g., HPV-related risks) and survival patterns. Future studies integrating incidence data from cancer registries (e.g., REDECAN) could address this gap.

Conclusion

Anal cancer mortality in Spain increased substantially between 1999 and 2023. Men experienced steady rises, while women showed a sharp acceleration after 2009, largely reflecting higher HPV exposure in cohorts born after 1949.

Addressing this challenge requires urgent expansion of gender-neutral HPV vaccination, catch-up vaccination for high-risk groups, and the introduction of targeted screening strategies. Equally critical is ensuring timely diagnosis and effective treatment access. Proven tools—vaccination and evidence-based screening—are already available. Coordinated and sustained public health action is essential to reverse current trends and reduce future mortality.

References

1. Deshmukh AA, Damgacioglu H, Georges D, et al. Global burden of HPV-attributable squamous cell carcinoma of the anus in 2020, according to sex and HIV status: A worldwide analysis. *Int J Cancer*. 2023;152(3):417-428. doi:10.1002/ijc.34269

2. Kang YJ, Smith M, Canfell K. Anal cancer in high-income countries: Increasing burden of disease. *PLoS One*. 2018;13(10):e0205105. doi:10.1371/journal.pone.0205105

3. Mignozzi S, Santucci C, Malvezzi M, Levi F, La Vecchia C, Negri E. Global trends in anal cancer incidence and mortality. *Eur J Cancer Prev*. 2024;33(2):77-86. doi:10.1097/CEJ.0000000000000842

4. Cancer (IARC) TIA for R on. Global Cancer Observatory. Accessed July 7, 2025. https://gco.iarc.fr/

5. Clifford GM, Georges D, Shiels MS, et al. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. *Int J Cancer*. 2021;148(1):38-47. doi:10.1002/ijc.33185

6. Sohail AH, Flesner SL, Quazi MA, et al. Emerging trends and demographic disparities in anal cancer mortality across the United States census regions: An analysis of National Center for Health Statistics mortality data. *Colorectal Dis*. 2024;26(11):1913-1921. doi:10.1111/codi.17167

7. Garg A, Damgacioglu H, Sigel K, et al. Future patterns in burden and incidence of squamous cell carcinoma of the anus in the United States, 2001-2035. *J Natl Cancer Inst*. 2024;116(9):1508-1512. doi:10.1093/jnci/djae127

8. Cattelan L, Ghazawi FM, Le M, et al. Investigating epidemiologic trends and the geographic distribution of patients with anal squamous cell carcinoma throughout Canada. *Curr Oncol*. 2020;27(3):e294-e306. doi:10.3747/co.27.6061

9. Heer E, Hackl M, Ferlitsch M, Waldhoer T, Yang L. Trends in incidence of anal cancer in Austria, 1983-2016. *Wien Klin Wochenschr*. 2020;132(15-16):438-443.

doi:10.1007/s00508-020-01622-z

10. Meyers AL, Dowty JG, Mahmood K, et al. Age-specific trends in colorectal, appendiceal, and anal tumour incidence by histological subtype in Australia from 1990 to 2020: a population-based time-series analysis. *medRxiv*. Published online April 24, 2025:2025.04.21.25326138. doi:10.1101/2025.04.21.25326138

11. Urbute A, Sand FL, Belmonte F, Iversen LH, Munk C, Kjaer SK. Trends in rectal cancer incidence, relative survival, and mortality in Denmark during 1978-2018. *Eur J Cancer Prev*. 2022;31(5):451-458. doi:10.1097/CEJ.0000000000000728

12. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. *Int J Epidemiol*. 2017;46(3):924-938. doi:10.1093/ije/dyw276

13. Emile SH, Horesh N, Freund MR, et al. Trends in the Characteristics, Treatment, and Outcomes of Rectal Adenocarcinoma in the US From 2004 to 2019: A National Cancer Database Analysis. *JAMA Oncol*. 2023;9(3):355-364. doi:10.1001/jamaoncol.2022.6116

14. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*. 2023;73(3):233-254. doi:10.3322/caac.21772

15. Junkins A, Chu DI, Burkholder GA, et al. Demographic, clinical, and social characteristics of anal cancer among patients stratified by age (<50 and ≥50 years) in Alabama between 2012 and 2018. *Cancer Epidemiol*. 2024;92:102612. doi:10.1016/j.canep.2024.102612

16. Benson AB, Venook AP, Al-Hawary MM, et al. Anal Carcinoma, Version 2.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2023;21(6):653-677. doi:10.6004/jnccn.2023.0030

17. Eng C, Ciombor KK, Cho M, et al. Anal Cancer: Emerging Standards in a Rare Disease. *J Clin Oncol*. 2022;40(24):2774-2788. doi:10.1200/JCO.21.02566

18. Dabán-López P, Fernández-Martínez NF, Petrova D, et al. Epidemiology of human papillomavirus-associated anogenital cancers in Granada: a three-decade population-based study. *Front Public Health*. 2023;11:1205170. doi:10.3389/fpubh.2023.1205170

19. de Souza DLB, Curado MP, Bernal MM, Jerez Roig J. What is the future burden of HPV-related cancers in Spain? *Clin Transl Oncol*. 2014;16(2):213-219. doi:10.1007/s12094-013-1064-7

20. Fernandez-Alonso V, Gil-Prieto R, Amado-Anton-Pacheco M, Hernández-Barrera V, Gil-De-Miguel Á. Hospitalization burden associated with anus and penis neoplasm in Spain (2016-2020). *Hum Vaccin Immunother*. 2024;20(1):2334001. doi:10.1080/21645515.2024.2334001

21. Cirera L, Bañón RM, Maeso S, et al. Territorial gaps on quality of causes of death statistics over the last forty years in Spain. *BMC Public Health*. 2024;24(1):361. doi:10.1186/s12889-023-17616-1

22. Ruiz M, Cirera Suárez L, Pérez G, et al. [Comparability between the ninth and tenth revisions of the International Classification of Diseases applied to coding causes of death in Spain]. *Gac Sanit*. 2002;16(6):526-532. doi:10.1016/s0213-9111(02)71975-4

23. Revision of the European Standard Population - Report of Eurostat's task force - 2013 edition. Accessed April 1, 2023. https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/ks-ra-13-028

24. Joinpoint Regression Program. Accessed April 3, 2024. https://surveillance.cancer.gov/joinpoint/

25. Rosenberg PS, Check DP, Anderson WF. A web tool for age-period-cohort analysis of cancer incidence and mortality rates. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2014;23(11):2296-2302. doi:10.1158/1055-9965.EPI-14-0300

26. Arnold M, Abnet CC, Neale RE, et al. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology*. 2020;159(1):335-349.e15. doi:10.1053/j.gastro.2020.02.068

27. Lazaretti CR, Meine GC. Trends in Mortality of Anal Cancer in Brazil, 2012-2021. *Journal of Coloproctology*. 2025;45:e1-e6. doi:10.1055/s-0045-1809674

28. Zhang J, Ke Y, Chen C, et al. HPV cancer burden by anatomical site, country, and region in 2022. *Sci Rep*. 2025;15(1):21048. doi:10.1038/s41598-025-06700-8

29. Andújar JDA, Ramírez RB, Gascó NV, et al. Human papillomavirus prevalence and distribution in a Spanish population since the start of the vaccination program. *Preprints*. Preprint posted online March 19, 2024. doi:10.22541/au.171084505.51015074/v1

30. HIV Clinical Guidelines Now Recommend High Resolution Anoscopy as Part of Anal Cancer Screening Program for People with HIV | National Institutes of Health. Accessed August 30, 2025. https://www.oar.nih.gov/update-clinical-guidelines-high-resolution-anoscopy-anal-cancer-screening

31. Screening for Anal Dysplasia and Cancer in Adults With HIV - Clinical Guidelines Program. Accessed August 30, 2025. https://www.hivguidelines.org/guideline/hiv-anal-cancer/

32. Stier EA, Clarke MA, Deshmukh AA, et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. *Int J Cancer*.

2024;154(10):1694-1702. doi:10.1002/ijc.34850

Table 1. Wald test statistics for age–period–cohort effects in anal cancer mortality, Spain, 1999–2023

		Men		Women	
Hypothesis	**df**	**χ^2**	***p*-value**	**χ^2**	***p*-value**
Net drift = 0	1	17.99	<0.001	0.92	0.34
All age deviations = 0	9	10.95	0.28	8.83	0.45
All period deviations = 0	3	4.34	0.23	7.21	0.07
All cohort deviations = 0	13	40	<0.001	44.83	<0.001
All period RR = 1	4	18.96	0.001	9.39	0.05
All cohort RR = 1	14	84.27	<0.001	48.83	<0.001
All local drifts = net drift	11	38.51	<0.001	42.73	<0.001

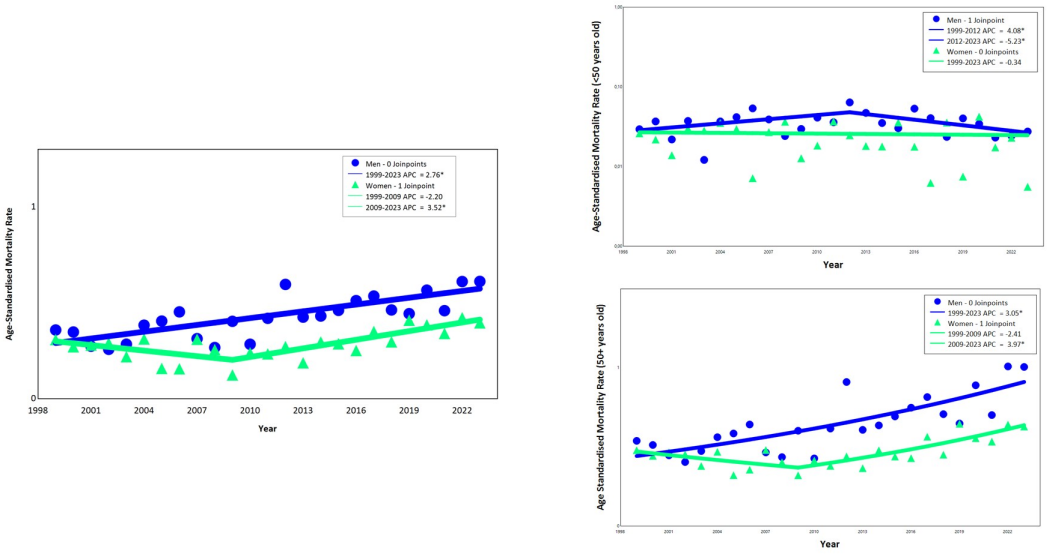

Figure 1: Sex-Specific Trends in Age-Standardised Mortality Rates for Anal Cancer in Spain, 1999–2023

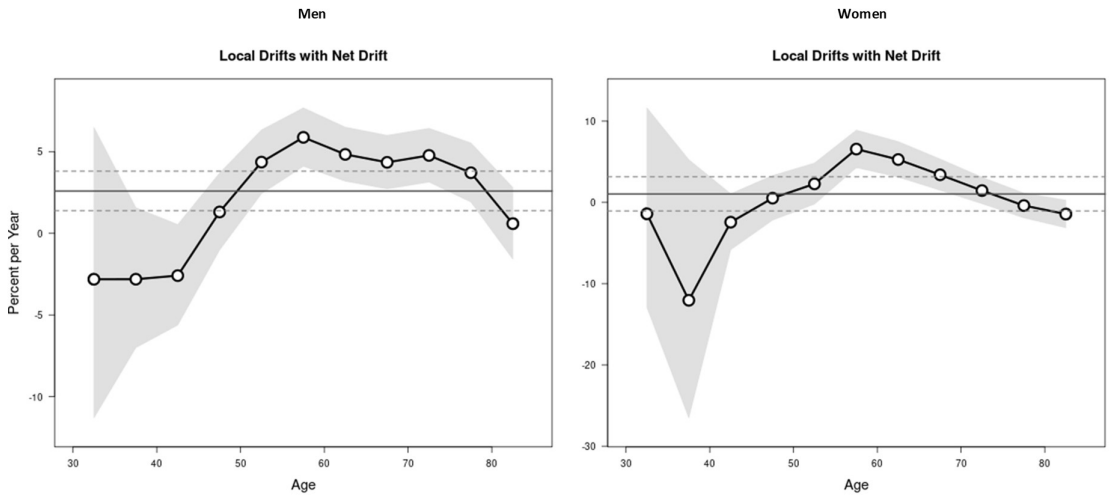

Figure 2: Net and Local Drift in Anal Cancer Mortality by Sex and Age Group, Spain, 1999–2023

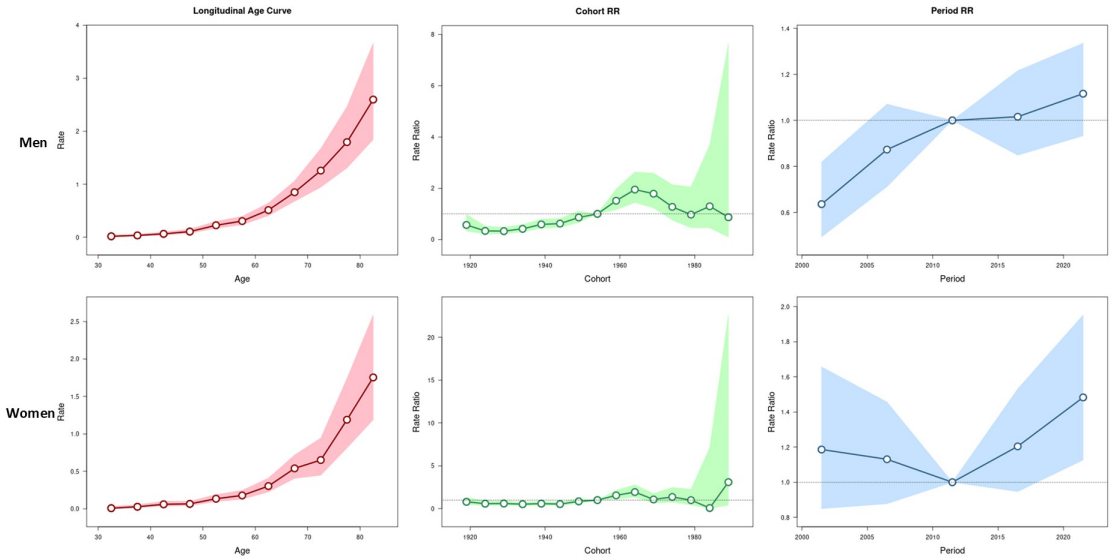

Figure 3: Age, Period, and Cohort Effects on Anal Cancer Mortality by Sex in Spain, 1999–2023