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Hidden inequalities in anal cancer mortality in Spain, 1999-2023: implications for targeted prevention

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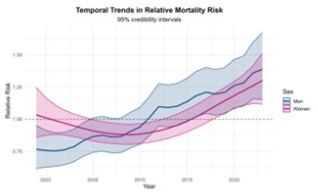
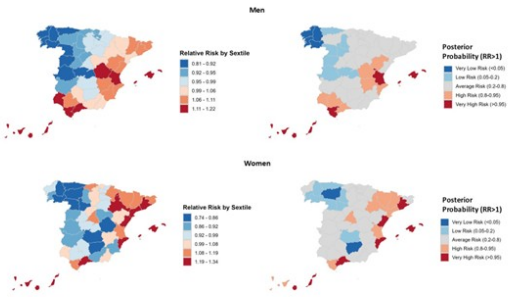
Hidden Inequalities in Anal Cancer Mortality in Spain, 1999–2023

Data: Spanish National Institute of Statistics mortality records (ICD-10: C21)
Method: Bayesian spatiotemporal analysis, 52 provinces, 1999–2023



Men – steady national increase;
Women – late surge post-2015.



Hotspots: Coastal & Insular Provinces.

CONCLUSION: Male mortality driven by national temporal trends. Female mortality shaped by regional inequalities. Targeted HPV vaccination and equitable screening urgently needed.

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Hidden inequalities in anal cancer mortality in Spain, 1999-2023: implications for targeted prevention

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and revising it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that any questions related to its accuracy or integrity are appropriately investigated and resolved.

Ethics and Informed Consent Statement: This study used publicly available and de-identified data; therefore, obtaining informed consent was not required. The study was conducted in accordance with the principles of the Declaration of Helsinki and adheres to the STROBE reporting guideline.

Data Availability: The data supporting the conclusions of this study are publicly available at: https://www.ine.es/

Lay Summary

Anal cancer is an uncommon but preventable malignancy linked to Human Papillomavirus (HPV) infection. In Spain, mortality has risen steadily over the past two decades, yet local trends have not been systematically explored. Using advanced Bayesian spatial models, we examined anal cancer deaths across the 50 provinces and the autonomous cities of Ceuta and Melilla from 1999 to 2023, identifying clear geographic and sex-specific inequalities. Male mortality showed a nationwide, time-driven increase, while female mortality was more geographically uneven, with higher risks in southern and insular regions such as Las Palmas, Málaga, and the Balearic Islands. These findings suggest that men are affected by a broad, systemic epidemic, whereas women face regional vulnerabilities likely shaped by healthcare access and social factors. Expanding HPV vaccination to all genders, integrating anal screening in HIV care, and directing prevention resources to high-risk provinces are crucial steps to reduce this preventable burden.

ABSTRACT

Background: Anal cancer mortality has increased across high-income countries, yet subnational patterns remain poorly characterized. This study provides the first comprehensive, sex-stratified, spatiotemporal analysis of anal cancer (ICD-10 C21) mortality in Spain from 1999 to 2023.

Methods: We conducted an ecological, descriptive, province-level analysis of mortality using data from the National Institute of Statistics. Sex-stratified Bayesian hierarchical models were applied to estimate smoothed relative risks (RRs) by province and year, incorporating spatial, temporal, and interaction effects. Model selection was guided by the Deviance Information Criterion and Widely Applicable Information Criterion. Posterior probabilities (PP) were used to identify high-risk provinces (PP > 0.95).

Results: Among 160 candidate models, optimal structures differed by sex: males showed intrinsic Conditional Autoregressive (iCAR) spatial prior with RW1 temporal prior and Type IV interaction; females showed iCAR with RW2 temporal prior and Type III interaction. Mortality rose in both sexes: male RR increased steadily to 1.39 in 2023; female RR followed a nonlinear trajectory with delayed surge to 1.30. Variance decomposition indicated male mortality was mainly temporal (80.2%), female mortality largely spatial (58.1%). Male hotspots clustered in southern/insular provinces (e.g., Las Palmas RR=1.22, Cádiz 1.18, Valencia 1.18); female hotspots were more dispersed (e.g., Las Palmas 1.34, Málaga 1.33, Barcelona 1.26).

Conclusions: Anal cancer mortality in Spain is rising, revealing persistent sex-specific and geographic inequalities beyond national temporal trends. Precision prevention—via gender-neutral HPV vaccination, targeted screening, and prioritization of hotspot provinces—is urgently needed.

Keywords: Anal Neoplasms. Human Papillomavirus Infections. Spatial Analysis. Bayesian Analysis. Mortality. Spain

Key points

What is known about the subject: Anal cancer is a rare but preventable malignancy primarily caused by persistent HPV infection. Its incidence and mortality are increasing in high-income countries, with notable sex and regional disparities. In Spain, mortality has risen steadily despite stable incidence rates.

What the study adds: This study provides the first nationwide, sex-stratified spatiotemporal analysis of anal cancer mortality in Spain (1999–2023). Using Bayesian disease mapping, it reveals distinct epidemiological dynamics: male mortality is mainly driven by uniform temporal increases, while female mortality shows marked spatial heterogeneity. High-risk clusters are concentrated in southern and insular provinces.

Implications for clinical practice and public health: Findings underscore the need for gender-neutral HPV vaccination, targeted anal cancer screening within HIV care, and geographically tailored prevention strategies to reduce growing regional and sex-specific disparities in Spain.

Introduction

Anal cancer, a relatively rare malignancy largely driven by persistent Human Papillomavirus (HPV) infection (1–3), presents a growing public health concern in high-income countries. Globally, incidence and mortality trends are upward, with most cases being Anal Squamous Cell Carcinoma (SCC) linked to HPV-16 (1,4). While anal cancer accounts for a small fraction of the global cancer burden, its impact is amplified by its preventable aetiology and marked disparities across populations (1–3,5–7).

Worldwide, both incidence and mortality of anal cancer are rising, with the highest rates in Central, Eastern, and Northern Europe, and lower rates in Asia and Latin America (2,6). This increase is linked to higher HPV prevalence, ageing populations, and changing sexual behaviours (2,4–6). Incidence has grown fastest among women and older adults, while mortality continues to rise in both sexes despite stabilising male incidence in some regions (5).

In Spain, anal cancer presents a worrying picture. Although incidence remains low and stable, mortality has risen sharply—by 2.8% per year in men and 3.5% in women between 1999 and 2023 (2,8,9). High-risk groups, including people living with HIV (PLWH) and men who have sex with men (MSM), experience incidence rates many times higher than the general population (10–12). These concentrated burdens may also conceal wider, underexplored geographical and temporal disparities across Spain's provinces (13,14). Understanding these local patterns is vital for targeted prevention and efficient healthcare planning.

This study provides the first comprehensive spatiotemporal analysis of anal cancer mortality across all Spanish provinces and autonomous cities from 1999 to 2023, using an ecological, descriptive spatiotemporal approach.

Methods

We conducted an ecological, descriptive, province-level study to examine anal cancer mortality trends (ICD-10 code C21) in Spain from 1999 to 2023, covering all 50 provinces and the autonomous cities of Ceuta and Melilla. Mortality and population data were sourced from the National Institute of Statistics (INE) and disaggregated by province, sex, year, and 5-year age groups (0–4 to 85+) to allow robust age standardisation. Expected deaths were calculated using indirect standardisation, applying national age-specific rates to provincial populations. While Standardised Mortality Ratios (SMRs) were used for initial descriptive exploration, a Bayesian hierarchical framework was adopted for the main spatiotemporal analysis to improve the stability and precision of small-area estimates in this rare outcome.

Provincial adjacency was defined using graph-based neighbourhood structures, primarily with Queen contiguity. To maintain a fully connected spatial graph—necessary for stable estimation of random effects—a k-nearest neighbour approach was applied where required.

We used hierarchical Bayesian spatiotemporal models to estimate smoothed relative risks (RRs) of mortality through a Poisson log-linear mixed model: $\log(O) \sim \text{Poisson}(\log(E) + \log(RR))$. The log(RR) term was decomposed into baseline, spatial, temporal, and spatiotemporal components. Four spatial structures were tested: intrinsic Conditional Autoregressive (iCAR), Besag–York–Mollié (BYM), BYM2, and Leroux CAR models. Temporal variation was modelled using first- and second-order random walks (RW1, RW2). Spatiotemporal interactions followed Knorr-Held Types I–IV and an additive form, allowing flexible province-specific trends. Penalised Complexity (PC) priors were applied to all random effect hyperparameters using default settings recommended for disease mapping applications ($U=1$, $\alpha=0.01$ for spatial and temporal precision hyperparameters; $U=0.5$, $\alpha=0.01$ for interaction terms). These priors penalise unnecessary complexity by shrinking effects toward simpler base models (constant risk or no trend) unless strongly supported by the data, thus improving model stability and parsimony(15).

Models were fitted using the Integrated Nested Laplace Approximation (INLA) via the R-INLA package. We assessed 160 candidate models (80 per sex), combining 4 spatial, 2 temporal, 5 interaction, and 2 PC prior configurations. Model selection was based on the Deviance Information Criterion (DIC) and Widely Applicable Information Criterion (WAIC), favouring parsimony and predictive performance.

Excess mortality was expressed as the posterior probability (PP) that RR > 1. Risk levels were defined as: PP < 0.20 (low), 0.20–0.80 (moderate), and PP > 0.80 (high). Strong evidence for mortality hotspots was set at PP > 0.95. Spatiotemporal patterns were visualised using choropleth maps generated with R.

Results

Across the 160 Bayesian spatiotemporal models tested, the best-performing structures showed consistent and robust results for both sexes. For men, the optimal model combined an intrinsic Conditional Autoregressive (iCAR) spatial prior, a first-order random walk (RW1) temporal prior, and a Type IV spatiotemporal interaction (DIC/WAIC = 2,797.53). For women, the best fit also used an iCAR spatial prior but paired with a smoother second-order random walk (RW2) and a Type III interaction (DIC = 2,687.65). The close clustering of top models (ΔWAIC ≤ 0.77 for men; ≤ 0.42 for women) supports the robustness of model selection. Higher fit indices for men (≈110 units higher) indicate greater structural complexity and variability in male mortality data.

Variance decomposition revealed distinct sex-specific drivers of mortality. Among men, temporal variation explained 80.2% of total variance, confirming that mortality was primarily shaped by national temporal trends. Spatial effects contributed 18.5%, and spatiotemporal interactions only 1.3%. In women, spatial effects dominated (58.1%), followed by temporal (31.1%) and interaction (10.9%) components, indicating stronger geographical heterogeneity and regional influences.

National trends in relative mortality risk (RR) differed sharply by sex (Figure 1). In men, RR rose steadily, exceeding unity around 2011 and reaching 1.39 by 2023, with

acceleration after 2015. In women, RR first declined to 0.88 (2008–2010), then increased, surpassing unity around 2016 and reaching 1.30 by 2023. These patterns suggest lagged but converging upward mortality trends in both sexes.

Spatially, cumulative RR maps showed marked provincial disparities (Figure 2). In men, high-risk clusters (posterior probability (PP) > 0.95 for RR > 1) were concentrated in southern and island provinces, including Las Palmas (RR = 1.22), Santa Cruz de Tenerife (1.21), Valencia (1.18), Cádiz (1.18), and the Balearic Islands (1.18). Low-risk areas were mainly in the north-west. For women, elevated risks were more widespread, with hotspots in Las Palmas (RR = 1.34), Málaga (1.33), the Balearic Islands (1.31), and Barcelona (1.26), while low-risk areas clustered in north-western and central Spain.

Temporal evolution maps (Figure 3) highlighted further contrasts. For men, the Type IV interaction showed high precision (380.40), reflecting a stable, synchronised national increase with limited local variation. Even high-risk provinces such as Valencia (RR = 1.15 in 2023; PP = 0.91) exhibited only small year-to-year fluctuations (±0.15). In women, the Type III interaction showed low precision (16.67), indicating greater local variation. Provinces such as Barcelona (RR = 1.14; PP = 0.84) and Alicante (RR = 1.13; PP = 0.80) showed notable increases after 2010, suggesting that regional determinants played a larger role in shaping female mortality trends.

Discussion

This study provides the first comprehensive, sex-stratified spatiotemporal analysis of anal cancer mortality across Spain's 52 provinces and autonomous cities (1999–2023) using a Bayesian hierarchical framework. The findings reveal rising mortality, marked geographical variation, and distinct sex-specific risk dynamics. As an ecological and descriptive study, these results provide hypothesis-generating evidence for targeted prevention.

Our results corroborate the concerning, sustained increase in anal cancer mortality for both sexes over the 25-year study period. The male relative risk (RR) increased almost linearly, crossing unity around 2011 and peaking at 1.39 by 2023, with accelerated

growth post-2015. Female trends were more complex, initially declining before rising steadily above unity from 2016, ultimately reaching RR = 1.30 in 2023. This narrowing of the sex gap and the overall upward trajectory align with patterns documented across other high-income countries (2,3). This increase is largely attributable to the HPV epidemic and cofactors such as immunosuppression (e.g., HIV) and smoking in cohorts now entering high-risk age ranges, reflecting the cumulative effect of changing sexual behaviours and HPV exposure from preceding decades (6,9,16).

The divergent spatiotemporal patterns revealed by our variance decomposition analysis and the optimal model structure provide novel and crucial insights into the epidemiology of anal cancer in Spain. The predominance of temporal variation in males (80.2% of total variance) suggests that male mortality is driven by a dominant, diffuse temporal factor that affects the population broadly and uniformly across provinces. The optimal model for men incorporated a first-order random walk (RW1) temporal prior and a Type IV spatiotemporal interaction. The RW1 structure indicates that male mortality exhibits rougher, less inherently smooth year-to-year fluctuations, with the risk in any given year being largely dependent on the immediately preceding year. This systemic, pervasive trend is highly consistent with a birth cohort effect related to HPV exposure and the evolving epidemiology of HIV and its treatment (8–10). The observed RW1 dynamics and linear increase is likely influenced by the paradoxical effect of highly active antiretroviral therapy (HAART). Whilst HAART prolongs the survival of people living with HIV (PLWH), particularly men who have sex with men (MSM)—a population with concentrated risk (17,18), it allows sufficient time for progression from anal intraepithelial neoplasia (AIN) to invasive cancer (16), thus contributing to a sustained, uniform national rise. The Type IV interaction, which allows both the temporal trend to vary by province and the spatial pattern to change over time, reinforces the complex, responsive nature of the male epidemic to localized, year-specific factors.

In stark contrast, female mortality risk is primarily spatially structured (58.1% of total variance). The optimal model for women favoured a smoother second-order random walk (RW2) temporal prior and a Type III spatiotemporal interaction. The RW2 prior suggests that female mortality follows smoother, more gradual temporal evolution,

with the current year's risk being dependent on the two preceding years, indicating greater stability and predictability in long-term trajectories. This pronounced spatial heterogeneity suggests that for women, regional or localised factors play a more defining role than national temporal shifts. This pattern often reflects entrenched social and structural inequities, as provinces with greater socioeconomic deprivation frequently present worse cancer outcomes(19). The distinct, non-linear female temporal trend—characterised by an initial decline followed by a sharp late-period surge—signals an emerging crisis. The RW2 structure potentially reflects slower-changing underlying risk factors such as cumulative HPV exposure in older cohorts or persistent regional healthcare disparities. Whilst the early decline may reflect temporary benefits from opportunistic cervical cancer screening (20), the late surge is concerning, likely driven by older, vulnerable cohorts facing increasing HPV-related cancer risk (9). Furthermore, the Type III interaction, which permits the spatial risk pattern to change over time but forces a constant temporal trend across all provinces, strongly supports the dominance of fixed, underlying geographic and structural factors in driving female mortality disparities. Critically, the spatially dominant risk for women shifts the focus from a uniform national epidemic to geographical disparities in structural health factors and access to timely, specialised care.

These fundamental differences in model structure—RW1/Type IV for men vs. RW2/Type III for women—suggest distinct underlying causal mechanisms (abrupt, responsive changes vs. smooth, entrenched stability) and necessitate fundamentally sex-specific surveillance strategies. The selection of the iCAR spatial prior for both sexes, however, confirms the importance of geographical neighbourhood effects (spatial autocorrelation) as a consistent factor in anal cancer risk, regardless of sex.

Spatial analysis identified clusters of elevated risk. Male hotspots (PP > 0.95) concentrated in southern coastal and insular regions (e.g., Las Palmas, Cádiz). Female high-risk provinces showed similar coastal concentration (e.g., Málaga, Barcelona). These patterns may reflect population mobility and tourism-related sexual networks in coastal areas (11,21), or higher HIV prevalence in urban centres. These geographical patterns may reflect multiple intersecting factors, such as higher population mobility and tourism-related sexual networks in coastal and insular provinces(11,21), larger

MSM populations and higher HIV prevalence in urban centres(22), and regional variation in healthcare access, screening uptake, or socioeconomic factors(23). Furthermore, the spatiotemporal interaction term illuminated unique, localised risk surges for women in provinces such as Alicante and Barcelona post-2015, which warrant investigation into specific historical cohort effects and regional preventive care deficiencies (13).

The primary contribution of this work is revealing geographically structured inequalities that persist beyond national trends. These findings demand a shift towards tailored interventions. First, the consistent upward mortality trends underscore the imperative for enhanced primary prevention through HPV vaccination. Whilst Spanish programmes target adolescents, gender-neutral HPV vaccination must be rigorously expanded beyond adolescent girls to explicitly include and achieve high coverage in high-risk groups, most notably MSM and PLWH. Direct vaccination of males is the only pathway to adequately protect the MSM subnetwork from this escalating risk.

Second, the pronounced geographical disparities and the temporal dominance of male risk strongly suggest that screening and prevention resources must be preferentially allocated to the identified high-risk provinces. The landmark ANCHOR trial demonstrated that treatment of high-grade squamous intraepithelial lesions (HSIL) significantly reduces anal cancer incidence in PLWH (24). Consequently, anal cancer screening must be seamlessly integrated into HIV care protocols for all PLWH, particularly within the high-risk provinces identified, a strategy strongly supported by contemporary clinical guidelines to prevent the late-stage diagnoses driving mortality(21).

Third, the sex-specific patterns demand tailored prevention strategies. For men, the volatile RW1 temporal dynamics suggest that mortality responds to short-term changes, necessitating interventions that focus on HIV care settings and sexual health clinics serving MSM, alongside promotion of vaccination amongst young males(25) and real-time monitoring systems capable of detecting emerging risk shifts. Conversely, the persistent spatial disparities in female mortality warrant deeper investigation into the role of structural health inequities and potential long-term impacts of economic

factors (e.g., the post-2008 financial crisis), which may have reduced healthcare access and contributed to stalled progress in regional cancer control (26). The smoother RW2 temporal patterns in women enable more confident long-term planning and resource allocation, but demand sustained, dedicated attention to mitigating the entrenched geographical inequities (Type III interaction) that drive risk. For women, integration of anal cancer awareness into cervical cancer screening programmes remains an appropriate complementary strategy (27).

A major strength is the use of Bayesian disease mapping with INLA, which stabilises estimates for rare cancers (15).

This study also has limitations inherent to its ecological design, which precludes individual-level causal inference. First, the potential for ecological fallacy implies that proposed mechanisms—such as the impact of HAART, tourism-related sexual networks, or macroeconomic shocks—should be interpreted as hypotheses grounded in existing literature, not as demonstrated causal pathways in these data. Second, although Spanish death certification practices and ICD-10 (C21) coding were stable during 1999–2023, minor misclassification or changes in diagnostic awareness over time could have subtly influenced temporal trends. Third, internal migration may introduce spatial exposure misclassification, as province of residence at death may not coincide with the locations where HPV infection and co-exposures occurred decades earlier. Despite these constraints, the consistent, geographically structured inequalities identified here offer a solid empirical basis for precision public health strategies.

Conclusions

Anal cancer mortality in Spain is rising, with clear sex-specific and geographic inequalities. Precision prevention—through gender-neutral HPV vaccination, targeted screening, and resource prioritization in hotspot provinces—is urgently needed to curb these hidden disparities.

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Table S1: *Top 10 optimal model specifications (ranked by lowest DIC) among 160 candidates per sex (4 spatial structures × 2 temporal priors × 5 interaction types × 2 PC prior configurations). Values are rounded to two decimal places for presentation. The optimal model (rank 1) was selected for each sex and used in the main analysis.*

Sex	Rank	Spatial Effect	Temporal Effect	Interaction Type	PC Priors	DIC	WAIC
Men	1	iCAR	RW1	Type IV	TRUE	2797.53	2797.53
Men	2	iCAR	RW2	Type III	FALSE	2797.73	2797.59
Men	3	iCAR	RW1	Type III	TRUE	2798.08	2797.78
Men	4	iCAR	RW2	Type III	TRUE	2798.32	2798.00
Men	5	BYM	RW1	Type IV	FALSE	2798.38	2798.30
Men	6	iCAR	RW1	Type IV	FALSE	2798.40	2798.42
Men	7	iCAR	RW2	Type I	TRUE	2799.16	2799.68
Men	8	Leroux	RW1	Type IV	TRUE	2799.27	2799.26
Men	9	Leroux	RW1	Type III	FALSE	2799.35	2799.13
Men	10	Leroux	RW1	Type IV	FALSE	2799.36	2799.36
Women	1	iCAR	RW2	Type III	FALSE	2687.65	2687.82
Women	2	Leroux	RW2	Type III	FALSE	2687.75	2687.47
Women	3	Leroux	RW2	Type III	TRUE	2688.01	2688.13

Sex	Rank	Spatial Effect	Temporal Effect	Interaction Type	PC Priors	DIC	WAIC
Women	4	BYM	RW2	Type III	FALSE	2688.40	2687.88
Women	5	BYM	RW2	Type III	TRUE	2688.43	2688.24
Women	6	iCAR	RW2	Type III	TRUE	2688.80	2689.69
Women	7	BYM2	RW2	Type III	FALSE	2689.05	2688.59
Women	8	BYM2	RW2	Type III	TRUE	2689.97	2689.57
Women	9	BYM	RW1	Type III	FALSE	2690.00	2689.22
Women	10	iCAR	RW1	Type III	TRUE	2690.22	2689.99

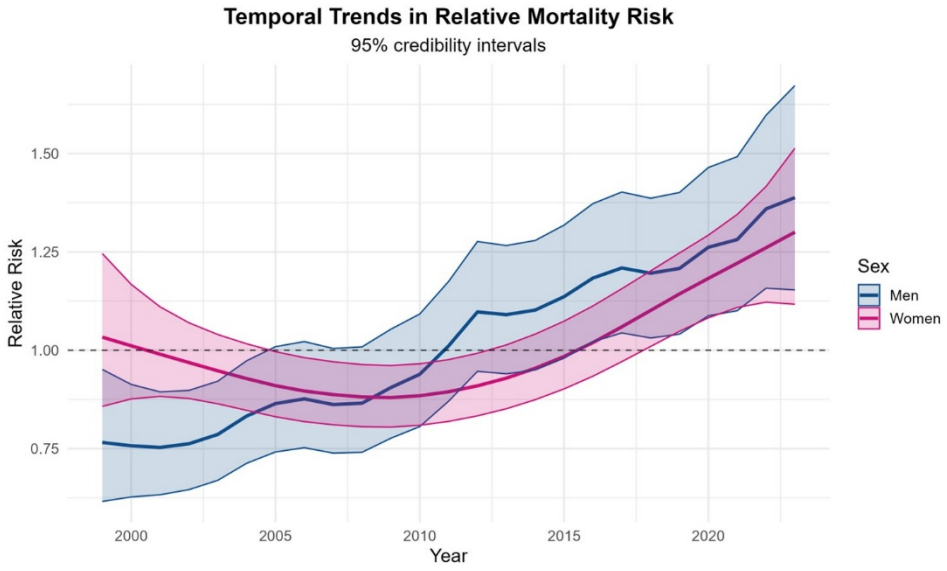

Figure 1: Temporal Trends in Sex-Specific Relative Risk of Anal Cancer Mortality in Spain, 1999–2023

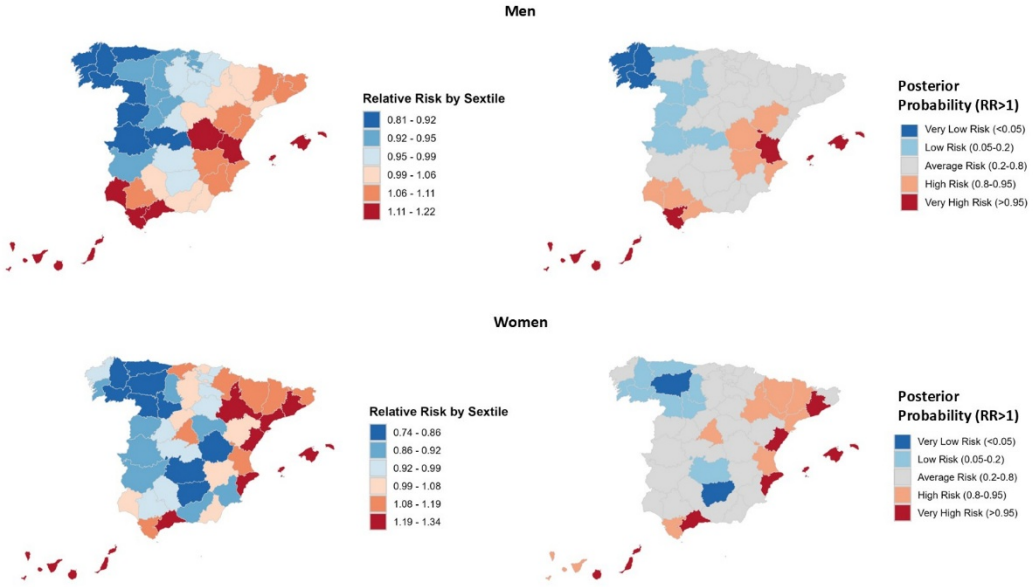

Figure 2: Spatial and Spatio-Temporal Trends Distribution of Anal Cancer Mortality Risk in Spanish Provinces in men, 1999–2023

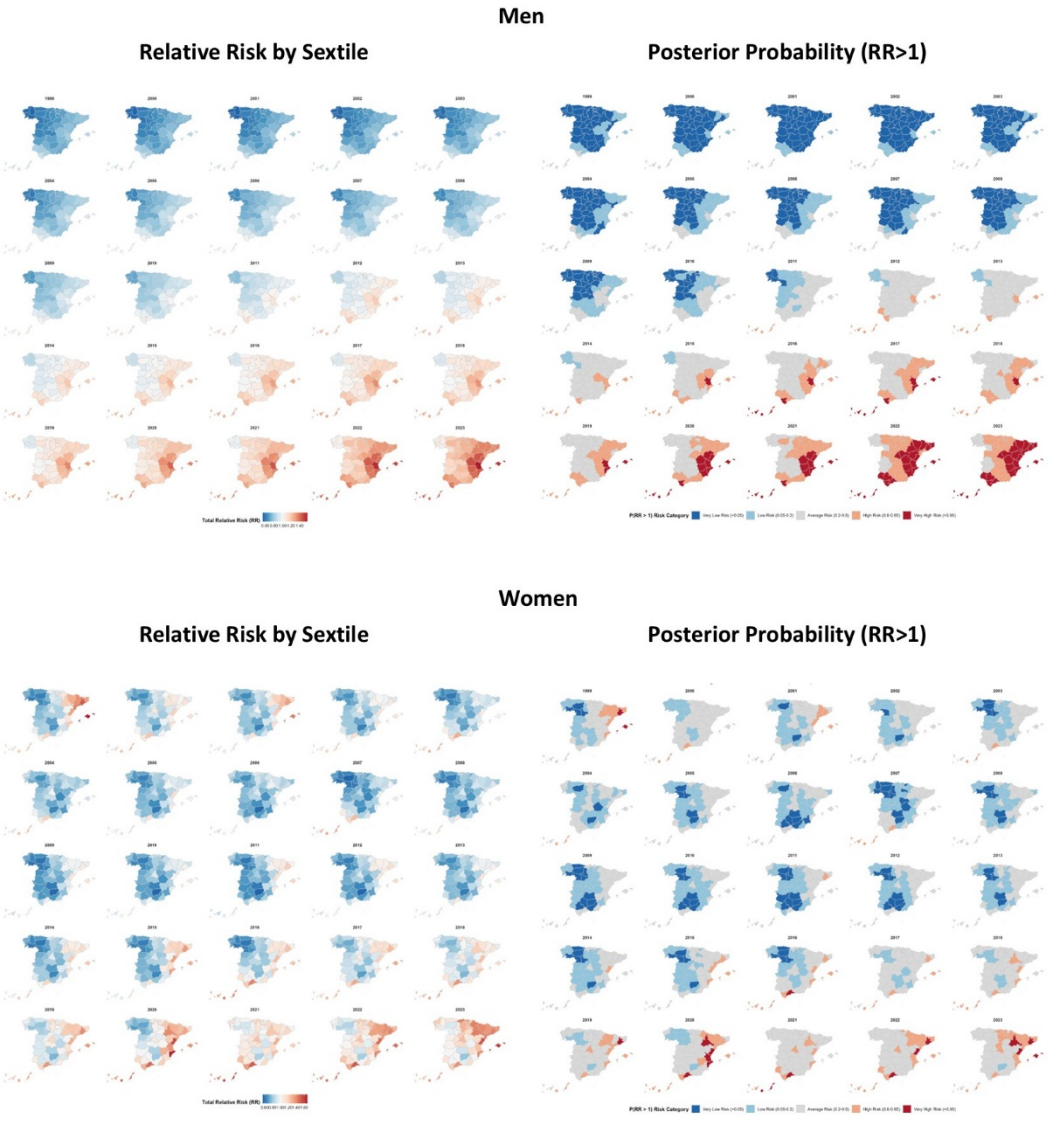

Figure 3: Spatial and Spatio-Temporal Trends Distribution of Anal Cancer Mortality Risk in Spanish Provinces in women, 1999–2023