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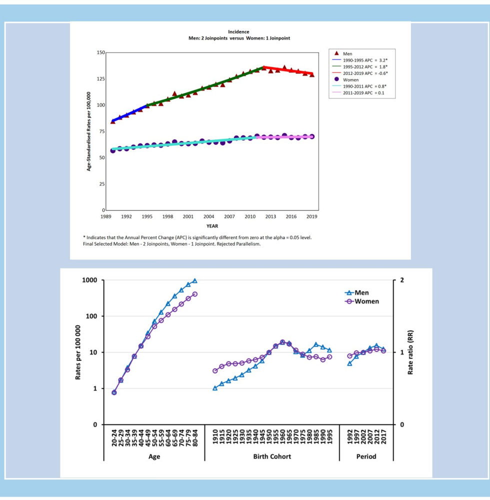
This study examined how age, period and birth cohort influence the incidence of colorectal cancer (CRC) in Spain from 1990 to 2019. Using data from the Global Burden of Disease Study 2019, the researchers identified patterns that showed a steady increase in CRC incidence rates, which were significantly higher in men. Different trends emerged for each sex: men had three phases of increase, slowdown and subsequent decline, while women had a single increase followed by stabilization. The study revealed temporal and age-related changes in CRC risk, which was consistently higher in men. Individuals born since the early 20th century had an increased risk, which peaked in the 1960s and remained stable until the late 1990s. The findings highlight the need for a comprehensive approach to CRC prevention, addressing age, period and cohort factors, and promoting lifestyle changes to reduce incidence and improve public health in Spain.



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Investigating temporal patterns of colorectal cancer incidence in Spain: a comprehensive analysis of age, period and cohort effects, 1990-2019

Lucía Cayuela[1], Gema Flox-Benítez[1,2], Clara Peiró Villalba[1], Álvaro Giráldez-Gallego[3,4], Aurelio Cayuela[5]

[1]Department of Internal Medicine. Hospital Severo Ochoa. Leganés, Madrid. Spain. [2]Palliative Care Working Group. Spanish Society of Internal Medicine (SEMI). Madrid, Spain. [3]Liver Diseases. Institute of Biomedicine of Seville (IBiS). Seville, Andalusia. Spain. [4]Unit for the Clinical Management of Digestive Diseases. Hospital Universitario Virgen del Rocío. Seville, Andalusia. Spain. [5]Unit of Public Health, Prevention and Health Promotion. South Seville Health Management Area. Seville, Spain

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Correspondence: Aurelio Cayuela. Unit of Public Health, Prevention and Health Promotion. South Seville Health Management Area. Hospital Universitario de Valme. Seville, Spain

e-mail: aurelio.cayuela@gmail.com

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Ethics statement: as the data extracted from the Global Burden Study 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.

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Conflict of interest: the authors declare no conflict of interest.

Artificial intelligence: the authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Data availability statement: the data that support the findings of this study are openly available at: https://vizhub.healthdata.org/gbd-results/.

ABSTRACT

Aim: this study aimed to evaluate how age, period, and cohort (A-P-C) impact on colorectal cancer (CRC) incidence in Spain from 1990 to 2019.

Method: using data from the Global Burden of Disease Study 2019, joinpoint analysis was used to identify long-term trends and A-P-C modelling to quantify net drift, local drift, longitudinal age curves, and rate ratios (RRs) of period and cohort effects.

Results: CRC incidence increased steadily in Spain from 1990 to 2019, with a more significant rise in males than in females. The age standardized rates rose from 84.9 to 129.3 cases per 100,000 in males and from 56.9 to 70.3 cases per 100,000 in females. Joinpoint analysis revealed distinct patterns for men and women: male incidence showed three phases (a surge until 1995, a slowdown until 2012, and a subsequent decrease) while female incidence showed a single increase until 2011 and then stabilized. Local drifts increased in all age groups over 45, with stability in males under 45 and a decrease in females aged 30-39. The risk of CRC increased with age, with males consistently having a higher risk than females. The risk of CRC increased over time for both men and women but at different rates. The risk for cohorts born in the early to mid-20th century peaked in the 1960s and remained stable until the late 1990s.

Conclusion: the increasing incidence of CRC in Spain, with distinct patterns by gender and birth cohort, underlines the importance of preventive strategies adapted to temporal and demographic variations to address this public health challenge.

Keywords: Colorectal cancer. Incidence. Age. Period. Cohort. Spain.

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INTRODUCTION

Colorectal cancer (CRC) is a major global health problem. With an estimated 1.9 million new cases and 904,019 deaths in 2022, it is the fourth most common cancer worldwide (1). More than a half of all CRC cases are diagnosed in regions with a high human development index, particularly in Europe, East Asia, and North America (2,3). The age-standardized incidence rate (ASIR) of CRC has steadily increased worldwide since 1990 (2,4), and this trend is expected to continue (5,6). While the ASIR of CRC has also increased in Europe, it has stabilized in recent years (7).

The Global Burden of Disease (GBD) study, which provides the most comprehensive data on disease, injury and risk factors worldwide, provides detailed estimates of CRC incidence in 204 countries and territories, including Spain, from 1990 to 2019 (2,8,9). Age-period-cohort (A-P-C) analysis is a valuable tool for understanding the complex interplay of factors that contribute to changing patterns of CRC incidence and mortality (10,11). It has been widely used in different settings, including Spain and other countries, to disentangle the effects of ageing, period-specific changes in risk factors and cohort-specific exposures on the burden of disease (3,4,6,7,12-14).

Incidence rates of CRC in Spain have traditionally been lower than in other European countries; however, the trend has been increasing over the period 1975-2004. This trend showed a slight decrease in both sexes around 1995, coinciding with a turning point (13,14). Despite this slight decline, CRC remains as an important public health problem (15-17).

To gain a deeper understanding of the factors driving CRC trends in Spain, this study aimed to update and evaluate the impact of A-P-C effects on CRC incidence using GBD-2019 data in Spain from 1990 to 2019. The findings will provide valuable insights for developing personalized prevention strategies.

MATERIAL AND METHODS

An ecological trend study of CRC incidence in Spain from 1990 to 2019 was performed.

Data source

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CRC incidence data in Spain from 1990 to 2019 was obtained, and categorized by sex and age, using the Global Health Data Exchange online query tool. This tool provides access to a comprehensive dataset of health indicators, including CRC incidence, from various sources worldwide. The data for Spain is available at: https://vizhub.healthdata.org/gbd-results/.

This study included all CRCs as defined by the International Classification of Diseases (ICD) coding systems. Both ICD-10 codes (C18-C21, D01.0-D01.3) and ICD-9 codes (153-154, 230.3-230.6) were used to capture the full spectrum of CRCs. This decision aligns with the colorectal continuum model, which recognizes colon and rectal cancers as a single entity arising from a common precursor (18).

In addition, the Data Input Sources Tool provides a detailed overview of the data sources used in the GBD 2019 study, including the specific sources for CRC incidence data in Spain. The main sources of data used for GBD estimation are cancer registries, vital registration systems, sample registration systems, and verbal autopsies (9). This information is available at: https://ghdx.healthdata.org/gbd-2019/data-input-sources.

These data sources are carefully vetted and documented to ensure the accuracy and transparency of the GBD estimates as suggested in the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER), a statement that promotes best practices in reporting health estimates.

The Spanish National Statistics Institute provided population data for the period 1990 to 2019, disaggregated by age, sex, and year (available at: https://www.ine.es/). The population data was estimated on July 1st of each year.

Statistical analyses

ASIRs were estimated by sex using the direct method and the revised European Standard Population (19). The Joinpoint Regression Program, version 4.9.1.0, was used to estimate rates and mortality trends (available at https://surveillance.cancer.gov/joinpoint/). Using the software's default settings, the turning points in the trend and the annual percentage change (APC) for each identified period were calculated. The average annual percentage change (AAPC) between 1990 and 2019, which is a geometrically weighted average of the individual APCs, was also estimated. The weights correspond to the duration of each period within a given period. To assess whether the trends are parallel for both sexes, the "Pairwise comparison" option of the software was used. All calculated rates are given per 100,000 persons. The ratio of males to females was also estimated.

To apply the A-P-C model, the dataset was structured into six five-year periods, spanning from 1990-1994 to 2015-2019. Additionally, the data were divided into 13 five-year age groups, ranging from 20-24 to 80-84 years old. This configuration resulted in a total of 18 birth cohorts, labelled according to the central year of birth, ranging from 1910 to 1995. For each age group and five-year period, a matrix of age-specific death rates was computed, which served as a key element of the A-P-C model analysis.

The A-P-C effects were assessed using the National Cancer Institute A-P-C tools (available at https://analysistools.nci.nih.gov/apc/). The following estimable functions were used: longitudinal age-specific rates, period and cohort rate ratios, and local drifts with net drift. The longitudinal age curve gives the fitted longitudinal age-specific rates in reference cohorts adjusted for period deviations, while the period (or cohort) relative risk (RR) is the period (or cohort) RR adjusted for age and non-linear cohort (or period) effects in a period (or cohort) relative to the reference. The net drift is the overall log-linear trend by calendar period and birth cohort and gives the overall annual percentage change, whereas the local drifts are the log-linear trend by calendar period and birth cohort for each age group and gives the annual percentage change for each age group. All A-P-C analyses used the central age, calendar period and birth cohort group as the reference group. Wald's Chi-squared tests were used to test the significance of estimable functions. Statistical significance was established at $p < 0.05$.

The data used did not require informed patient consent as it was publicly available. Furthermore, the data used in the GBD study adhered to the GATHER, ensuring the credibility and integrity of the findings.

RESULTS

Over the period 1990-2019, an estimated 1,010,186 cases of CRC were diagnosed in Spain. The average annual growth rate was 3.2 %, with a slightly higher increase for males (3.6 %) than for females (2.7 %). Figure 1 presents the ASIR of CRC in Spain from 1990 to 2019, stratified by sex and complemented with joinpoint analysis findings. The graph highlights a consistent upward trend in CRC ASIR for both men and women, with a more pronounced rise

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in males (AAPC: 1.4 %) compared to females (AAPC: 0.7 %). The incidence rate in males rose from 84.9 cases per 100,000 in 1990 to 129.3 in 2019. For females, the rate increased from 56.9 to 70.3. The male-to-female ratio was 1.8 over the whole period, reflecting a higher CRC incidence rate in males than in females. This ratio increased from 1.5 in 1990 to 1.9 in 2019.

Joinpoint analysis demonstrated distinct patterns in CRC ASIR between men and women, indicating non-parallel trends. In males, the analysis revealed three distinct periods: a significant increase from 1990 to 1995, with an annual per cent change (APC) of 3.2 % ($p < 0.05$); a slowing of the upward trend from 1995 to 2012, with an APC of 1.8 % ($p < 0.05$), and a subsequent decrease from 2012 to 2019, with an APC of -0.6 % ($p < 0.05$). In contrast, the incidence trend for females exhibited a single period of increase from 1990 to 2011, with an APC of 0.8 % ($p < 0.05$), followed by a period of stabilization from 2011 to 2019, with an APC of 0.1 % that was not statistically significant.

Figure 2 shows the net drift (annual percentage change in overall expected age-adjusted rates) and local drift (age-specific rates over time) of CRC incidence in Spain from 1990 to 2019. The overall net drift per year was 0.9 % (95 % CI: 0.7 % to 1.1 %) for males and 0.3 % (95 % CI: 0.1 % to -0.5 %) for females. In particular, there was an increase in local drift in all age groups for both sexes from the age of 45. However, for males under 45, there was stability across all age groups. A similar pattern was observed for females, except for a significant decrease in the 30-39 age group, while the other age groups remained stable.

Figure 3 shows the longitudinal age curves, estimated cohort relative risk (RR) trends and estimated period RR trends for CRC incidence rates in Spain by sex. The longitudinal trends (age effect) were generally consistent for both sexes, with a consistently higher incidence risk observed in men. The risk of CRC incidence increased steadily with increasing age in both women and men. The highest incidence rates were found in the 80-84 age group.

In Spain, the RR of CRC incidence showed a steady upward trend over different periods. The RR increased from 0.85 for males and 0.95 for females in 1990-1994 to 1.10 and 1.04, respectively, in 2010-2014. Notably, this upward trend diverged between the sexes, stabilizing for females and decreasing for males.

For men and women born between the early 20th century and the mid-20th century, the risk of CRC incidence showed a steady upward trend, peaking in the 1960s. This increased risk remained at a relatively constant level until the late 1990s. Furthermore, Wald tests revealed that all net drifts, local drifts, cohort effects, and period effects were statistically significant for both sexes (all p-values < 0.001). These findings indicate that the incidence of CRC exhibited a statistically significant difference in local drifts and net drifts, as well as age, period, and cohort deviations. These differences suggest the potential influences of age, cohort, and period on the observed temporal trends in CRC incidence (Table 1).

DISCUSSION

Based on the latest GBD 2019 data, this study examines the trends in CRC incidence in Spain over the last three decades. At the same time, we identify the epidemiological characteristics of CRC in Spain by analyzing age, period and cohort effects of CRC incidence. The results of the study serve as a valuable tool for designing effective CRC prevention strategies.

CRC incidence rates have exhibited distinct patterns across different regions. In developed Western nations, CRC incidence rates have stabilized or even declined, while rapidly developing countries like Shanghai have witnessed an upward trend. Japan, Singapore, and Hong Kong experienced rapid increases in CRC incidence followed by stabilization, mirroring their economic development (20). Conversely, a study found that CRC incidence rates decreased in Somalia, Eswatini, South Africa, Central African Republic, and Libya from 2010 to 2019, a trend contrary to the overall increase observed in most other African countries (21).

CRC ASIR trends in Spain have followed the overall European trend, increasing from 1990 to 2019 (7). However, since 2003, CRC incidence rates have stabilized across Europe (7). Notably, in Spain, the stabilization of CRC incidence rates in females lagged behind the European trend by approximately eight years. Conversely, a significant decrease in CRC incidence rates in males was observed from 2012 onwards, widening the gap between male and female incidence rates.

The increasing incidence of CRC in Spain has been linked to changes in diet, reduced physical activity and ageing (13,14). Economic development has led to changes in dietary habits, with increased consumption of processed foods and reduced intake of fiber and fruit (22,23). These dietary changes have contributed to obesity, a risk factor for CRC (24). Ageing also increases the risk of CRC through genetic mutations and exposure to harmful lifestyle factors

(25).

As regards age effects, CRC incidence typically rises with age, but most populations see a slight decline in incidence at advanced ages. United Kingdom, the United States, and Australia exhibit a more pronounced decline in CRC incidence compared to Japan, Hong Kong, Shanghai, Singapore, and India (20). Spain stands apart, with incidence peaking in the 80-84 age group.

In Spain, CRC incidence trends exhibit distinct patterns across age groups. In younger individuals (aged < 45 years), CRC incidence rates are generally stable, except for a slight decrease in women aged 30-39 years. This is in contrast to the global trend of increasing CRC rates in younger adults (26). In older age groups (> 45 years), CRC incidence rates tend to rise, with men having slightly higher rates than women (similar to what has been observed in other studies) (27). This trend is likely due to a combination of factors, such as increased exposure to risk factors over time, a longer time for precancerous lesions to develop into cancer, and a decline in the effectiveness of the immune system in detecting and eliminating abnormal cells (28).

Studies have shown that CRC incidence rates have increased in Spain over time, affecting all age groups simultaneously (14). This phenomenon, known as period effects, has also been observed in other countries (20). Our analysis showed a significant increase in CRC incidence rates for both sexes between 1990 and 2014, especially for males. However, after 2014, a clear shift emerged, with CRC rates stabilizing in females and even declining in males. Due to the short-term nature of these observations, longer-term monitoring is essential to capture the complex mechanisms driving these shifts.

Western populations, particularly those born in the 1950s and 1960s, exhibit an escalating trend in CRC incidence, reflecting a cohort-specific vulnerability (20). Asian populations, excluding India, present a converse trend, showcasing a decline in CRC incidence among individuals born in the 1950s. Notably, Japan mirrors Western patterns, experiencing an increasing trend in CRC incidence among those born in the 1960s (3,20). Hong Kong, Shanghai and Singapore showed signs of an upward trend in their more recent cohorts (29). In contrast, Spain has maintained a stable CRC risk for individuals born since the 1970s. It is important to note, however, that the confidence intervals for these trends in Spain are wider, indicating some uncertainty in the stability assessment. Despite the potential efficacy of screening strategies and colonoscopic polypectomy in reducing CRC incidence in Western countries, their impact on the current younger age groups is anticipated to be less pronounced compared to older generations. This discrepancy arises from the standard recommendation of CRC screening for individuals aged 50 and above (30).

The study has many strengths. It used a robust statistical methodology including A-P-C modelling to disentangle the complex interaction of A-P-C effects on CRC incidence. The long follow-up of older birth cohorts not only increased the reliability and power of the results but also enhanced international comparability. In particular, the study treated CRC as a single entity, recognizing the differential impact of risk factors on different subsites (colon *vs* rectum, left *vs* right colon).

However, the study has several limitations. First, reliance on routinely collected data is limited by the age-related increase in CRC incidence, which may underestimate cohort effects in younger individuals. Second, the linear dependence between age, period and cohort poses a challenge to model identifiability and requires caution when interpreting the results. Finally, the study could not examine temporal variation in risk factors and screening due to a lack of individual-level data.

CONCLUSION

This study provides valuable insights into the complex factors influencing CRC incidence in Spain and offers a roadmap for effective prevention strategies. By addressing the interplay between age, period and cohort effects, as well as lifestyle and dietary changes, Spain can strive to further reduce CRC incidence.

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

Null hypothesis		Males		Females	
	df	Chi-squared	p-value	Chi-squared	p-value
Net drift = 0	1	61.1	< .001	11.3	< .001
All age deviations = 0	11	2,067.9	< .001	1,580.2	< .001
All period deviations = 0	4	119.3	< .001	19.7	< .001
All cohort deviations = 0	16	126.5	< .001	137.4	< .001
All period RR = 1	5	156.3	< .001	27.4	< .001
All cohort RR = 1	17	1,267.9	< .001	391.1	< .001
All local drifts = net drift	13	125.6	< .001	136.0	< .001

RR: rate ratios.

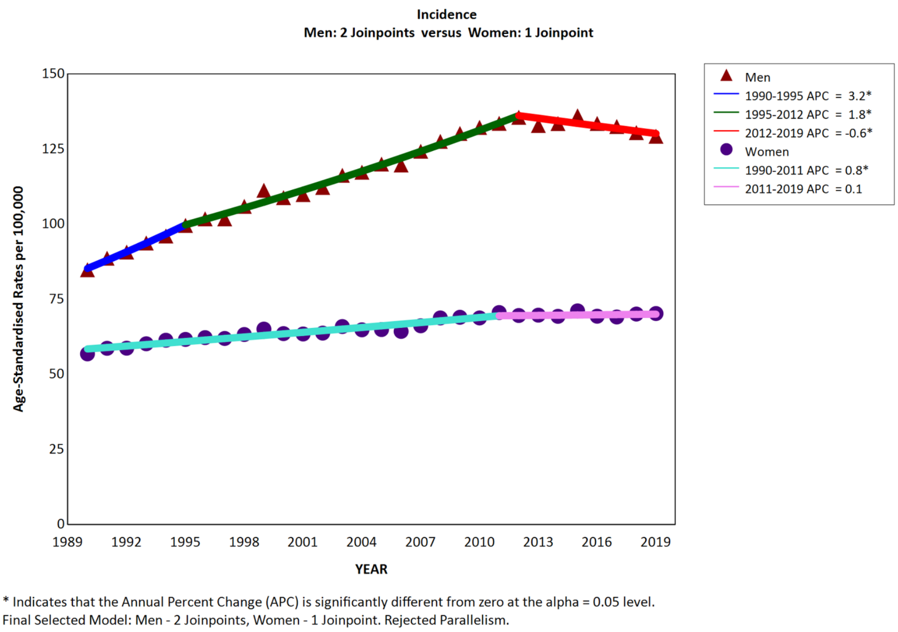

Fig. 1. Age standardized incidence rates (all ages) and trends estimated by joinpoint analysis for colorectal cancer in Spain over the period 1990-2019 by sex.

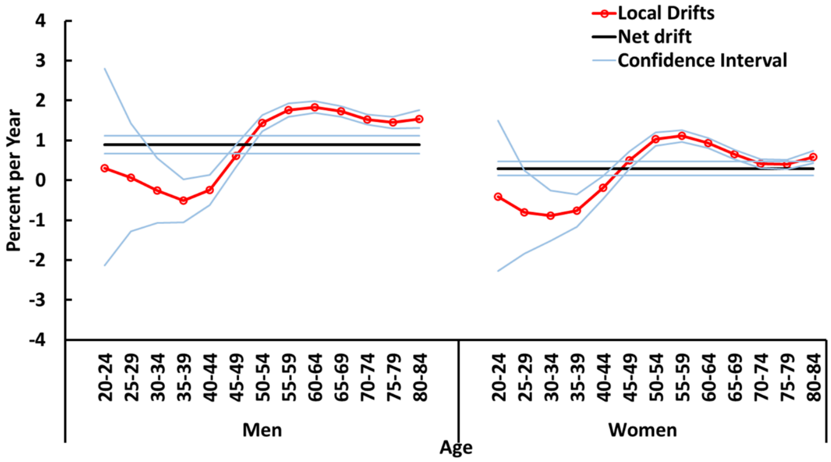

Fig. 2. Local and net drift of colorectal cancer incidence in Spain from 1990 to 2019, for men and women.

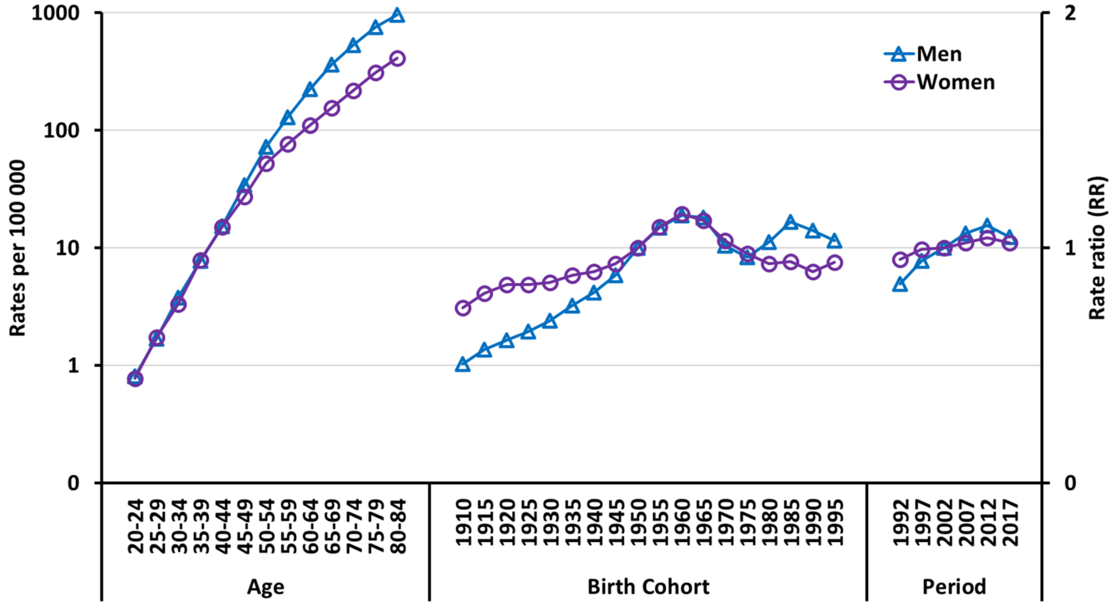

Fig. 3. Age-period-cohort (APC) modelling results for colorectal cancer incidence in Spain from 1990 to 2019, for males and females.