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Authors:
Lucía Cayuela, Victoria Achaval, Gema Flox-Benítez, Aurelio Cayuela Domínguez

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Shifting trends in pancreatic cancer incidence across generations in Spain (1992-2021)

Lucía Cayuela (a)	luccayrod@gmail.com	https://orcid.org/0000-0003-1524-0501
Victoria Achaval (a)	vikachaval@gmail.com	https://orcid.org/0000-0001-8992-766X
Gema Flox-Benítez (a,b)	gflox@hotmail.com	https://orcid.org/0009-0006-5364-7918
Aurelio Cayuela (c)	aurelio.cayuela@gmail.com	https://orcid.org/0000-0002-4936-9402

Institutions:

a) Department of Internal Medicine, Hospital Severo Ochoa, Leganés, Spain.

b) Palliative Care Working Group of the Spanish Society of Internal Medicine (SEMI).

c) Unit of Public Health, Prevention and Health Promotion. South Seville Health Management Area. Seville, Spain.

Correspondence: Aurelio Cayuela. Unit of Public Health, Prevention and Health Promotion. South Seville Health Management Area. Hospital Universitario de Valme. Seville, Spain. Mail: aurelio.cayuela@gmail.com

Final Declarations

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Author Contributions: All authors contributed to the conception and design of the study, data acquisition, analysis, and interpretation. They were involved in drafting the manuscript 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 Statement: This study used anonymized data from the Global Burden of Disease (GBD) study and was conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. Since no identifiable personal data were used and participants could not be traced, informed consent and ethics committee approval were not required. The study also adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER), which support the credibility and transparency of the findings.

Data Availability: The data supporting the conclusions of this study are publicly available at: https://vizhub.healthdata.org/gbd-results/

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Background: This study examines trends in pancreatic cancer (PC) incidence in Spain from 1992 to 2021, focusing on sex and age-specific patterns and the influence of age, period, and birth cohort.

Methods: Data from the Global Burden of Disease 2021 study and population estimates from the Spanish National Statistics Institute were analyzed. Age-standardized incidence rates (ASIR) were calculated. Joinpoint regression and Age-Period-Cohort (A-P-C) models were applied to assess temporal trends and the effects of age, period, and birth cohort, with a particular focus on early-onset pancreatic cancer (EOPC), defined as diagnosis before age 50.

Results: PC cases in Spain nearly doubled from 3,970 in 1992 to 7,830 in 2021. For individuals aged 50 and older, ASIR steadily increased before stabilizing or declining after 2018. In those under 50, trends varied by sex: a decline in men (average annual percentage change (AAPC): −1.2%) and a slight initial increase followed by a sharper decrease in women (AAPC: −0.0%). A-P-C analysis identified age as the primary incidence driver, with modest period effects and significant cohort effects. Peak relative risks occurred in men born 1952-1957 and women born 1962-1967, with subsequent cohorts showing declining risk.

Conclusions: PC incidence in Spain has risen, largely due to an aging population. However, favourable cohort effects, likely linked to reduced smoking and healthier lifestyles, along with recent declines in ASIR, suggest the effectiveness of public health efforts. Despite declining EOPC trends, the increasing burden in older adults underscores the need for ongoing research and targeted prevention strategies.

Keywords: Pancreatic neoplasms. Incidence. Aged. Age distribution. Joinpoint analysis. Age-period-cohort analysis. Spain.

Tendencias cambiantes en la incidencia del cáncer pancreático a través de generaciones en España (1992-2021)

Antecedentes: Este estudio analiza las tendencias en la incidencia del cáncer pancreático (CP) en España entre 1992 y 2021, destacando los patrones por edad y sexo, y el impacto de la edad, el periodo y la cohorte de nacimiento.

Métodos: Se utilizaron datos del estudio Global Burden of Disease 2021. Se calcularon tasas de incidencia estandarizadas por edad y se aplicaron modelos de regresión Joinpoint y Edad-Periodo-Cohorte (E-P-C) para evaluar las tendencias y los efectos de la edad, el periodo y la cohorte. Se prestó especial atención al cáncer pancreático de inicio temprano, diagnosticado antes de los 50 años.

Resultados: Los casos de CP en España casi se duplicaron de 3,970 en 1992 a 7,830 en 2021. En mayores de 50 años, la TIE aumentó y luego se estabilizó o disminuyó. En menores de 50 años, las tendencias fueron mixtas: los hombres mostraron una disminución, mientras que las mujeres mostraron un aumento seguido de una caída. El análisis A-P-C mostró que la edad fue el principal factor, con efectos modestos del periodo y efectos significativos de la cohorte. Los picos de riesgo relativo se observaron en hombres nacidos entre 1952 y 1957 y en mujeres nacidas entre 1962 y 1967, con cohortes posteriores mostrando una disminución del riesgo.

Conclusiones: La incidencia de CP ha aumentado principalmente por el envejecimiento de la población, pero los esfuerzos de salud pública, como la reducción del tabaquismo, están mostrando efectos positivos. La carga creciente en adultos mayores resalta la necesidad de estrategias de prevención y detección temprana.

Palabras clave: Neoplasias pancreáticas; Incidencia; Edad avanzada; Distribución por edad; Análisis Joinpoint; Análisis Edad-Periodo-Cohorte; España

Lay summary

This study analyses trends in pancreatic cancer (PC) in Spain from 1992 to 2021. While the total number of cases nearly doubled, recent data show a decline in age-standardized incidence rates since 2018, likely due to better tobacco control, diet, and healthcare. PC rates increase sharply after age 50, with a growing burden among older adults, while cases in younger people remain stable or decrease. The gender gap in PC is narrowing, partly due to changes in smoking and lifestyle factors. The findings suggest that public health efforts, especially in smoking control, have helped reduce PC risk in younger generations, but the rising incidence in older adults calls for continued prevention strategies.

Introduction

Pancreatic cancer (PC) remains one of the most lethal malignancies worldwide, largely due to late-stage diagnosis, aggressive tumour biology, and limited treatment options[1]. In 2022, GLOBOCAN estimated 510,992 new PC cases and 467,409 deaths globally, with nearly identical age-standardized incidence and mortality rates (4.7 and 4.2 per 100,000, respectively), underscoring its high fatality[2].

A growing concern in cancer surveillance is the increasing incidence of PC among younger individuals[3–6]. Early-onset pancreatic cancer (EOPC), typically defined as diagnosis before age 50, is emerging as a distinct clinical and epidemiological entity. Emerging evidence suggests that early-onset pancreatic cancer (diagnosed before age 50) may represent a distinct entity with potentially different genetic predispositions and tumour biology compared to later-onset disease. Despite the younger patients' generally better physical status, EOPC often exhibits a disproportionately aggressive course, likely reflecting a complex interplay of genetic susceptibility, environmental exposures, and modifiable risk factors[4,7,8]. The Global Burden of Disease (GBD) 2021 study reports a 73% increase in global EOPC cases between 1990 and 2021, accompanied by parallel rises in prevalence and mortality[6,9].

In Spain, the global rise in PC incidence is similarly evident, representing a growing public health concern. Although prior investigations[10–15], including a recent REED (2024)

publication[11], have predominantly described national mortality patterns using death-certificate data and diverse statistical approaches, comprehensive analyses of incidence trends remain scarce. Leveraging the Global Burden of Disease (GBD) 2021 Study, this work characterizes PC incidence in Spain from 1992 through 2021. We apply Joinpoint regression to detect significant temporal shifts and employ Age-Period-Cohort (A-P-C) modelling to partition the contributions of ageing, calendar period, and birth cohort[5,16–19]. By focusing on incidence dynamics and placing particular emphasis on EOPC, our study seeks to uncover novel insights with direct implications for clinical management and population-level prevention strategies in Spain.

Methods

Study Design and Data Sources

This ecological trend analysis explored temporal patterns in pancreatic cancer (PC) incidence in Spain from 1992 to 2021. Incidence data were sourced from the Global Burden of Disease (GBD) 2021 Study, coordinated by the Institute for Health Metrics and Evaluation (IHME). The GBD study integrates data from national and regional cancer registries, vital statistics systems, hospital records, surveys, and verbal autopsies. Data were accessed via the Global Health Data Exchange platform (https://ghdx.healthdata.org). Age- and sex-specific incidence counts were extracted for each year from 1992 to 2021.

In GBD 2021, pancreatic cancer was identified using the International Classification of Diseases, 10th Edition (ICD-10), specifically the codes C25-C25.9 and Z85.07, which encompass both common and less common pancreatic malignancies. Further details regarding the methodology and data processing for quantification are available in published studies[20].

Population estimates, disaggregated by age, sex, and year, were obtained from the Spanish National Statistics Institute (INE) (https://www.ine.es). These mid-year estimates were used as denominators for calculating age-specific and age-standardized incidence rates (ASIR).

Statistical Analysis

ASIRs were calculated using the direct method, with the 2013 European Standard Population as the reference. Rates were stratified by sex and age group (<50, ≥50, and all ages), expressed per 100,000 population.

Temporal trends were assessed using Joinpoint regression (version 5.0.2, National Cancer Institute). This method identifies significant changes in trends (joinpoints) and calculates the annual percent change (APC) for each segment. Additionally, the average annual percent change (AAPC) for the entire study period was computed, weighted by segment length.

To investigate the effects of age, calendar period, and birth cohort on pancreatic cancer (PC) incidence, we employed the NCI's age-period-cohort (A-P-C) web tool (https://analysistools.nci.nih.gov/apc/). The analysis included six 5-year periods (1992–1996 to 2017–2021) and sixteen 5-year age groups (15–19 to 90–94 years), resulting in 21 overlapping 5-year birth cohorts (central years ranging from 1902 to 2002). Age-specific incidence matrices were input into the A-P-C model, which calculated various indexes, including net drift, local drifts (annual percentage change for each age group), longitudinal age curves (age-specific rates), period rate ratios (comparisons of age-specific rates across periods), and cohort rate ratios (comparisons of age-specific rates across cohorts). Statistical significance was determined using Wald's chi-square tests. Further details on the methodology of the A-P-C web tool are provided in previous literature[21].

Ethics

As the study is based on publicly available and de-identified data from the GBD 2021 database, ethical approval and informed consent were not required.

Results

The number of PC cases in Spain nearly doubled from 3,970 in 1992 to 7,830 in 2021. Although the proportion of cases in individuals under 50 decreased from 6.0% (237 cases) to 3.7% (286 cases), the absolute number of cases in this age group remained stable. In contrast, the proportion of cases in individuals aged 50 and older increased from 94.0% (3,734 cases) to 96.3% (7,544 cases).

Temporal Trends in ASIR (All Ages)

For both sexes, the ASIR showed a moderate increase. Among men, the overall AAPC was +0.4%, with three distinct phases: a significant rise from 1992 to 2004 (APC: +1.0%), a slower increase from 2004 to 2018 (APC: +0.5%), and a decrease from 2018 to 2021 (APC: -2.7%).

In women, ASIR increased from 11.56 per 100,000 in 1992 to a peak of 14.44 in 2016, then decreased to 13.16 in 2021. The overall AAPC was +0.4%. Joinpoint analysis revealed a non-significant decrease from 1992 to 1998 (APC: -0.3%), a significant rise from 1998 to 2017 (APC: +1.2%), and a subsequent decrease from 2017 to 2021 (APC: -2.1%).

Trends Among Individuals Aged 50 and Older

Among men aged 50 and older, ASIR increased from 39.75 per 100,000 in 1992 to 48.69 in 2017, then decreased to 44.91 in 2021. The overall AAPC was +0.4%. Joinpoint analysis identified a significant increase from 1992 to 2004 (APC: +1.1%), followed by a slower rise from 2004 to 2018 (APC: +0.6%) and a decline from 2018 to 2021 (APC: -2.6%). For women aged 50 and older, ASIR rose from 28.63 in 1992 to 35.81 in 2016, then decreased to 32.71 in 2021. The AAPC was +0.4%. Joinpoint analysis revealed stable rates until 1998, followed by a significant rise from 1998 to 2017 (APC: +1.2%) and a subsequent decline from 2017 to 2021 (APC: -2.0%).

Trends in Individuals Under 50 Years of Age

For individuals under 50, trends varied. Among men, ASIR decreased from 1.57 per 100,000 in 1992 to 1.07 in 2021, with an overall AAPC of -1.2%. Joinpoint analysis showed an initial increase from 1992 to 2003 (APC: +0.8%), followed by a decline from 2003 to 2018 (APC: -1.8%) and a sharper decrease from 2018 to 2021 (APC: -5.7%).
In women, ASIR increased from 0.64 in 1992 to a peak in the mid-2000s, then declined to 0.66 in 2021. The overall AAPC was negligible (-0.0%). Joinpoint analysis showed an increase from 1992 to 2007 (APC: +1.6%), followed by declines from 2007 to 2018 (APC: -0.8%) and from 2018 to 2021 (APC: -5.3%).

Age-Period-Cohort Analysis

The age-period-cohort (A-P-C) analysis revealed significant age, period, and cohort effects on PC incidence in Spain from 1992 to 2021, with marked differences between sexes (Table 1, Figures 2 and 3).

Net drift was non-significant in both men (−0.24%) and women (+0.31%), indicating stable overall trends over time (Figure 2). In contrast, **local drift** revealed age-specific variation. In men, incidence declined in the 30–49 age groups and increased from age 55 onward, peaking at +0.9% annually in the 85–89 age group. Rates remained stable for men in the 15–29 and 50–54 age groups. In women, declines were observed in ages 20–34, with increases from age 45 onward, peaking at +1.3% in the 55–59 group. Rates remained stable for women in the 15–19 and 35–44 age groups.

Age effects were strong and exponential (Figure 3, left panel). Among men, incidence increased from 0.04 per 100,000 at ages 15–19 to 135.80 at ages 90–94. In women, rates rose from 0.03 to 153.43 across the same age span. Men had higher rates in most age groups, except ≥90, where women surpassed men.

Period effects were modest (Figure 3, centre panel). Men's period relative risks (RRs) remained relatively stable, with a slight decline by 2019. In women, RRs increased modestly, peaking in 2014, then stabilized through 2019.

Cohort effects were more pronounced (Figure 3, right panel). In men, cohort RRs rose steadily from early 20th-century birth cohorts, peaking in those born around 1952–1957, followed by a sharp decline in more recent cohorts. Women showed a similar pattern with a slightly delayed peak in the 1962–1967 cohorts, also followed by declining RRs. These trends highlight strong generational effects influencing pancreatic cancer risk.

Discussion

This study analyses PC incidence trends in Spain from 1992 to 2021, showing a significant increase in cases, primarily driven by demographic aging. The proportion of cases in individuals aged 50 and over rose from 94.0% to 96.3%, reflecting the growing influence of age on the national PC burden. However, recent data reveal a more nuanced trend, with age-standardized incidence rates (ASIRs) stabilizing and declining in recent years. This aligns with trends observed in high-income countries and global estimates from GBD[4,6,9,16,22] and GLOBOCAN[5,23] studies, which identify PC as a growing global health challenge. Notably, the

number of cases in those under 50 has remained stable, leading to a decreasing share of total cases in this age group. These findings suggest that while aging continues to drive the overall burden of PC, changes in risk factor exposure and public health interventions may be moderating incidence trends at the population

Despite a modest overall rise in ASIRs (AAPC: +0.4% in both sexes), Joinpoint analysis revealed a shift from increasing rates in the early 2000s to a plateau, followed by a significant decline starting around 2018. Between 2018 and 2021, ASIRs fell by −2.7% in men and −2.1% in women, likely reflecting the delayed impact of tobacco control, dietary improvements, and healthcare advances. Cohort effects identified through A-P-C analysis help contextualize key inflection points in incidence trends. The rise in ASIR for both sexes beginning in the late 1990s coincides with increasing relative risks among mid-20th-century birth cohorts (peaking in 1952–1957 for men and 1962–1967 for women), likely reflecting greater lifetime exposure to risk factors. In contrast, the decline in ASIR observed from 2017–2018 aligns with lower relative risks in more recent cohorts, suggesting shifts in environmental exposures, lifestyle behaviors, or diagnostic practices. A-P-C modelling thus provides valuable insight into the generational forces driving the trends revealed by Joinpoint analysis.

Age- and Sex-Specific Trends

Spain's PC incidence demonstrated distinct age- and sex-specific trends, with a narrowing gender gap, particularly among younger individuals. Among those aged ≥50, ASIRs initially rose, then slightly declined, maintaining a male-to-female ratio of approximately 1.4. In contrast, trends among those under 50 were more favourable, with a decline in men (male-to-female ratio dropping from 2.5 to 1.6) and a rise followed by a steeper decline in women. These shifts, despite low EOPC rates, reflect changes in generational risk and the impact of public health efforts, particularly in narrowing the gender gap, especially among those under 50. This contrasts with rising EOPC rates in regions like Shanghai, where westernized diets and obesity are contributing to increasing incidence[16].

The male-to-female ASIR ratio of approximately 1.4 is consistent with global patterns, reflecting a mix of behavioural, occupational, and biological factors[24]. Historically, men have had greater exposure to tobacco and alcohol, which contributes to this disparity[11,13].

However, as the smoking prevalence gap narrows in Spain[11], this may signal a future reduction in sex disparities in PC incidence, akin to trends seen in lung cancer[25].

Age-Period-Cohort Analysis

The Age-Period-Cohort (A-P-C) framework elucidates these patterns further. Age remains the primary driver of PC incidence, with steep increases after age 55 and peaking in the oldest age groups, particularly among men[18,26]. This aligns with international findings, reflecting the cumulative exposure to risk factors such as smoking, obesity, and diabetes, as well as biological aging processes—such as impaired DNA repair and reduced immune surveillance—which increase cancer susceptibility[5,9,16,18,22], and potentially differing biological mechanisms in early- versus late-onset disease.

Spain's cohort patterns suggest that long-term public health interventions have effectively reduced PC risk, especially among men. Relative risks rose steadily until the 1952–1957 birth cohorts, followed by a sharp decline, likely due to early and effective tobacco control policies. Women exhibited a similar trajectory but with a temporal lag, consistent with later smoking uptake and cessation compared to men[25,27].

This favourable generational pattern contrasts with global trends. For example, in Shanghai, rising PC risks were observed among cohorts born between 1983 and 1993[18] , while U.S. studies identified increasing incidence in more recent birth cohorts, particularly among non-Hispanic whites[26] identified increasing incidence in more recent U.S. birth cohorts, particularly among non-Hispanic whites. French data also show significant increases in lifetime risk for men born between 1900 and 1950[28]. Spain's deviation from these patterns underscores the success of sustained public health efforts—especially tobacco control, but also improvements in diet, physical activity, and healthcare access—in reducing generational PC risk. These findings highlight the potential of comprehensive, long-term public health strategies in altering cancer trajectories and offer a model for countries still experiencing rising cohort-specific trends[5,16].

Period effects on PC incidence in Spain were modest, suggesting that recent advances in diagnostics and healthcare access had limited impact on long-term trends. This contrasts with stronger period effects observed in other regions[18,19,28]. Spain's relatively stable period-specific relative risks—with a slight decline in men and a modest increase in

women—indicate that aging and cohort-related exposures are more influential than short-term healthcare improvements [5,26]. These trends likely reflect gradual reductions in generational risk driven by sustained public health efforts and lifestyle changes.

Public Health and Prevention

Our findings underscore the importance of age-specific PC prevention strategies. For older, high-risk individuals, enhancing early detection is crucial. The American Gastroenterological Association (AGA) and the National Comprehensive Cancer Network (NCCN) recommend genetic testing for individuals with a family history of PC or early-onset diagnoses to identify genetic risk factors[29]. For younger individuals, prioritizing genetic screening and reducing early-life exposures is essential. Population-wide interventions targeting modifiable risks, such as tobacco use, obesity, and diabetes, are crucial, as the recent ASIR decline since 2018 suggests potential benefits. However, with Spain's aging population, scaling up prevention efforts will be necessary to manage the expected increase in absolute cases.

Strengths and Limitations

This study draws on nationally representative data from the GBD 2021 dataset and applies robust methods, including Joinpoint regression and A-P-C modelling, to analyze long-term trends. Limitations include its ecological design, which precludes individual-level causal inference, and reliance on modelled rather than registry-based data, potentially affecting accuracy—especially in underrepresented age groups. Regional trends cannot be assessed, and ICD-10 coding limits subtype and biological detail. Future studies should explore regional and molecular subtype variations as data become available.

Conclusion

PC incidence in Spain has increased over the past three decades, largely driven by aging and historical risk factors. However, declining cohort-specific risk related to reduced smoking and healthier lifestyles, along with recent declines in ASIR, suggest that public health interventions are having an impact. While EOPC incidence trends are declining, the growing burden among older adults emphasizes the need for continued research and

targeted .

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prevention strategies.

Table 1: Wald Chi-square test results for estimable parameters in the age-period-cohort (APC) model of pancreatic cancer incidence in Spain (1992–2021), by sex.

		MEN		WOMEN	
NULL HYPOTHESIS	**df**	**Chi-Square**	**P-Value**	**Chi-Square**	**P-Value**
NETDRIFT = 0	1	1.9	0.171	2.4	0.125
ALL AGE DEVIATIONS = 0	14	3446.2	<0.001	2024.7	<0.001
ALL PERIOD DEVIATIONS = 0	4	12.5	0.014	32.2	<0.001
ALL COHORT DEVIATIONS = 0	19	211.0	<0.001	69.5	<0.001
ALL PERIOD RR = 1	5	15.2	0.010	34.1	<0.001
ALL COHORT RR = 1	20	389.6	<0.001	424.7	<0.001
ALL LOCAL DRIFTS = NET DRIFT	16	205.0	<0.001	64.8	<0.001

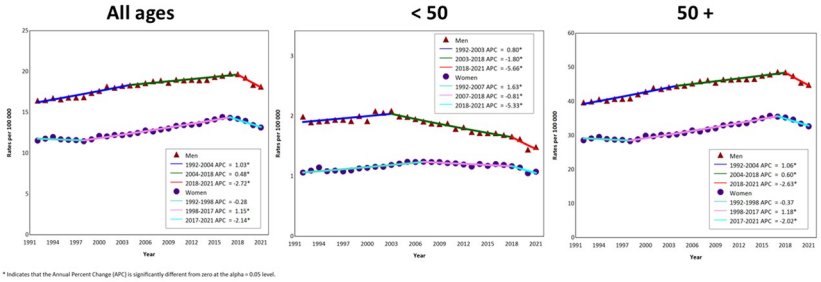

Figure 1. Age-standardized incidence rates of pancreatic cancer per 100,000 population in Spain (1992–2021), by sex and age group (<50, 50+, and all ages), with joinpoint regression analysis results.

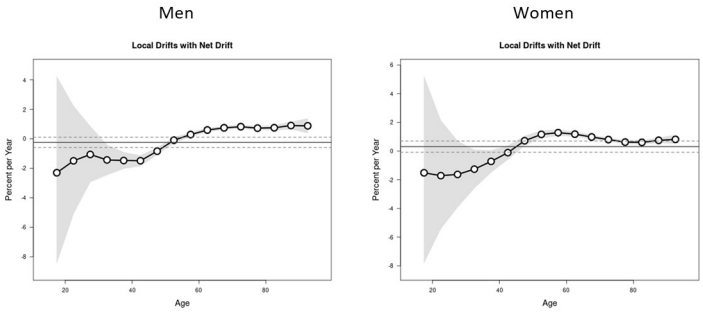

Figure 2. Local and net drifts in pancreatic cancer incidence rates, with 95% confidence intervals (shaded regions for local drift, horizontal lines for net drift).

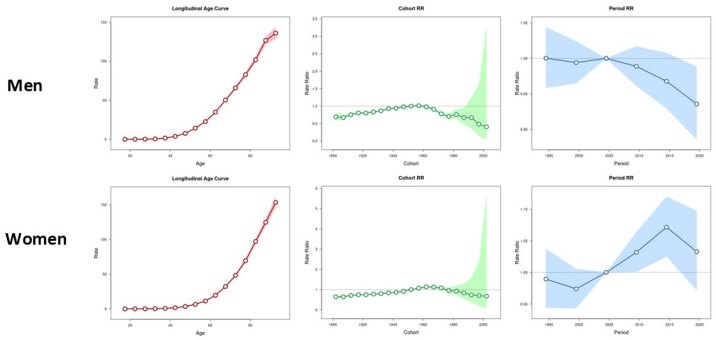

Figure 3. Age-period-cohort analysis of pancreatic cancer incidence: Longitudinal age trends, period relative risks (RRs), and cohort relative risks (RRs), with 95% confidence intervals (shaded).