RESEARCH ARTICLE

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Spatio-Temporal Distribution of Colorectal Cancer Incidence in Córdoba, Argentina

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Abstract

Objective: To study the trend of colorectal cancer (CRC) incidence, considering its spatiotemporal distribution and its association with the level of urbanisation in Córdoba, Argentina (2004-2014). **Methods:** An ecological and longitudinal study was conducted in the province of Córdoba (the second most populated of the country) using annual data for the period 2004-2014. Age-standardised incidence rates (ASIR) (standard national and world population) by sex were calculated for Córdoba and its 26 departments for CRC using the provincial tumour registry database. Joinpoint regression models were adjusted to provincial ASIRs. Departments ASIRs were mapped in quintiles. The departments were grouped into three strata according to urbanisation: High (n1=6, >107,000 people); Intermediate (n2=13, 33,000-107,000 people); and Low (n3=7, <33,000 people). The spatio-temporal correlation analysis of the departments' rates was fulfilled using the multilevel modelling strategy. **Results:** ASIRs of CRC in Córdoba province were 30.9 ±1.5 and 24.3 ±1.5 cases/100,000 for men and women, respectively. During 2004-2014, ASIRs tended to decrease (annual per cent change: -0.6; CI95% -1.8, 0.6). Maps reflected different geospatial patterns by sex. CRC incidence in males was higher than in females in all strata (high urbanisation, incidence rate ratios (IRR): 1.66; intermediate, IRR: 1.59; and low, IRR: 1.40). There was a significant downward temporary variation in the most populous departments (3% per year). **Conclusions:** CRC presents a non-random spatial pattern across the territory with a decreasing temporal variation in the most populous departments. Differential incidence and temporospatial tendency burden in Córdoba involve sex and urbanisation. Men continue to be the population at the greatest risk; this pattern is more noticeable in most urban settings.

Keywords: Colorectal neoplasms- urbanisation- mixed-effects model- epidemiology

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Introduction

Colorectal cancer (CRC) is the third most diagnosed malignancy and the second leading cause of cancer death worldwide (IARC, 2020). CRC incidence rates vary widely around the world, with distinct gradients between levels of human development and trends pointing toward widening disparities and a growing burden in countries in transition (Bray et al., 2018). Currently, CRC is considered one of the most obvious indicators of cancer transition in countries undergoing socioeconomic development. Colorectal cancer rates show a strong positive gradient with the Human Development Index (IARC, 2020; Vuik et al., 2019). The National Programme for the Prevention and Early Detection of Colorectal Cancer (created in 2013) reports a slightly higher incidence of CRC in men (1.2:1) and a more frequent age of diagnosis between 50 and 75 years old in both sexes (80%) (Gualdrini and Iummato, 2011).

Only a few studies focus on spatio-temporal trends because the data must come from areas with population-based cancer registries (PBCRs), which are the gold standard for providing data on cancer incidence in a population. Since 2003 the province of Córdoba has had a Population Tumour Registry (PTR) that complies with IARC standards. Diaz et al., (2009) analysed the spatial distribution of cancer incidence in the province and found a non-random spatial distribution of CRC.

The global number of cancer patients is expected to increase in the next 50 years due to the strong influence of demographic changes, such as ageing and population growth (Soerjomataram and Bray, 2021). In Latin America, the incidence of CRC will increase by 65% (>2.2 million) by 2030 (Sierra and Forman, 2016). Therefore, the current understanding of CRC patterns and their local evolution is imperative to guide prospects for burden and

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reduction through cancer prevention and care.

Argentina and, particularly, Córdoba have high rates of CRC (the second most incident cancer) (Abriata, 2015; Díaz, 2009) associated with socio-environmental factors. Among them it is relevant to highlight the particular dietary pattern of Argentina, with a high consumption of red meat cooked at high temperatures with methods that form a toasted crust. This process generates high concentrations of heterocyclic aromatic amines and polycyclic aromatic hydrocarbons, which produce cell toxicity (Navarro et al., 2004; Pou et al., 2014; Reartes et al., 2016) and are recognized as carcinogenic (IARC, 2016). In addition, in this geographical area, there is a high prevalence of smoking, overweight and obesity, -recognized modifiable risk factors for CRC- as well as an ageing population. In this context, the objective of this study was to identify the trend in the incidence of the second most incident malignant cancer in Córdoba, considering its spatiotemporal distribution and assessing its association with the degree of urbanisation, from 2004 to 2014.

Materials and Methods

Study Design and Data

An ecological time-series study was conducted between 2004 and 2014 in Córdoba, Argentina using data from the PTR, which covers a central area of Argentina with 3.7 million people (about 9% of the national population and the second most populated, 80% of the population in cities), the province of Cordoba (INDEC, 2022). The province is divided into 26 departments. The Capital Department is the most densely populated, with 2,367 people/km2; five departments have between 100,000 and 200,000 people, and only two have less than 5,000 people (the lowest population density, minimum 1.3 people/km2). The provincial territory presents a mixed geography, with a variety of topographies, climates, and socio-environmental differences.

The PTR dataset includes all incident cases identified by age, sex, and tumour location. In addition, department population size data were obtained through population estimates by exponential interpolation based on census information published by the National Institute of Statistics and Census (INDEC, 2012). Age-adjusted standardised incidence rates (ASIRs) per 100,000 person-years by sex, and 5-year age groups of CRC (ICD-10:C18-C20) were calculated for all the departments (n=26) and years. To facilitate decision-making at the local level, ASIRs for maps were standardised using the national population (DEIS, 2017). Instead, for ease of comparison with the literature, the standard world population was used (Segi et al., 1957) in statistical models and tables. This geo-referenced information was incorporated into QGIS 3.22 software to build maps for selected time points at the department aggregation level.

Data Analyses

A joinpoint regression analysis (Kim et al., 2000; Joinpoint-Regression Programme, 2022) was performed to achieve greater descriptive accuracy of overall temporal trends to obtain the annual per cent change (APC) of provincial ASIRs and their 95% Confidence Intervals (CI) by sex. Models were selected according to the Bayesian Information Criterion.

To analyse the differences in ASIRs between sexes and urbanisation of the departments, we estimated summary measures, decomposed the standard deviation between and within components, and used hypothesis tests for paired data (Student's t-test).

Subsequently, a multilevel modelling strategy was carried out to account for the spatial correlation analysis of departments rates (Skrondal and Rabe-Hasketh, 2004). First, the ASIRs moving averages (3 years) were used to control the influence of small-area estimation, which is expected in departments with a small population size (Chatfield, 2004). The departments were grouped into three strata defined in terms of their level of urbanisation: High (n1=6; HU) with more than 107,000 people; Intermediate (n2=13; IU) with departments between 33,000 and 107,000 people, and Low (n3=7; LU), with less than 33,000 people.

We adjusted Negative Binomial regression models for each stratum of urbanisation, including a random effect for department variation (Rabe-Hesketh, 2012). In addition, each model considered the year and sex as covariates, nested into geographic analysis units (departments). Thus, the effects of sex and year on CRC incidence rates were estimated as follows:

$$\log(\mu_{ij}) = \beta_{0j} + \beta_1 \, \mathrm{Sex}_{ij} + \beta_2 \, \mathrm{Year}_i \,,$$

$$for\ j = 1;\ \ldots.;\ 26, i = 1; \ldots..;\ 11$$

The random-effects β_{0j} are assumed to be normally distributed with mean 0 and variance σ_j^2 and represent the unobserved heterogeneity coming from the county variability. Incidence rate ratios (IRR) of CRC were obtained by exponentiating log (μ_{ij}). The predicted versus the observed values were used in model checking. Stata 17.0 (StataCorp LP) software was used for the exploratory and modelling analysis.

Results

ASIRs at the province level

Between 2004 and 2014, 10,540 people were diagnosed with CRC in the province of Córdoba. Males were more affected than women the masculinity index being 1.2:1. Mean ASIR was higher in males, 30.9/100,000 males-year (95% CI: 29.9-32.0) (Table 1).

The ASIRs trends for males, females, and both sexes during the 11 years recorded are displayed in Table 1, which shows that men have always had higher incidences than females. The linear joinpoint analysis showed a decreasing trend in ASIR in both sexes, with an APC of -0.6 [95% CI:-1.8-0.6].

Spatial analysis

Figure 1 shows, in grayscale, departments ASIRs, for females and males, using the national population as reference, at the beginning and at the end of the period,

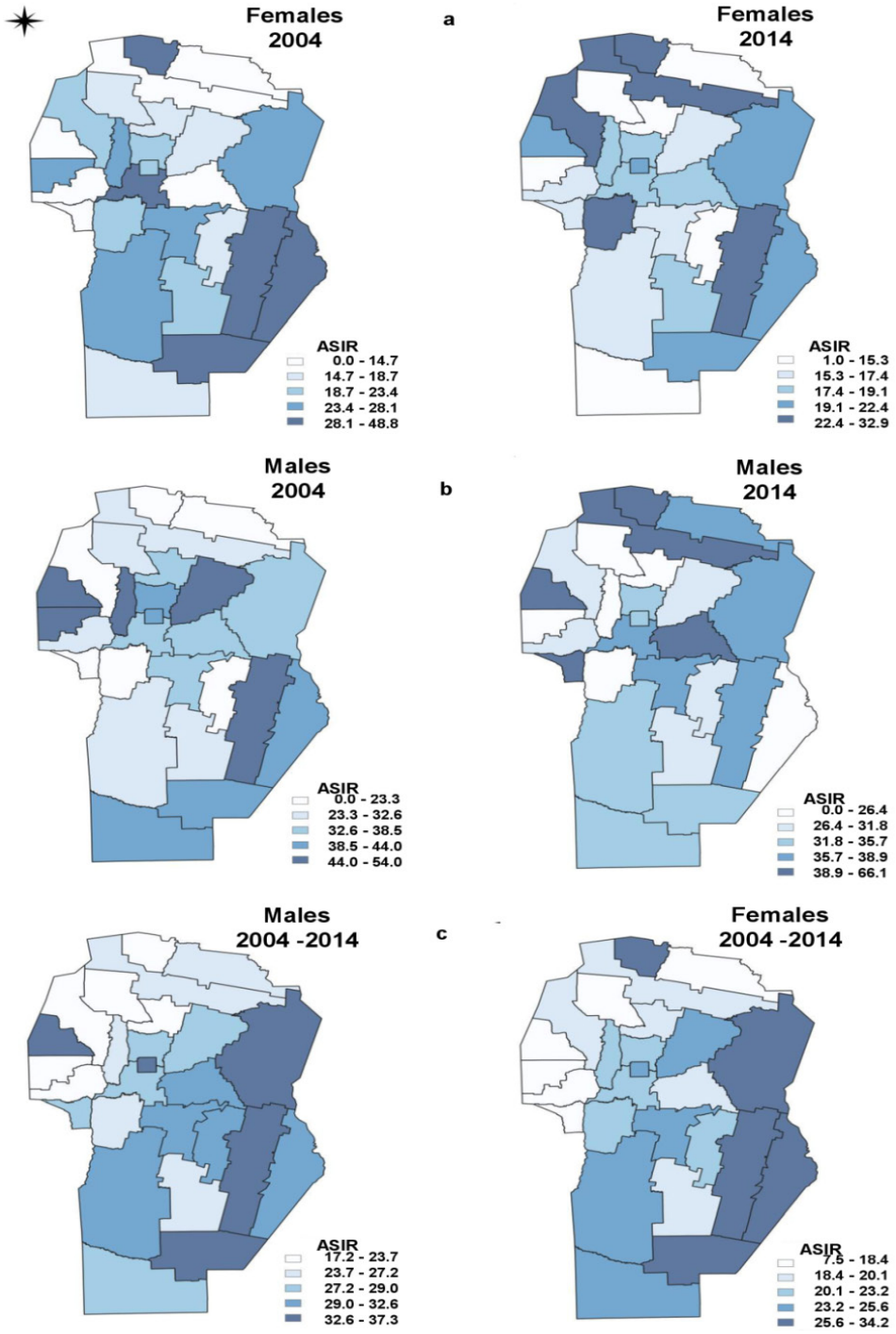

Figure 1. Geographical Distribution of Colorectal Cancer Age-adjusted and Standardised (National Reference Population) Incidence Rates in the Province of Cordoba, 2012-2014. a, Females; b, Males; c, Whole period

Table 1. Casuistry, Incidence Rates, Adjusted for Age and Standardised by the World Population (ASIR), and Annual Percent Change (APC), Province of Córdoba, Period 2004-2014.

	Cases	Annual mean	Age (Mean) (95% CI)	ASIR 2004 (95% CI)	ASIR 2014 (95% CI)	ASIR (2004-2014) (95% CI)	APC (95% CI)
Total	10,540	958	67.1 (66.8-67.4)	22.4 (20.6-25.5)	20.0(18.6-22.5)	27.5 (26.6-28.5)	-0.6 (-1.8-0.6)
Female	4,767	397	67.9 (67.5-68.3)	18.0 (16.1-19.7)	15.3 (13.7-16.9)	24.3 (23.3-25.3)	-0.9 (-2.4-0.7)
Male	5,773	525	66.4 (66.1-66.7)	28.1 (25.6-30.6)	26.1 (23.2-27.6)	30.9 (29.9-32.0)	-0.4 (-1.6-0.8)

CI: confidence interval; ASIR: Age-standardised incidence rate per 100,000 inhabitants, reference standard world population. Annual Percentage Change (APC) values and their corresponding confidence intervals were obtained by using ASIRs, using 0-joinpoint models (model with the best fit according to the Bayesian information criterion). The values were obtained by fitting a regression line to the natural logarithm of rates, using the natural year as the predictor variable and a Poisson variance to account for data over-dispersion. The APC represents the annual rate of change of the measured variable, expressed in percentage. The confidence interval reflects the precision of the estimation and provides a plausible range of values for the true rate of change.

and during the whole period (2004-2014). Darker areas represent the highest rates.

Departments bearing the highest loads differed at the beginning and at the end of the period for both, men and women. In 2004, higher rates for females were observed in eastern departments (Figure 1a). In males, rates were more heterogeneous, with the higher ones in the north at the end of the period reaching 66.1 cases/100,000 people (Figure 1b). On the other hand, in females, the highest rates were not located in a restricted area.

When ASIRs were mapped for males and females for the whole period (Figure 1c), a clear geographical distribution pattern was observed in both sexes. As it can be seen, the central and eastern regions have the greatest burden of CRC. The similarity of ASIRs distribution among sexes occurred exclusively in terms of their geospatial pattern. As shown by the scales, males had significantly higher rates than females. The map for women showed an upward northwest- southeast gradient, while for men, higher rates were mainly located in the central-eastern and southern areas. Sixty per cent of the departments ASIRs were higher than the local average rate for males. Only four (15%) departments had higher rates than the provincial average for females.

Table 2. Summary Measures the ASIRs of Colorectal Cancer by Strata of Urbanisation. Córdoba, Argentina, 2004-2014

	Mean	SD	Min	Max	(95%CI)	p-value
High urbanisation						
Total	21.56	6.3	11.64	39.36	20.20-22.85	
Between		0.94	20.25	23.65		
Within		6.23	11.1	37.27		
Women	16.19	2.3	11.64	21.66	15.62-16.76	0.008*
Men	26.94	4.01	15.98	39.36	25.9-27.92	
Intermediate urbanisation						
Total	21.38	7.42	4.43	41.52	20.20-22.56	
Between		0.55	20.39	22.08		
Within		7.4	3.73	40.85		
Women	16.49	4.89	4.43	30.7	15.68-17.30	0.087
Men	26.28	6.19	6.98	41.52	25.25-27.30	
Low urbanisation						
Total	17.46	13.15	0	62.79	14.00-20.95	
Between		1.78	15.65	20.01		
Within		13.04	-2.55	60.23		
Women	13.08	11.71	0	56.11	10.40-15.74	0.38
Men	21.83	13.13	0	62.79	18.85-24.81	

ASIR, Age-standardised incidence rate per 100,000, reference standard world population; SD, standard deviation; *, p-value<0.05

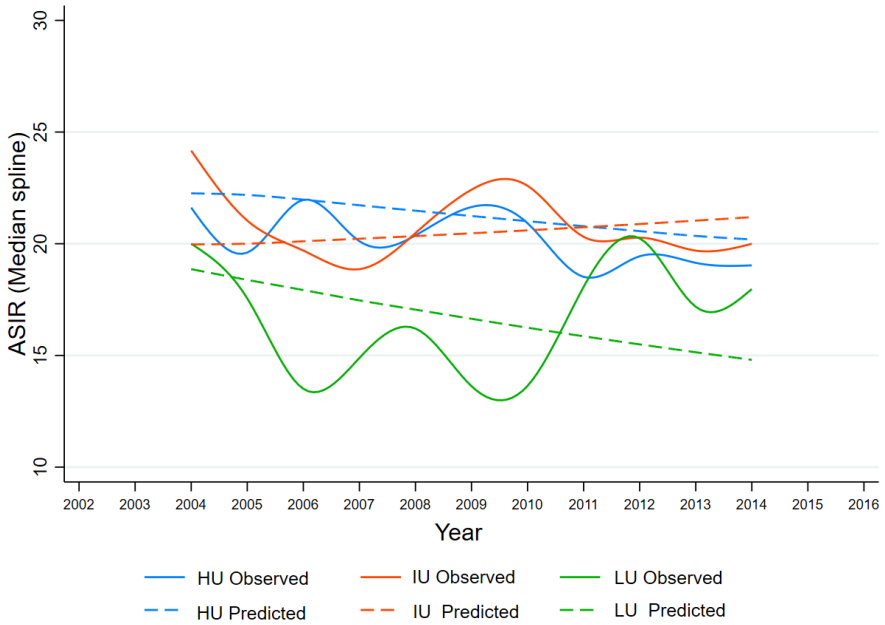

Figure 2. Temporary Trend of Colorectal Cancer Smoothed Age-Standardised Incidence Rate (ASIR) Observed and Predicted. HU, High urbanisation; IU, Intermediate urbanisation; LU, Low urbanisation

Table 3. Effect of Sex and Year on the Incidence Rates Ratio (IRR) of CRC According to Urbanisation, Córdoba 2004-2014

		High urbanisation	Intermediate urbanisation	Low urbanisation
Sex	IRR (p-value)	1.66 (0.000)*	1.59 (0.000)*	1.40 (0.001)*
	(95%CI)	(1.54-1.79)	(1.51-1.67)	(1.16-1.68)
Year	IRR (p-value)	0.97 (0.001)*	0.99(0.033)*	0.98(0.944)
	(95%CI)	(0.97-0.99)	(0.98-0.99)	(0.95-1.04)
Department variation	Variance	0.61 (0.19-1.92)	0.2 (0.09-0.44)	0.79 (0.27-2.29)

Base level, sex female, year 2004; CRC, Colorectal Cancer; CI, Confidence Interval; *, p-value <0.05

Higher means of ASIRs were found in the two strata with HU (Table 2), representing the 19 most populated departments of the province (73%). Significant differences between sexes were only found in ASIR measurements in HU departments (p=0.008).

Spatio-temporal analysis

As described, multilevel models were fitted to incorporate the hierarchical source of spatial variability of the standardised rates. Initially, the model, including urbanisation as a covariate, showed significant IRRs (3.50, 95%CI: 1.89-6.41, and 18.64, 95%CI: 9.35-37.17) for IU and LU, and HU, respectively. Then, when separate models were fitted according to urbanisation categories, sex and age effects were significant (Table 3, Figure 2). As it can be seen, ASIRs showed a downward trend during the period, and men had 1.66, 1.59, and 1.40 times more risk of CRC than women along all the urbanisation strata.

Discussion

This work focused on an 11-year analysis of age- and sex-adjusted incidence rates for colorectal cancer. Our findings reveal that, on average, ASIRs values for this neoplasm are similar to values at the national level and of such magnitude that they place this province at the level of regions with medium-high incidence in the international context. In addition, we found that the incidence had an effect modification by sex and urbanisation. In other words, the risk of being diagnosed with CRC was higher in men, particularly in the most urbanised departments. In fact, the risk was estimated to be 66% higher in men than in women in these areas. Additionally, we observed that the incidence of CRC was higher in more populated areas, with an average of 5 more cases per 100,000 incident cases than in less populated areas.

In our territory, the average age of diagnosis was 66, as expanded later, with no evidence of early-onset colorectal cancer patterns in young individuals; therefore, in Córdoba, advanced age continues to be one of the main risk factors. Specifically, the temporal analysis showed a significant downward trend of ASIRs.

The disease's magnitude and incidence rates in our territory (ASIR total: 27.5, female 24.3, men 30.9 cases/100,000 people) were similar to those estimated for Argentina by Globocan (Ferlay et al., 2010; Abriata et al., 2015; SIVER, 2014). However, except for Uruguay, this contrasts markedly with the figures for all Latin American and the Caribbean countries, which, together with most Asian countries, have low values in the global spectrum (Torre et al., 2016; Garau et al., 2019). One of the reasons could be that Argentina has undergone essential transformations in its population and health structure (CEPAL, 2022), which can be interpreted in light of demographic, health, and nutritional transitions (Peláez et al., 2017; Fanta and Tumas, 2020).

This cancer represents 10% of all malignant neoplasms worldwide, nationally (IARC, 2020) and provincially (RPTC, 2017), and it is one of the most frequent and deadliest. Its impact on the epidemiological profile makes it a marker of cancer transitions and human development (Fidler et al., 2016). Incidence rates tend to increase steadily in countries as the Human Development Index (HDI) improves, except in those countries with screening programmes where rates stabilise or decrease (Arnold et al., 2017; Bray, 2014). For Córdoba, the last computed HDI was equal to 0.82, ranking eighth among the 24 Argentine provinces. This HDI is associated with the strong growth (8%) of Córdoba geographic gross product and with population ageing (demographic coefficient of old age was 15.5%) (UNESCO, 2010). All these characteristics accompany the process of urbanisation related to high ASIR.

In our study, CRC was consistently higher among men than women, in agreement with values reported in most countries (Garau et al., 2019). The reason for the male risk excess is not wholly understood. Several investigations hypothesise there could be a potential hormonal protective effect in women (Kim et al., 2015). Some known risk factors for CRC -such as smoking, high consumption of red and processed meats, or central obesity- are more common among men than women in many societies (Amitay et al., 2022) and also in Argentina (ENFR, 2018).

The incidence of early-onset colorectal cancer (diagnosed before 50 years) has been increasing around the world (Arnold et al., 2017; Araghi et al., 2019). In our work, the mean age at diagnosis (67.14 years [CI95%:66.88-67.40]) was similar to results published in several publications (Gualdrini and Iummato, 2011). Although the period analysed (2004-2014) is relatively small, we also performed age-period-cohort models (not shown) and found that incidence rates increased significantly with age. In addition, we observed a sudden increase in the incidence risk for the cohorts born after the 1960s, suggesting that some changes may be happening in their habits and socio-environmental conditions. Not

just age but genetic vulnerabilities may influence the onset of CCR (25% are hereditary cancers). Even so, the role of exogenous and mostly modifiable risk factors -such as smoking, sedentary lifestyle, alcohol consumption, and unhealthy eating- is still highly relevant (Muñoz et al., 2022). The latter - one of Argentina's characteristic factors- could explain the higher incidence rates of this cancer, compared to other Latin American countries (Feng et al, 2017). The 4th National Survey of Risk Factors results indicate that 27% of the population smokes, 25% is exposed to second-hand smoke, and 47% show insufficient levels of physical activity. Only 5% cover the daily recommendation for fruits and vegetables (ENFR, 2018). In addition, many previous studies show strong roots in specific dietary patterns that make up the cultural identity of the Argentine population, associated with the risk of CRC, such as high consumption of red meat (Pou et al., 2012; Reartes et al., 2016). Additionally, obesity becomes relevant as a public health problem because it is a disease in itself and a metabolic risk factor associated with cancer (Jochem and Leitzmann, 2016). In Córdoba (and in the rest of the country), more than 50% of people are overweight, of which 25% have obesity (Aballay, 2020).

The geographical and contextual characteristics of the province mean that the incidence rates are not distributed homogeneously throughout the territory (Figure 1). Our findings corroborate research by Diaz et al. (2009; 2010) on the effect of clustering at the department level in the ASIRs distribution and that this spatial effect was conditional on sex, based on the the 2003-2005 period. The 2004-2014 ASIRs maps (Figure 1c) show a spatial pattern of CRC with a decreasing incidence gradient from highly populated areas to departments with low population density. A plausible explanation for these variations could be that populations rapidly adopt the urban-industrial food system associated with the recent demographic, nutritional, and epidemiological transition.

Nevertheless, this spatial pattern also presents dissimilarities according to sex. In women, ASIRs show an ascending northwest-southeast gradient, consistent with the downward slope of the unsatisfied basic needs in the same direction. The opposite happens when superimposing a map of environmental contaminants concentration associated with CRC risk, such as arsenic. Aballay et al., (2011) reported a spatial association between female CCR occurrence and the presence of arsenic in underground water in Córdoba. The areas with the lowest arsenic concentrations also have lower ASIRs. While for men, the highest ASIRs are concentrated mainly in the centre-east and south agricultural areas that belong to municipalities with higher economic levels. These characteristics could also be related to well-known high-risk practices, such as increased consumption of red meat, roast meat, and saturated fat.

We have found different occurrences according to the level of urbanisation. Some authors (Kuddus et al., 2020) support that the association between urbanisation and higher incidence could be linked to infrastructure conditions, specific exposures, behaviours, and lifestyles of these areas. Córdoba is not alien to this pattern (Fanta and Tumas, 2020).

Regarding the analysis of temporal trends, despite having high human development indicators, Córdoba does not match any of the patterns described in the literature (Arnold et al., 2017). In the most populous departments, the decrease was 3% per year. During the same period of the present research, we have also reported significant mortality differences between sexes, an increasing and significant trend in men (APC:0.61), and a decreasing but not linear trend in women (APC:-0.7) (Pou et al., 2009; Pou et al., 2017).

The CRC is one of the most preventable tumours (Santucci et al., 2020); however, in more than 60% of cases in Argentina, the disease is already advanced and the survival reduced. The years of life lost due to premature death from CRC for both sexes were 46.1 years (Bourel et al., 2010). In Córdoba, 31% of the population did not have health coverage, which could cause less access to screening and diagnostic methods and, therefore, late diagnoses that affect mortality.

In Argentina, the 50+ age group will have increased by 40% in 2040, so it is estimated that new annual cases will increase by 53.1%, considering this demographic aspect only (Ferlay et al., 2019). In addition, the effect of the exogenous and mostly modifiable risk factors mentioned above should be added. Therefore, post 2014 data analysis may show a greater number of new cases associated with implementing the National Programme for the Prevention and Early Detection of CRC. According to our data, ASIRs decrease in our context, but the CRC diagnosis is late, so mortality is still very high. Thus, public awareness of prevention should be improved and screening coverage increased.

Finally, this study is, as far as we know, the first to analyse the spatio-temporal distribution of the incidence of this neoplasm at the local level but in a territory that can be considered representative of the national context. So, the causal network as the pattern of this pathology and its association with known and unknown biological, social, and environmental factors is complex to identify. Therefore, we proposed an ecological study using multilevel models as a methodological alternative, in order to bring the context closer to the explanation of causality. It would be of great interest to consider some of the mentioned factors in future studies, possibly including them as indicators of latent variables.

The strength of this work is in the analysis of the CRC's casuistry provided by a population-based registry which meets the quality standards required by the IARC, as PTR, as well as its full coverage of Argentina's second most populous province, with representative characteristics of the country.

Some limitations must be considered. It is essential to recognise that in less populous departments, lowercase numbers could produce labile rates with wide variation; for this reason, the moving average was used to smooth out the small-area effect. Additionally, our spatio-temporal analyses were based on CRC incidence data, which could be affected by differences in diagnostic techniques between hospitals, access to medical care, and cancer registry quality. However, this effect is almost insignificant since the latter is the only one with a population base for

the entire provincial territory.

This research is the first spatio-temporal description of the incidence of CRC in one of the most representative provinces of Argentina. The incidence is high in the province of Córdoba, with ASIR similar to national ones and consistently higher among men than women throughout space and time. The non-random spatial pattern of cancer incidence in Córdoba is due to local and regional factors, with a greater decreasing temporal trend in highly urbanized departments. Therefore, an increase in the absolute number of new cases associated with the demographic transition and an increase in exogenous and modifiable risk factors is highly expected.

Author Contribution Statement

Diaz MP contributed to the conception and design of the study. Canale MG carried out the preparation of the material, compilation, statistical analysis and wrote the first version of the manuscript. Muñoz SE contributed to the draft writing. All the authors commented on previous versions and approved the final manuscript.

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General

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Ethics approval Not applicable

As this is an ecological study, the approval of an ethics committee is not required. The data used in our research comes from the Provincial Tumour Registry of Córdoba (non-identified data) and open data sources available on official websites. Additionally, there is a specific cooperation agreement between the Provincial Tumour Registry of the Ministry of Health of Córdoba Province and the School of Medical Sciences of the National University of Córdoba.

Data availability

The data set generated and analysed during this study is not publicly available because they belong to the Provincial Tumour Registry. Due to ethical safeguards regarding the identifiability of individuals in small population localities, the PTR has made them available to us after signing a specific agreement with the authors. Therefore, the dataset is available from the corresponding author (pdiaz@fcm.unc.edu.ar) on reasonable request.

Conflict of Interest

The authors declare that there is no conflict of interest.

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