Spatio-temporal distribution of Colorectal Cancer incidence in Cordoba, Argentina

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Abstract

Purpose: To analyse the spatio-temporal distribution of CRC incidence in Cordoba and its association with the level of urbanisation in Argentina (2004-2014).

Methods: An ecological time-series study using data from an 11years (2004-2014) was conducted. Age-standardised incidence rates (ASIR) (standard national and world population) by sex were calculated for the province and 26 counties for CRC in Cordoba using the provincial tumour registry database. Joinpoint regression models were adjusted to provincial ASIRs. Counties’ ASIRs were mapped in quintiles. The counties were grouped into three strata according to urbanisation: High (n1=6, >107,000 inhabitants); Intermediate (n2=13, 33,000-107,000 inhabitants); and Low (n3=7, <33,000 inhabitants). Spatio-temporal correlation analysis of counties’ rates was fulfilled using the multilevel modelling strategy.

Results: ASIRs of CRC in Cordoba 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, IRR: 1.66; intermediate, IRR: 1.59; and low, IRR: 1.70). There was a significant downward temporary variation in the most populous counties (3% per year).

Conclusions: CRC presents a non-random spatial pattern across the territory with a decreasing temporal variation in the most populous counties. Differential incidence and temporospatial tendency burden in Cordoba involve sex and urbanisation. Men continue to be the population at greatest risk; this pattern is more noticeable in less urban settings.

Introduction

Colorectal cancer (CRC) is the third most diagnosed malignancy and the second leading cause of cancer death worldwide [1]. 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 [2, 3]. Currently, CRC is considered one of the most obvious indicators of the epidemiological and a critical marker of demographic transitions [4, 5].

In Argentina, 15,605 new cases of CRC were diagnosed in 2020 (ASIR 31.0 and 20.6 cases per 100,000 men and women, respectively) [6]. It ranks second (12.1%) of all cancer sites (including skin cancer) after breast cancer (16.7%) [1]. The National Program 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%) [7].

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. The province of Cordoba has had a Population Tumour Registry (PTR) that complies with IARC standards since 2003. In 2009, Diaz et al. analysed the spatial distribution of cancer incidence in the province and found a non-random spatial distribution of CRC [8].
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 [9]. In Latin America, the incidence of CRC will increase by 65% (>2.2 million) by 2030 [10]. Therefore, the current understanding of CRC patterns and their local evolution is imperative to guide prospects for burden and reduction through cancer prevention and care. Having already the casuistry of the first decade, this work aims to delve into the incidence of CRC in Cordoba from 2004 to 2014 by analysing the spatio-temporal distribution and its association with the level of urbanisation.

**Materials And Methods**

**Study Design and Data**

An ecological time-series study was conducted between 2004 and 2014 in Cordoba, Argentina using data from the PTR, which covers a central area of Argentina with 3.7 million inhabitants (about 9% of the national population and the 2nd most populated, 80% of the population in cities), the province of Cordoba [11]. The province is divided into 26 counties. The Capital County is the most densely populated, with 2,367 inhabitants/km²; five counties have between 100,000 and 200,000 inhabitants, and only two with less than 5,000 inhabitants and the (lowest population density, minimum 1.3 inhabitants/km²) [12]. The provincial territory presents mixed geography, with a variety of reliefs, climates, and socio-environmental differences. The PTR dataset included all incident cases’ age, sex, residence, and tumour location. In addition, county population size data were obtained through population estimates by exponential interpolation based on census information published by the National Institute of Statistics and Census [13]. Age-adjusted standardised incidence rates (ASIRs) per 100,000 person-years by sex and 5-year age groups of CRC (CIE-10:C18- C20) were calculated for all the counties (n = 26) and years. To facilitate decision-making at the local level, ASIRs for maps were standardised using the national population [14]. Instead, for ease of comparison between regions, the standard world population was used [15] in those included in the statistical models and tables. This georeferenced information was incorporated into QGIS 3.22 Software [16] to build maps for selected time points at the county aggregation level.

**Data Analyses**

Joinpoint regression analysis [17, 18] 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 (95%CI) by sex. Models were selected according to the Bayesian Information Criterion.

To analyse differences in ASIRs between sexes and urbanisation of the counties, 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 counties’ rates [19]. First, the ASIRs’ moving averages (3 years) were used to control the influence of small-area estimation, which is expected in counties with a small population size [20]. The counties were grouped into three strata defined in terms of their level of urbanisation: High (n1 = 6; HU) with more than 107,000 inhabitants; Intermediate (n2 = 13; IU), those with counties between 33,000 and 107,000 inhabitants, and Low (n3 = 7; LU), with populations less than 33,000 inhabitants.
We adjusted Negative Binomial regression models for each stratum of urbanisation, including a random effect for county variation [21]. In addition, each model considered the year and sex as covariates, nested into geographic analysis units (counties). Thus, the effects of sex and year on CRC incidence rates were estimated as follows:

$$\log \left( \mu_{ij} \right) = \beta_0 j + \beta_1 \text{Sex}_{ij} + \beta_2 \text{Year}_i, \ for j = 1; \ldots; 26, i = 1; \ldots; 11$$

The random-effects $\beta_{0j}$ are assumed to be normally distributed with mean 0 and variance $\sigma_j^2$ and represent the unobserved heterogeneity coming from the county variability. Incidence rate ratios (IRR) of CRC were obtained by exponentiating $\log \left( \mu_{ij} \right)$. The predicted versus observed values were used in model checking. Stata 17.0 (StataCorp LP) software was used for the exploratory and modelling analysis [22].

**Results**

**ASIRs at the province level**

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

<table>
<thead>
<tr>
<th>Cases</th>
<th>Annual mean</th>
<th>Age (Mean) [95% CI]</th>
<th>ASIR 2004 [95% CI]</th>
<th>ASIR 2014 [95% CI]</th>
<th>ASIR (2004–2014) [95% CI]</th>
<th>APC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10,540</td>
<td>958</td>
<td>67.14</td>
<td>22.48</td>
<td>20.01</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[66.88–67.40]</td>
<td>[20.6–25.5]</td>
<td>[18.6–22.5]</td>
<td>[26.6–28.5]</td>
</tr>
<tr>
<td>Female</td>
<td>4,767</td>
<td>397</td>
<td>67.95</td>
<td>18.06</td>
<td>15.30</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[67.54–68.37]</td>
<td>[16.1–19.7]</td>
<td>[13.7–16.9]</td>
<td>[23.3–25.3]</td>
</tr>
<tr>
<td>Male</td>
<td>5,773</td>
<td>525</td>
<td>66.45</td>
<td>28.11</td>
<td>26.11</td>
<td>30.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[66.12–66.78]</td>
<td>[25.6–30.6]</td>
<td>[23.2–27.6]</td>
<td>[29.9–32.0]</td>
</tr>
</tbody>
</table>

CI: confidence interval; ASIR: Age-standardised incidence rate per 100,000 inhabitants, reference standard world population.

The ASIRs trends for males, females, and both sexes during the 11 years recorded are displayed in Table 1, showing that men always had higher incidences than females. 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, counties’ ASIRs, for females and males, using the national population as reference, at the beginning and the end of the period; and the whole period (2004–2014). Darker areas represent the highest rates.

Counties bearing the highest loads differ at the beginning and end of the period for both, men and women. In 2004, higher rates for females were observed in those counties in the East (Fig. 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 inhabitants (Fig. 1b). On the other hand, in females, the highest rates were not located in a restricted area.

When ASIRs are mapped for males and females for the whole period (Fig. 1c), a clearer geographical distribution pattern is observed in both sexes. As it can be seen, the central and eastern regions have the greater burden of CRC. The similarity of ASIRs distribution among sexes occurs exclusively in terms of their geospatial pattern. As shown by the scales, males have significantly higher rates than females. The map for women shows an upward Northwest- Southeast gradient, while for men, higher rates are mainly located in the central-eastern and southern areas. 60% of the counties had ASIRs higher than the local average rate for males. Only four (15%) counties had higher rates than the provincial average for females.

Higher means of ASIRs were found in the two strata with HU (Table 2), representing the 19 most populated counties of the province (73%). Significant differences between ASIR means by sexes were found only for the HU counties (p = 0.008).
Table 2
Summary measures the ASIRs of colorectal cancer by strata of urbanisation. Cordoba, Argentina, 2004–2014

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>[95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High urbanisation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21.56</td>
<td>6.30</td>
<td>11.64</td>
<td>39.36</td>
<td>20.20-22.85</td>
<td></td>
</tr>
<tr>
<td><em>Between</em></td>
<td>0.94</td>
<td>20.25</td>
<td>23.65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Within</em></td>
<td>6.23</td>
<td>11.10</td>
<td>37.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>16.19</td>
<td>2.30</td>
<td>11.64</td>
<td>21.66</td>
<td>15.62-16.76</td>
<td>0.008*</td>
</tr>
<tr>
<td>Men</td>
<td>26.94</td>
<td>4.01</td>
<td>15.98</td>
<td>39.36</td>
<td>25.9-27.92</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate urbanisation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21.38</td>
<td>7.42</td>
<td>4.43</td>
<td>41.52</td>
<td>20.20-22.56</td>
<td></td>
</tr>
<tr>
<td><em>Between</em></td>
<td>0.55</td>
<td>20.39</td>
<td>22.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Within</em></td>
<td>7.40</td>
<td>3.73</td>
<td>40.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>16.49</td>
<td>4.89</td>
<td>4.43</td>
<td>30.7</td>
<td>15.68-17.30</td>
<td>0.087</td>
</tr>
<tr>
<td>Men</td>
<td>26.28</td>
<td>6.19</td>
<td>6.98</td>
<td>41.52</td>
<td>25.25-27.30</td>
<td></td>
</tr>
<tr>
<td><strong>Low urbanisation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17.46</td>
<td>13.15</td>
<td>0</td>
<td>62.79</td>
<td>14.00-20.95</td>
<td></td>
</tr>
<tr>
<td><em>Between</em></td>
<td>1.78</td>
<td>15.65</td>
<td>20.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Within</em></td>
<td>13.04</td>
<td>-2.55</td>
<td>60.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>13.08</td>
<td>11.71</td>
<td>0</td>
<td>56.11</td>
<td>10.40-15.74</td>
<td>0.38</td>
</tr>
<tr>
<td>Men</td>
<td>21.83</td>
<td>13.13</td>
<td>0</td>
<td>62.79</td>
<td>18.85-24.81</td>
<td></td>
</tr>
</tbody>
</table>

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

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, for the HU, respectively. Then, when separate models were fitted according to urbanisation categories, sex and years effects were significant (Table 3, Fig. 2). As it can be seen, ASIRs showed a downward trend during the period, except for LU counties, and men had 1.66, 1.59, and 1.70 times more risk of CRC than women along all the urbanisation strata.
Table 3
Effect of sex and year on the Incidence Rates Ratio (IRR) of CRC according to urbanisation, Cordoba 2004–2014

<table>
<thead>
<tr>
<th></th>
<th>High urbanisation</th>
<th>Intermediate urbanisation</th>
<th>Low urbanisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td><strong>IRR (p-value)</strong></td>
<td><strong>IRR (p-value)</strong></td>
<td><strong>IRR (p-value)</strong></td>
</tr>
<tr>
<td></td>
<td>[95%CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.66 (0.000*)</td>
<td>1.59 (0.000*)</td>
<td>1.70 (0.001*)</td>
</tr>
<tr>
<td></td>
<td>[1.54–1.79]</td>
<td>[1.51–1.67]</td>
<td>[1.25–2.31]</td>
</tr>
<tr>
<td>Female</td>
<td>1.00 (0.999)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.95–1.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td><strong>IRR (p-value)</strong></td>
<td><strong>IRR (p-value)</strong></td>
<td><strong>IRR (p-value)</strong></td>
</tr>
<tr>
<td></td>
<td>[95%CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004–2014</td>
<td>0.97 (0.001*)</td>
<td>0.99 (0.033*)</td>
<td>1.00 (0.999)</td>
</tr>
<tr>
<td></td>
<td>[0.97–0.99]</td>
<td>[0.98–0.99]</td>
<td>[0.95–1.04]</td>
</tr>
<tr>
<td><strong>County variation</strong></td>
<td><strong>Variance [95%CI]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.61</td>
<td>0.20</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>[0.19–1.92]</td>
<td>[0.09–0.44]</td>
<td>[0.17–1.68]</td>
</tr>
</tbody>
</table>

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

**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, the ASIRs of this neoplasm presented similar values to those at the national level and of such magnitude that they are internationally positioned among the regions of medium-high incidence. In addition, we found that the incidence of CRC is conditioned by sex and urbanisation. Higher incidence risks were found in men at all strata, reaching up to 70% more than in women in less populated counties and descent of at least five ASIR points from high to low urbanised counties was estimated. In our territory, the average age of diagnosis was 66 years, as expanded later, with no evidence of early-onset colorectal cancer patterns in young individuals; thus, only associated with advanced age. Specifically, the temporal analysis showed a significant downward trend of ASIRs, except in the less populated areas.

The disease’s magnitude and incidence rates in our territory (ASIR total: 27.5, female 24.3, men 30.9 cases/100,000 inhabitants) were similar to those estimated for Argentina by Globocan [23–25]. However, except for Uruguay, this contrasts markedly with the figures for all the Latin America and the Caribbean countries, which, together with most Asian countries, have low values in the global spectrum [26–28]. Among the reasons, one could be that Argentina has undergone essential transformations in its population and health structure [29], which can be interpreted in light of demographic, health, and nutritional transitions [30–32].

This cancer represents 10% of all malignant neoplasms worldwide [1], national [6] and provincially [33], and is one of the most frequent and deadly. Its impact on the epidemiological profile makes it a marker of cancer transitions and human development [34]. Incidence rates tend to increase steadily with the improvement of the Human Development Index (HDI), except in countries with, other than with very high development, the implementation of screening programs, where they stabilise or decrease [35–37]. For Cordoba, 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 the Cordoba geographic gross product and the population ageing (demographic coefficient of old age was 15.5%) [38, 39]. All these characteristics accompany the process of urbanisation related to high ASIR.
In our study, CRC was consistently higher among men than women, coinciding with that reported in most countries [3, 28]. The reason for the male risk excess is not wholly understood. Several investigations hypothesise there could be a potential hormonal protective effect on women [40]. Whereas some known risk factors for CRC, such as smoking, high consumption of red and processed meat, or central obesity, are more common among men than women in many societies [41, 42] and also in Argentina [43].

Findings in countries with a very high HDI suggest a high risk in those under 50 [35, 44–46]. In our work, the mean age at diagnosis (67.14 years [CI95%: 66.88–67.40]) was similar to several publications [7]. Although the period analysed (2004–2014) is relatively small, we also performed age-period-cohort models (not shown) and found 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 is still highly relevant [47], such as smoking, sedentary lifestyle, alcohol consumption, and unhealthy eating. The latter could be one of Argentina’s characteristic factors that could explain the higher incidence rates of this cancer compared to other Latin American countries [48–50]. The 4th National Survey of Risk Factors results indicate that 27% of the population smokes, 25% is exposed to second-hand smoke, and 47% have insufficient physical activity. Only 5% cover the daily recommendation for fruits and vegetables [43]. 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 [51–54]. Also, obesity becomes relevant as a public health problem since it is a disease in itself and a metabolic risk factor associated with cancer [55, 56]. In Cordoba (and the country), more than 50% of people are overweight, of which 25% have obesity [57].

The geographical and contextual characteristics of the province mean that the incidence rates are not distributed homogeneously throughout the territory, which could be observed in Fig. 1. Our findings corroborate what was reported by Diaz et al. [8, 58] in previous years (2003-2005) on the effect of clustering at the county level in the ASIRs distribution and that this spatial effect was conditional on sex. The 2004–2014 ASIRs maps (Fig. 1c) show a spatial pattern of CRC with a decreasing incidence gradient from highly populated areas to counties 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, concordant 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. reported a spatial association between female CCR occurrence and the presence of arsenic in underground water in Cordoba. The areas with the lowest arsenic concentrations also have lower ASIRs [59]. 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 [53, 54].

We have found different occurrences according to the level of urbanisation. Some authors [60, 61] support that the association between urbanisation and higher incidence could be linked to infrastructure conditions, specific
exposures, behaviours, and lifestyles typical in these areas. Cordoba is not alien to this pattern [62].

Regarding the analysis of temporal trends, despite having high human development indicators, Cordoba does not match any of the patterns described in the literature [35]. In the most populous counties, the decrease was 3% per year. During the same period of the present research, other works of ours also reported significant mortality differences between sex, an increasing and significant trend in men (APC:0.61), while in women, it was decreasing although not linear (APC: -0.7) [63, 64].

The CRC is one of the most preventable tumours. [65][66][67], 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 [68]. In Cordoba, 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 age group of those over 50 will increase by 40% in 2040, so it is estimated that considering only this demographic aspect, new annual cases will increase by 53.1% [69]. In addition, the effect of the exogenous and mostly modifiable risk factors mentioned above should be added. Therefore, analysing data after 2014 would be expected to find a greater number of new cases associated with implementing the National Program 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, our research 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 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 [17].

This work’s strength was to analyse the CRC’s casuistry provided by a population-based registry which meets the quality standards required by the IARC, as PRT, and covers the entirety 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 counties, lowercase numbers could produce labile rates with wide variation; for this reason, the moving average was used to smooth out the small-area effect. Also, 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.

Conclusions

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 Cordoba, 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 Cordoba is due to local and regional factors, with the temporal trend decreasing only in high urbanisation counties. 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.

**Statements & Declarations**

**Acknowledgements**

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**Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions**

Maria del Pilar Diaz and Sonia E. Muñoz contributed to the conception and design of the study. Marcela G Canale carried out the preparation of the material and the compilation. All authors analysed the data. Marcela G. Canale wrote the first draft of the manuscript and all authors commented on previous versions. Finally, all authors read and approved the final manuscript.

**Ethics approval**

Not applicable.

**Consent to participate**

None.

**Consent for publication**

None.

**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 Provincial Registry of Tumours has provided them following the signing of a specific
agreement with the authors. Therefore, the dataset is available from the corresponding author (Maria del Pilar Diaz, E-mail: pdiaz@fcm.unc.edu.ar) on reasonable request.

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Figures
Figure 1

Geographical distribution of CRC age-adjusted and standardised (national reference population) incidence rates in the Province of Cordoba, 2012-2014

a: Female; b: Male; c: Whole period.
Figure 2

Temporary trend of CRC smoothed Age-standardised incidence rate (ASIR) observed and predicted