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Cancer mortality in Córdoba, Argentina, 1986-2006: an age-period-cohort analysis

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ABSTRACT

Aims and background. Cancer is the second main cause of death in Argentina, surpassed only by cardiovascular disease. However, analytical approaches isolating some of the known effects, such as age at death, period of death and birth cohort, have never been performed in cancer mortality studies in Argentina. The aim of this study was to analyze cancer mortality trends in a representative region of the country, the Córdoba province (1986-2006).

Methods and study design. Overall age-standardized (world population) mortality rates for cancer (all sites) were computed by a direct method. Joinpoint regression was fitted to the age-standardized mortality rates for both sexes to provide estimated and 95% confidence intervals of the annual percentage changes. The effects of age (15 age groups), period of death (1986-90, 1991-95, 1996-00 or 2001-06), and birth cohort (18 overlapping 10-year birth cohorts) covariates on mortality rates were estimated using a sequentially fitted Poisson regression model.

Results. During the study period, 102,737 people died of cancer in Córdoba, with the age-standardized mortality rates decreasing from 139.3 to 118.7/100,000 person-years. Although this reduction was more noticeable in men, the joinpoint regression model showed a significant change of the age-standardized mortality rates after 1996 in both sexes. Age-period-cohort analysis suggested that the cancer mortality trends may be linked with a strong age effect and a moderate or mild period and cohort effect, related to sex and place of residence.

Conclusions. Based on the observed cohort effect, it may be argued that there has been a lower exposure level to some risk factors, such as diet and other environmental factors, in Cordoba over the last decades. **Free full text available at www.tumorionline.it**

Key words: age-period-cohort model, Argentina, cancer mortality, Cordoba.

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Introduction

Each year, nearly seven million people die of cancer, and 11 million new cases (excluding skin cancers) are diagnosed. Moreover, an increase in these cancer incidence rates is expected in high- as well as in middle- and low-income countries[1].

Cancer mortality studies have shown considerable variations within regions and countries, and even between different geographic areas in the same country. In South America, the highest age-standardized cancer mortality rates (ASMR) in 2002 were found in Uruguay, Paraguay, Perú and Argentina (159, 128, 127 and 126.9/100,000, respectively), whereas Ecuador and Guyana presented the lowest rates (80.3 and 69.7/100,000, respectively)[2].

The latest report on Argentinian crude cancer incidence rates (except non-melanoma skin cancer), is based on the Bahia Blanca Registry, showing figures of 321 and 318/100,000 for males and females, respectively[3], with around 152 men and 100 women (per 100,000) dying of cancer annually[4]. Cancer is the second main cause of death, surpassed only by cardiovascular disease[5]. Some differences in mortality from cancer were also found between counties or between regions with different urbanization strata in Argentina[6-7]. For the area of the present study, in the Cordoba Province, according to the 2005 report of the National Institute of Statistics and Census, there was a crude mortality cancer rate of 160/100,000 inhabitants[8].

Several reports have described cancer mortality trends in Argentina[9-11,7]. Bosetti *et al.*[11] performed a complete description of the cancer ASMR using the WHO database (period 1970-2000) for Canada, the USA, and 10 other Latin American countries, including Argentina, but not considering the simultaneous effects of age at death, period of death and birth cohort. Similarly, Muñoz *et al.*[10] reported the 1966-91 mortality rate series for the 12 most common cancer sites and the total cancer mortality in Argentina, using only trends over time, whereas Loria *et al.*[7] and Matos *et al.*[9] focused on studying the geographical distribution of cancer mortality rates (CMR) in Argentina. Since potential changes are associated with environmental conditions applying in the year of birth, as well as changes in diagnosis and treatment strategies, we chose to perform an age-period-cohort (APC) analysis. For most human cancers, in fact, there is often an interval of several decades between the first exposure to a carcinogen and the clinical appearance of disease, or death. Thus, analyses of cancer mortality by birth cohort can provide useful information and help to explain some recorded features of cross-sectional curves[12].

Argentina has an extensive, sparsely populated territory (2,791,810 km^2)[13], with the exception of a few populous cities. Both Argentina and Uruguay, at the end of the 19th and the beginning of the 20th centuries, received a flood of European immigrants, so that in Argentina, in about 1910, immigrants outnumbered “creoles”. Even today, second or third generations of Spaniards or Italians comprise half of all Argentines. This unusual population distribution merits studies devoted to cancer and other chronic diseases in order to compare the results with those for the original European inhabitants, in which socio-economic, ethnic and cultural realities are interwoven factors.

This work analyses the cancer mortality trends in the Córdoba province, a representative region of Argentina situated in the central part of the country. Although Córdoba has only 10% of the country’s population, the population density and the urbanization level vary widely over the territory. Assuming there to be intraurban variations in the health indicators and the mortality rates, a study of cancer mortality through the population strata, according to the population size, seems justified[14].

The purpose of the present work was to describe the changes in the mortality rates over time, related to age at death, period of death and birth cohort, by applying an APC model[15]. This analytical approach has been widely used in other chronic disease studies and allows data to be obtained on the influence of age (age effect), short-term factors that affect all age groups at essentially the same time, as well as a period effect (changes in diagnostic standards and cure rates) and factors associated to lifetime exposure established early in life (cohort-effect). APC models are generally coupled to a preliminary description, such as joinpoint regression, to estimate the annual percentage changes in mortality rates and the number and location of joinpoints, thus permitting a pairwise comparison of the models applied to each data series.

The present research examines mortality trends for all cancer sites in Córdoba (Argentina) between 1986-2006, using joinpoint and age-period-cohort models.

Material and methods

Data on place of residence, age- and sex-specific cancer deaths (International Classification of Diseases [ICD], 9th and 10th revisions, codes C140 to 208 and C00 to C97 respectively)[16-17] were obtained from the Department of Statistics, Ministry of Health of Córdoba Province, Argentina. Population data were obtained from the 1980, 1991 and 2001 censuses available at the National Institute of Statistics and Census. For the population as a whole and for both sexes, intercensus population estimates were derived by linear interpolation between two adjacent records for each of the 15 age groups considered.

For these 15 age groups (<20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, >85 years), the overall ASMR were computed by a direct method and were expressed as rates/100,000. Place of residence was collapsed to a variable with three strata: Córdoba City (CC: 1,300,000 inhabitants), districts with more than 100,000 inhabitants (9), and districts with up to 100,000 inhabitants (LC). Joinpoint regression was fitted to the ASMR for both sexes to provide estimated and 95% confidence intervals (CI) of the annual percentage changes (EAPC) and also to detect points in time where significant changes in the trend occurred. As the joinpoint regression model describes continuous changes in rates, the annual rates over a given period of time could be examined and the points in time with significant changes in the direction of the trends detected[18]. We set three joinpoints for the calendar period from 1986 to 2006, and this analysis was performed using joinpoint software[19].

Data were tabulated into four periods of death (1986-1990 to 2001-2006) and 18 five-year overlapping 10-year birth cohorts, identified by the central year of birth from 1901 to 1986. For example, the central year 1941 cohort identified individuals aged 45-49 who died in the period 1986-1989. The effects of age, period of death and birth cohort covariates on mortality rates were estimated using a poisson regression model. The model assumes the number of deaths as a poisson random variable where the expectation parameter depends on the number of person-years and on explanatory variables[20-21]. In the APC analysis, it is not possible to identify the role of age, period and cohort separately because of the interdependency among these variables[22]. Age at death was the major temporal axis and birth cohort the second one. Birth cohort was chosen because potential changes associated with environmental conditions applying in the year of birth have occurred in Argentina as a result of urbanization process. These two major time scales contain biological likelihood criteria.

Since there is some controversy about the use of different APC models[23], to deal with this identification problem, Poisson models were fitted sequentially, and the CMR were estimated as follows. First, an age-cohort model was fitted. Then, by omitting an explicit intercept and choosing a suitable reference for the cohort, it was expected that the age effect would be a log incidence CMR for the reference cohort and the cohort effect would be a log relative risk (RR). The log of the fitted values from these models was then used as an offset variable in a model with a period effect.

The estimates from this APC model are age-cohort marginal estimates and period estimates, which are dependent on the estimates from the age-cohort model. These values are usually close to those obtained from the maximum likelihood approach[24], but no verification test can be performed.

The parameterization of our models was chosen on biological plausibility criteria, namely, age as the major time scale and cohort as the secondary time scale (the major secular trend), with the period as the residual time scale. The central year 1941 cohort was chosen as the reference cohort.

Data management, direct standardization of rates and poisson regression analysis were performed using STATA 10 statistical software (College Station, Texas, USA)[25].

Results

During the period 1986 to 2006, the population size of Córdoba Province grew from 2,626,692 to 3,766,090 million inhabitants, and 102,737 people died of cancer. Between 1986 and 2006, the ASMR decreased from 139.3 to 118.7/100,000 person-years (Table 1), and the reduction was more noticeable in males. For the province as a whole, the ASMR was lower for residents in CC than MC or LC, for most periods. Throughout the time period examined, the ASMR showed a decreasing trend. However, male rates always exceeded female rates.

The joinpoint regression model (Figures 1 and 2), reporting the changes in rates, showed a decreasing trend of the ASMR in men from 1986 to 1996 (EAPC -0.5, 95% CI, -1.2, 0.2), whereas in women an increase was recorded for the same period (EAPC 0.2, 95% CI, -0.6, 1.0). Then a significant change in the ASMR occurred after 1996, in both sexes (EAPC -1.98, 95% CI, -2.7, -1.3 in males and EAPC -1.57, 95% CI, -2.3, -0.8 in females).

Table 1 - Age-standardized cancer mortality rates by sex, period and county. Córdoba province, Argentina, 1986-2006

	Córdoba Province (Total)			Capital			More than 100,000 inhabitants			Less than 100,000 inhabitants		
	Person-years	Deaths	ASMR[a]	Person-years	Deaths	ASMR[a]	Person-years	Deaths	ASMR[a]	Person--years	Deaths	ASMR[a]
Overall												
1986-1990	13168099	21996	139.3	5533531	7624	132.5	4054885	7672	141.2	3579683	6700	147.5
1991-1995	14176384	23922	133.0	5949457	8560	132.5	4351032	8253	135.7	3875895	7109	135.5
1996-2000	14713105	25238	128.5	6175651	9128	127.7	4614073	8758	130.4	3923381	7352	130.6
2001-2006	18896648	31581	118.7	7811281	11815	121.7	6087038	11130	117.7	4998329	8636	116.4
Males												
1986-1990	6440249	12731	182.1	2654961	4099	172.7	1988269	4530	184.7	1797019	4102	192.2
1991-1995	6833179	13476	176.1	2847639	4502	171.4	2124545	4761	177.0	1860995	4213	183.5
1996-2000	7135839	13882	167.8	2953343	4724	164.3	2246031	4942	169.0	1936465	4216	172.3
2001-2006	9190393	16995	150.7	3764418	5982	153.5	2947149	6128	150.5	2478826	4885	147.9
Females												
1986-1990	6727850	9265	105.8	2878570	3525	105.3	2066616	3142	105.6	1782664	2598	108.0
1991-1995	7343205	10446	101.7	3101818	4058	106.9	2226487	3492	103.0	2014900	2896	100.0
1996-2000	7577266	11356	101.1	3222308	4404	104.1	2368042	3816	100.4	1986916	3136	101.8
2001-2006	9706255	14586	96.0	4046863	5833	101.3	3139889	5002	93.6	2519503	3751	91.5

[a]Age-standardized mortality rate per 100,000 (standard world population).

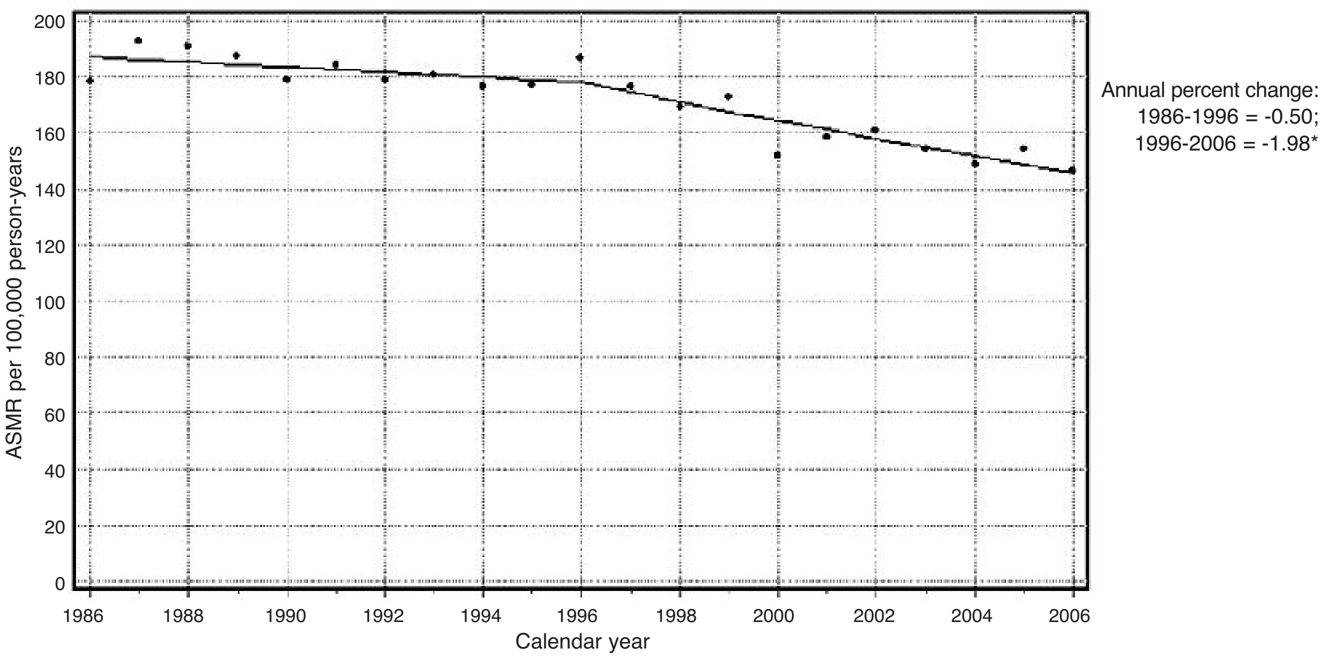

Figure 1 - Age-standardized (world population) cancer mortality rates (ASMR) for men in Córdoba Province, Argentina, 1986-2006.
*The annual percentage change is significantly different from zero.

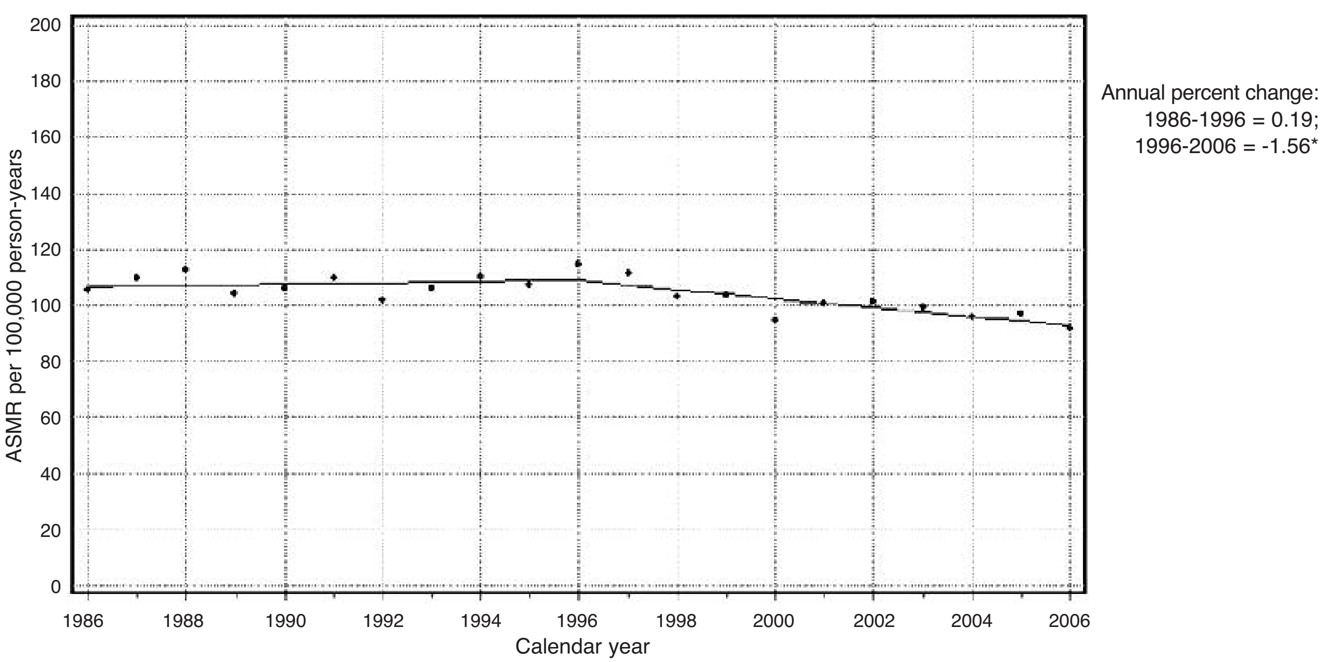

Figure 2 - Age-standardized (world population) cancer mortality rates (ASMR) for women in Córdoba Province, Argentina, 1986-2006.
*The annual percentage change is significantly different from zero.

Considering Córdoba province as a whole, the APC analysis showed an increasing age-specific CMR for cancer, with a ranking of 10.2 and 1337.31/100,000 person-years for the youngest and the oldest age-group, respectively. The RR for birth cohort decreased from 1.49 in 1901 to 0.40 in 1986, all values being statistically significant, except for the cohort centered in 1931 (results not shown here, Appendix in http://www.fcm.unc.edu.ar/escuelas/nutricion/catedras/estadistica/Appendix_Tumori.htm). The period RR were 0.99 (95% CI, 0.98, 1.00) for 1986-1990, 1.00 (95% CI, 0.99, 1.02) for 1991-1995, 1.01 (95% CI, 0.10, 1.02) for 1996-2000 and 0.99 (95% CI, 0.98, 1.00) for 2001-2006. An increased period effect was observed in all areas of Córdoba province in the period

1996-2000, whereas the subjects resident in CC and LC showed the highest RR values for 1991-1995 and 1986-1990, respectively (Figures 1 and 2).

When both sexes were considered separately (Figure 3), the same profiles were found, the CMR for males exceeding those for women and showing a strongly decreasing birth cohort RR, particularly for men. In women, in general, there were more variations over time. There was a similar pattern for the period effect with an increased RR for central periods, except for females resident in LC. The APC analysis, stratified by sex and stratum of population, showed a higher CMR for men, in all cases.

In men, the youngest age classes exhibited a higher CMR for residents in LC than in MC or CC, whereas mortality was higher in CC in the oldest age classes. Overall, the birth cohort effect showed a strongly decreasing trend in all the strata (Figure 4). It is noteworthy that the older generations (1901) had a higher birth cohort effect in LC (RR 1.62, 95% CI 1.37, 1.91) than overall in the male population (RR 1.38, 95% CI 1.25, 1.52).

Women showed a similar trend (Figure 5). In general, the birth cohort effect showed a decreasing trend for older generations (from 1901 to 1911). In recent years, these birth cohort effects were lower for residents in MC

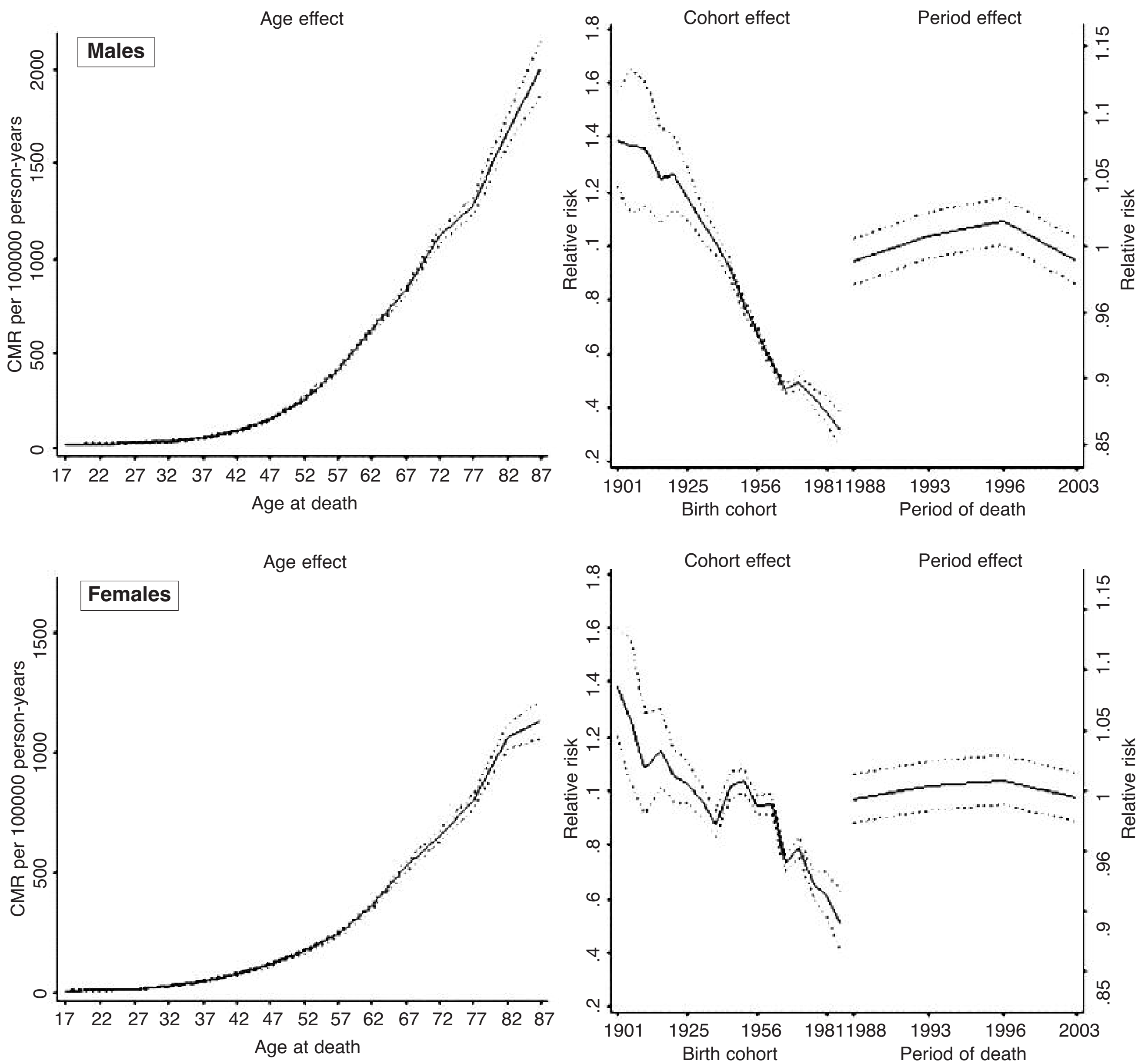

Figure 3 - Cancer mortality: age-period-cohort modeling for males (upper) and females (bottom) for Córdoba Province. Age values are expressed as rates/100,000 person-years. Period of death and birth cohort effects are expressed in relative terms against their weighted average set to unity. Solid line, effect estimate; dashed line, 95% CI.

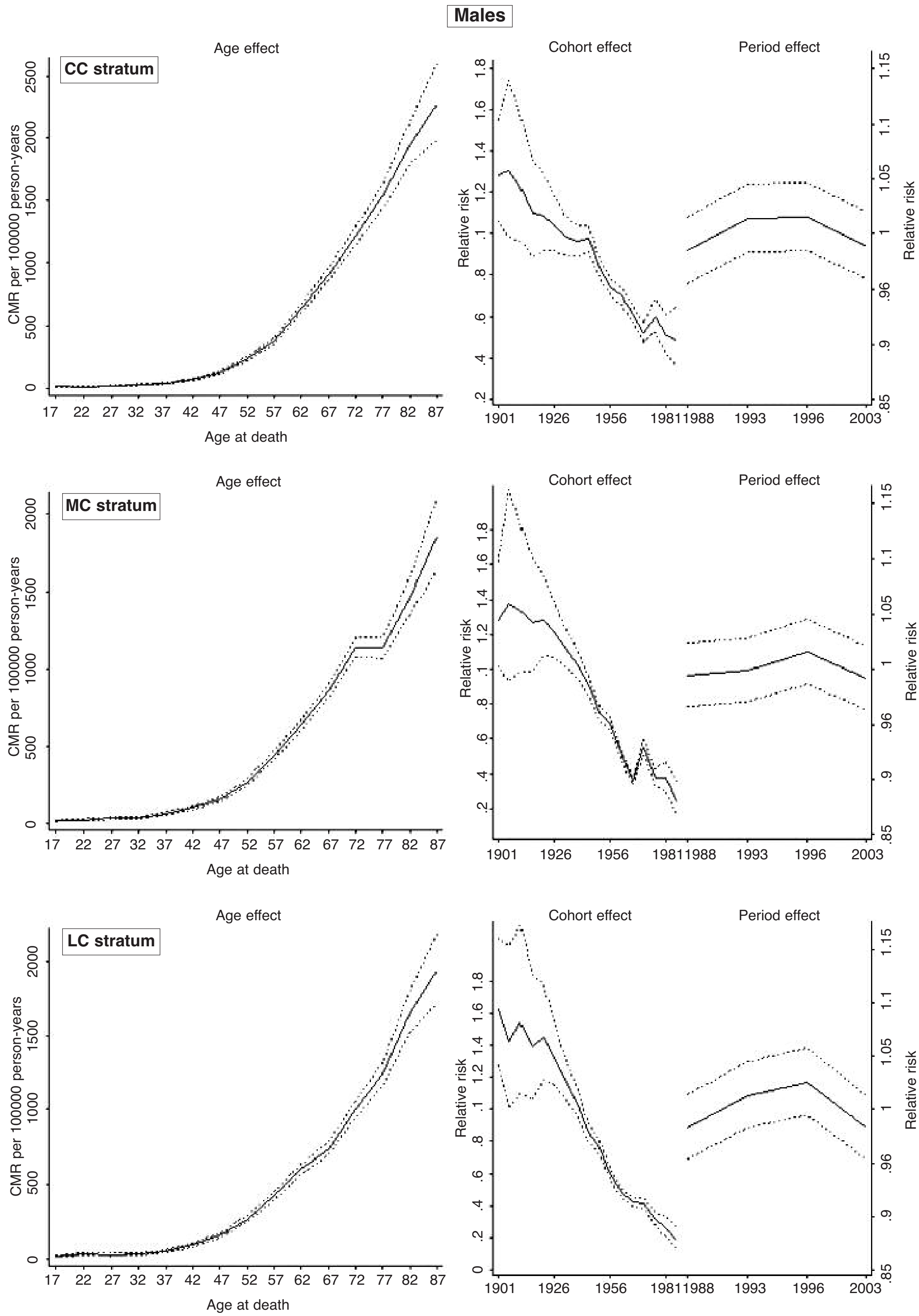

Figure 4 - Cancer mortality: age-period-cohort modeling for males for CC (upper), MC (middle) and LC (bottom) strata. Age values are expressed as rates/100,000 person-years. Period of death and birth cohort effects are expressed in relative terms against their weighted average set to unity. Solid line, effect estimate; dashed line, 95% CI.

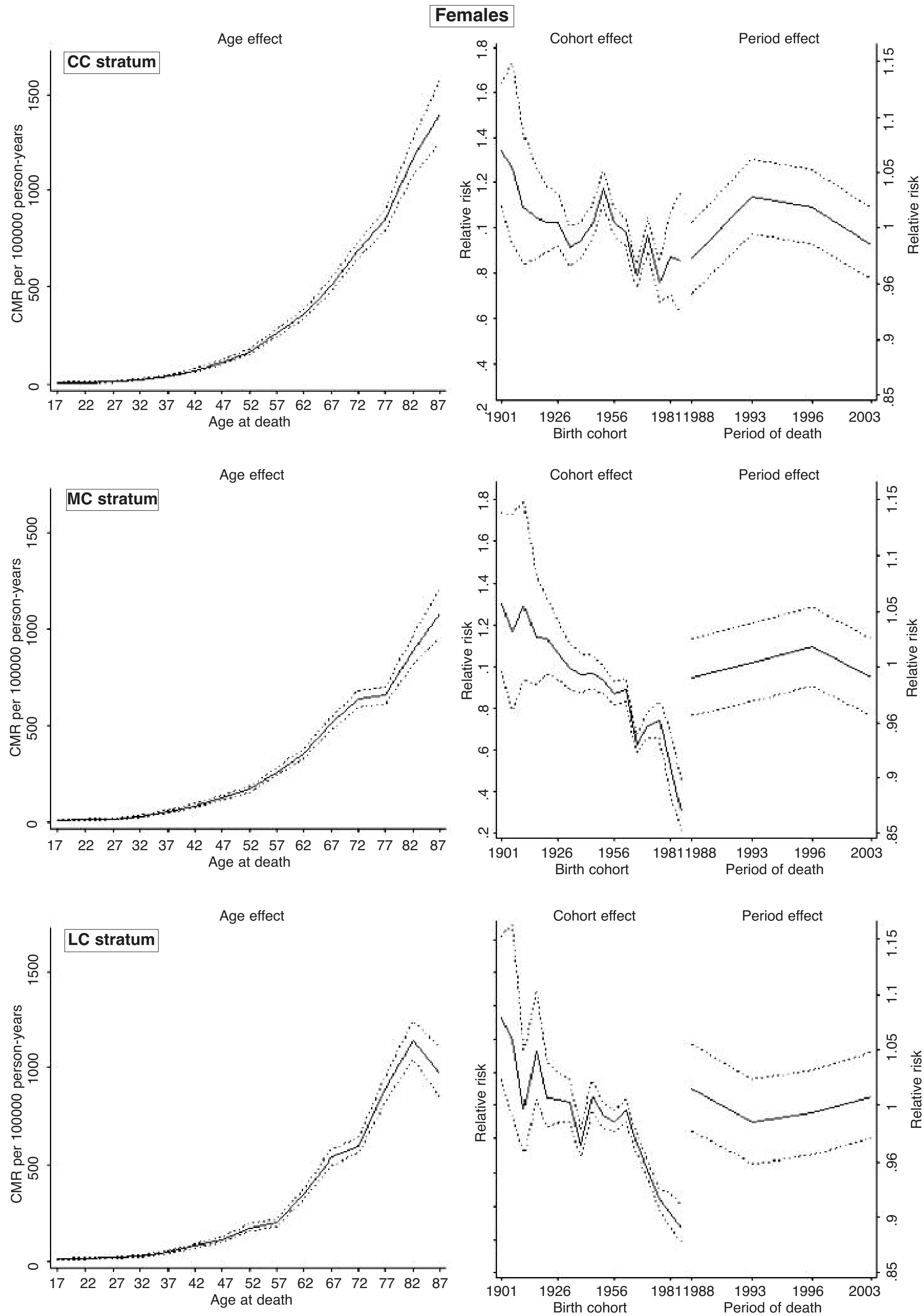

Figure 5 - Cancer mortality: age-period-cohort modeling for females for CC (upper), MC (middle) and LC (bottom) strata. Age values are expressed as rates/100,000 person-years. Period of death and birth cohort effects are expressed in relative terms against their weighted average set to unity. Solid line, effect estimate; dashed line, 95% CI.

(RR 0.31, 95% CI, 0.17, 0.56) and LC (RR 0.27, 95% CI, 0.15, 0.50).

Generally, after the cohort born in 1946, females had a higher RR than males. By strata, and considering the whole population, the RR were higher than the baseline cohort (1941) until around the 1930s decade. Thereafter, for the youngest generations, the RR were lower than those from this cohort and showed a decreasing trend, which was more accentuated for residents in MC.

Discussion

The results of the APC analysis suggest that the cancer mortality trends in Córdoba may be linked with a strong age effect and a moderate or mild period and cohort effect related to sex. Also, for the last study period (2001-2006), mortality rates obtained for all malignant neoplasms were similar to those reported by the International Agency for Research on Cancer (age-standardized world rates, for all sites except non-melanoma skin), at a national level: 152 and 100/100,000 in males and females, respectively[4]. It is reasonable to assume that the geographic area studied is representative of the Argentine urban and rural population: Córdoba has 26 districts, covering a variety of situations, ranging from regions with a small population to highly populated districts with mixed cultural traditions and different economic activities.

Our results indicate an increase in the absolute number of deaths from cancer, with a decreasing trend in the ASMR, a tendency also reported in other studies carried out in Argentina and other Latin American countries in recent years. Consistent with our findings, Bosetti *et al.*[11] observed decreasing CMR, particularly in men, in Argentina, Chile, Colombia, Costa Rica and Venezuela, over the period 1970-2000. However, our joinpoint analysis results are slightly different from those reported by Loria *et al.*[7] for Córdoba province, with the exception of male trends from 1996. These differences may be associated with the different study period considered, methodological differences in the construction of standardized rates (estimated populations and number of age groups considered), as well as different sources of information. In our opinion, the significant decline in the ASMR after 1996 in both sexes could be partially associated with changes in the death cause coding (from the 9th to 10th revision of the ICD) occurring since 1996 in Argentina.

Whereas it is known that in cancer descriptive epidemiology, two core statistics should ideally be included to quantify the disease burden in terms of occurrence and results (such as the cancer incidence and mortality rates)[26], a simultaneous assessment of changes in these indicators is often difficult to obtain. In fact, in a world-wide framework, it is easier to obtain statistics for mortality, which are more commonly used for comparisons between population groups[1].

Little information about cancer incidence is available in Argentina, where only two registries produce reports from the International Agency for Research on Cancer[3,27]. Hence, the mortality data are usually the most reliable for carrying out studies on the cancer burden evolution in our country, both at national and local levels. However, it is important to note that although epidemiological research has been a weak feature of the public health policies in this country, the quality of data from death certificates is considered to be very good[7,9].

It is recognized that patterns of cancer occurrence and their temporal evolution vary greatly according to the region or country of residence, urbanization or income levels[1,28]. Our results indicate that geographic differences also exist in the underlying trends of cancer mortality in Córdoba province. Although the ASMR recorded were higher in MC and LC areas than in CC until 1996-2000, MC and LC areas have recently consistently shown lower ASMR than CC. This is probably associated with a lower degree of urbanization in these regions and the former lack of medical facilities[29] (1986 to 2000), followed by a growing urbanization that has improved living conditions, likely changing the spatial patterning of socioeconomic disadvantage. This accelerated rate of urbanization in the last decade has already been suggested in the literature, in particular for low- and middle-income countries[6], although identifying the health impacts of urbanization is complex and requires further investigation.

As previously reported[4], lung and prostate malignant neoplasms are the most frequent types of cancer in men in Argentina, with an incidence rate of 45 and 41 per 100,000 person-years, respectively, whereas in women, breast cancer (88.0/100,000) is the most common. Therefore, considering that around a third of the annual incidence rate of all cancers is represented by these cancer types (32% for lung and prostate in men, and 34% for breast cancer in women), it is reasonable to assume that trends in overall cancer rates recorded in the present research could be substantially influenced by factors associated with lung, prostate and breast cancer mortality. This also provides a plausible explanation for the tendencies observed in the overall cancer rates.

An exhaustive bibliographic search about cancer mortality in Argentina indicates that this study is the first to analyze age period and cohort effects. Since previously published studies[7,9-11] are limited to describing the ASMR over time by year of death, variations in trends associated with these simultaneous effects have not been probed. This APC analysis performed in Argentina may be a useful tool to increase our understanding of the mechanisms of carcinogenesis as well as to evaluate the impact of new diagnostic instruments and therapies on cancer mortality[30]. However, cohort effects must be interpreted with caution. Unusual random variations may arise in cohort effects, particularly in the recent ones, where the number of cancers recorded is small[12].

The age effect is present for virtually every cause of death and reflects changes in mortality rates associated with chronological age. A significant age effect, which is consistent with the biology of this pathology, was observed in our study. This fact is possibly strengthened by population aging, as observed in recent decades in both developed and developing countries. In Argentina, the percentage of adults older than 65 years increased from 8.6% in 1980 to 10% in 2001[7]. This rise in the elderly population is associated with a general increase in life expectancy and, in turn, with a greater number of people with a higher vulnerability to cancer. Moreover, the improved cancer screening programs and cancer care protocols have increased the morbidity rates, thus making the occurrence of death not related to cancer even more likely at later ages in life.

Similarly, the observed favorable period effect in cancer mortality trends worldwide, reflected by increased survival rates, may be due to positive changes in screening leading to early detection and medical care over time rather than innovative protocols in the treatment of the main cancer sites. In fact, in Argentina, prostate and breast CMR continued to increase before the introduction of prostate-specific antigen screening[31] and mammography screening. However, despite the favorable period effect in mortality rates recorded in our study, which may indicate some improvements, these rates still remain very high in comparison to other countries, indicating a minor efficiency of public health interventions in this field to date.

Overall, our results show a decreasing RR for birth cohorts, which was more pronounced in men. Birth cohort mortality trends have previously been described for the elderly (>60 years of age) in seven European countries[32]. They showed different trends in cancer mortality according to cancer site and country, including an unfavorable pattern for the cohort effect of lung cancer in most of these countries. In the case of Argentina, most immigrants come from two European countries: Italy and Spain. In 1980, 25.7% of the immigrant population had been born in Italy and 19.7% in Spain[33], whereas these figures were higher in the early 20th century. Therefore, a comparison between Argentinian mortality trends and those observed in European countries may be useful when attempting to evaluate the "genetic load" from epigenetic (environmental) influences.

La Vecchia *et al.*[12] reported an increasing cohort effect in males until the 1950 and 1930 birth cohorts in Spain and Italy, respectively, followed by a subsequent decline. Although this differs from our results for males, it is interesting to note that around these cohorts (1946 in our study) the RR shifted from positive to negative. For females, these authors also observed decreasing RR in both countries, the value being negative from 1930, as found for Córdoba mortality trends in the MC area.

Some known risk factors associated with most cancer incidence sites in Córdoba are tobacco smoke (for lung cancer)[34], dietary habits (prostate and breast cancer)[1] and natural pollution (inorganic arsenic in the groundwater)[35]. Thus, trends in birth cohort RR are conditioned by smoking and eating habits and by early arsenic exposure in our population. Generally, the cohort-specific risk of lung cancer is related to the smoking patterns of that same generation. In Spain, for example, the increasing mortality among younger generations born since 1940 was accompanied by an increase in tobacco consumption among females during recent decades[36], whereas decreases in recent CMR were attributed to the favorable trends for tobacco-related cancer rates observed in the European Union[37]. Although our analysis included all cancer sites, lung cancer accounted for 15% of the overall cancer mortality in 2006[38]. In Argentina in 2005, the prevalence of current tobacco use among adults (≥15 years of age) was 25.4% in females and 34.6% in males[39]. For Córdoba, the prevalence of tobacco use reported at present is 31.2%, use being higher in men than in women, and also at low-income than high-income levels[40].

As pointed out above, changes in dietary habits have been proposed as a plausible explanation for variations in cancer mortality, as assessed by APC analysis. Although there is limited information on eating habits locally, dietary changes have been observed to be moving rapidly towards an urban-industrial food system associated with the recent demographic, nutritional and epidemiological transitions in Latin America[1]. In previous studies by our group[41-42] and in the latest American Institute for Cancer Research report[1], some specific characteristics of the Argentinian diet and dietary habits have been identified as likely causes for some specific cancers. These include the herbal hot drink named mate (or its related thermal effect) for esophageal cancer and contamination of water supplies with arsenic: a cause of lung cancer and (probably) of skin melanoma. In particular, for Córdoba Province, some evidence has been provided that arsenic ingestion increases the risk of lung, kidney, bladder and skin cancers[43] and also possibly bladder cancer[44-45]. It is noteworthy that this region has the highest level of arsenic exposure among the districts included in our MC stratum. In these areas, aqueducts from rivers low in arsenic have been built in recent decades to replace contaminated arsenic groundwater usage[43]. This may have contributed to the more accentuated decreasing trend for the birth cohort effect in MC, with later generations being exposed to lower levels of arsenic in drinking water.

As regards dietary habits in the Córdoba population, some information is available from several case-control studies carried out only in the provincial capital city. Navarro *et al.*[41] found that a high intake of saturated fats, present in the red meat usually consumed in Argentina, was associated with a higher risk not only for breast cancer but also for colorectal cancer. Moreover, it was found that the degree of risk depended on the cooking method[46,42]. In our opinion, the observed cohort-effect decrease could reflect favorable dietary changes in these aspects for recent generations. In fact, during the last two decades, red beef consumption at a national level dropped from 73.9 in 1993 to 68.5 kg/year/person in 2007[47].

In conclusion, the strong age effect on cancer mortality trends in Cordoba reflects the underlying aging process currently observed in this province as in most middle-income regions, which are undergoing a demographic transition. Moreover, based on the observed cohort effect observed, it is possible to argue that a lower exposure to some known and unknown risk factors has been taking place in Cordoba over the last decades, thus influencing a decreasing trend in cancer mortality. However, recorded variations between population strata and sexes need further analysis in order to clarify the role of these suggested determinants of cancer.

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