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Age-period-cohort effect on mortality from cervical cancer

ABSTRACT

OBJECTIVE: To estimate the effect of age, period and birth cohort on mortality from cancer of the cervix.

METHODS: Mortality data for cervical cancer in women aged over 30, between1980 and 2009, for the municipalities of Rio de Janeiro and Sao Paulo, Southeastern Brazil,were extracted from the Mortality Information System. The estimated annual percentage change was calculated for the periods 1980-1994 and 1995-2009. Age, period and cohort effects were assessed employing the Poisson regression model, using estimated functions, deviations, curvatures and drift through the library Epi statistical program R version 2.7.2.

RESULTS: The average mortality rate per 100,000 women for the period in Rio de Janeiro was 15.90 and 15.87 in Sao Paulo. There was a significant reduction in mortality from cervical cancer in the two periods (1980-1994 and 1995-2009) in both Rio de Janeiro, -1.20% (95%CI -2.20;-0.09) -1.46% (95%CI -2.30;0.61) and in Sao Paulo, -2.58% (95%CI -3.41;1.76) and -3.30% (95%CI -4.30;2.29). The analysis of effects of curvature indicated reduction in deaths in successive cohorts (RR < 1 in women born after the 1960s). There was marked reduction in relative risk (RR) from the 2000s onwards.

CONCLUSIONS: The study showed that, in the time period analyzed, the period had an effect on the reduction in mortality rates for cervical cancer, bearing in mind that there was a protective effect (RR < 1) from the year 2000 onwards and in women born after the 1960s

DESCRIPTORS: Uterine Cervical Neoplasms, mortality. Cohort Effect. Period Effect. Age Effect. Logistic Models.

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INTRODUCTION

Cervical cancer is a preventable neoplasia. It is a disease with a well-documented natural history, with well-defined stages and slow progression of lesions. These characteristics mean it can be detected at an early, treatable stage through Pap smear testing. In the last ten years, vaccinations against the HPV virus, a cause of this type of cancer, have become available.[12,17,19]

Although measures are taken for its prevention and early detection, cervical cancer is the third most common cancer in women and the fourth most common cause of mortality worldwide. It is the fourth most common cause of death in Brazil, moving to second place in less developed regions.[3,9,14,18]

In Brazil, the first preventative measures for this neoplasia, using the Pap smear, occurred in the state of Sao Paulo in the second half of the 1980s. Public cytopathology laboratories and a referral system to care for positive or suspected cases were set up in municipalities and regions of the state.[21] Cervical cancer screening campaigns also became part of the Ministry of Health's Comprehensive Women's Health Care Program (PAISM) in this decade. There preventative actions were expanded to cover the whole country in 1998, through the National Cervical Cancer Control Program (NCCCP), known as the Life-Woman Program.[13,20,21]

Analyses of mortality trends for this type of cancer show a reduction over the last three decades.[18] However, these analyses made use of rates which summarized age and period of death, without considering the effect of the birth cohort, an important factor in understanding the evolution of diseases.[4,6,15]

The age effect represents changes in rates associated with age. The incidence and mortality from chronic illness increase with age.[4,6,7,15]

Period effect refers to changes in incidence and mortality due to events occurring at specific periods, simultaneously affecting all age groups. Cohort effect is provoked by factors which affect a generation and promote changes of different rates of magnitude in successive age groups and successive periods. Allowing us to evaluate the risk associated with habits and exposures of long duration.[4,6,7,15]

Using age-period-cohort (APC) models enables period and cohort effects to be separated[4,6,7,15] and to identify whether changes in mortality rates are correlated with alterations in the level of exposure to the HPV virus (cohort effect) and to co-factors associated with the persistence of lesions caused by the virus or to changes in specific preventative measures (period effect).

This study aimed to estimate the age, period and birth cohort effect (APC) on mortality from cervical cancer.

METHODS

Information on deaths from cervical cancer, cancer of the uterine body and cancer of the uterus, part unspecified, in women aged ≥ 30 in Rio de Janeiro, and Sao Paulo, in Southeastern, Brazil, were included in this study. The data were taken from the Mortality Information System (SIM/DATASUS). The population data were obtained from DATASUS, based on population censuses from 1980, 1991, 2000 and 2010. Projections for intercensal populations for 1st July of the census years were estimated by the *Instituto Brasileiro de Geografia e Estatística* (IBGE).

The city of Sao Paulo was chosen as the state of Sao Paulo was the first place in Brazil where screening using Pap smears was implemented. The city of Rio de Janeiro was chosen as it is the second largest city in the country, it is located in the Southeast and has similar socio-economic conditions to Sao Paulo.

In the period in which the study took place there were two revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD) underway. In the ninth version, the three digit character for cervical cancer was 180; for cancer of the uterus, part unspecified 179; and for cancer of the body of uterus, 182. The codes from the tenth revision were C53, C55 and C54 respectively. Deaths classified as cancer of the uterus, part unspecified, were redistributed as cervical cancer and cancer of the uterine body according to the proportions of death certificates originally registered for each category for cause, year and age group. Specific mortality rates were calculated according to age groups and mortality rates standardized by the direct method after redistribution using the world standard population as proposed by Segi.[5] The redistribution was carried out by correcting cervical cancer mortality rates, considering the large proportion of deaths classified as cancer of the uterus, part unspecified.

The Estimated Annual Percent Change (EAPC) was calculated based on the equation:. in which m was estimated based on the regression model in which the logarithm of mortality rates was the dependent variable and the calendar year the independent variable. This calculation assumes that the rate increases or decreases in a linear fashion year on year, during the entire interval in question. The EAPC was calculated for two consecutive periods: 1980-1994 and 1995-2009.

The age, period and birth cohort effects (APC) were calculated using the Poisson regression model, which assumes that the number of deaths follows a Poisson distribution. In this model, the effects behave in a multiplicative manner on the rate, so that the expected

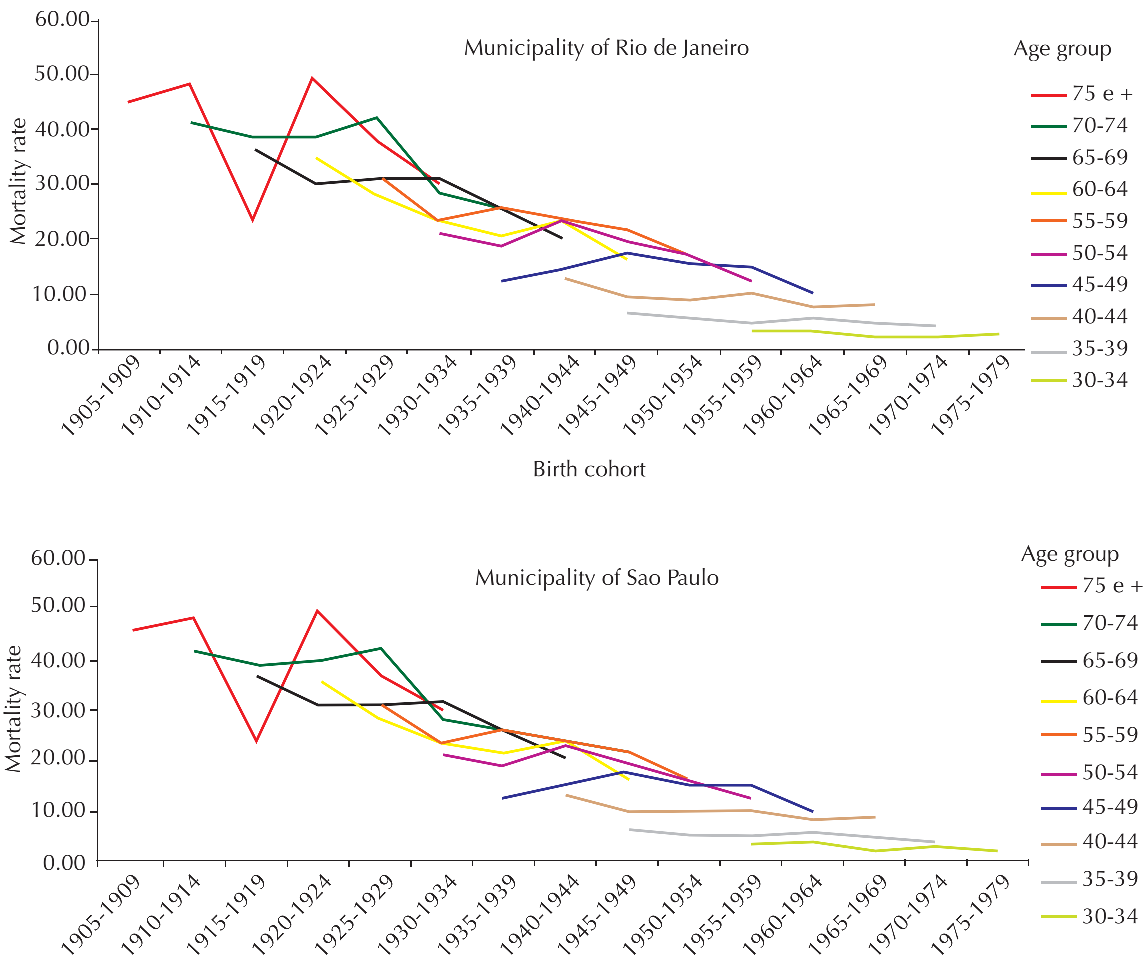

Figure 1. Cervical cancer mortality rates by birth cohort and age for deaths in the municipalities of Rio de Janeiro, and Sao Paulo, in Southeastern Brazil, 1980 to 2009.

value of the logarithm of the ratio is a linear function of the age, period and cohort effect:[4,6,7,15]

$$ln(E[r_{ij}]) = ln\left(\frac{\theta_{ij}}{N_{ij}}\right) = \mu + \alpha_i + \beta_j + \gamma_k$$

in which denotes the expected mortality rate at age *i*in the period *j*, the expected number of deaths at age *i*in period *j*, and denotes the population at risk of death at age *i* in period *j*: µ represents the mean effect, represents the age group effect *i*, represents the period effect *j*and the cohort effect *k*.

The age groups used were grouped by five year intervals, starting at 30-34 and ending at 75 and over, making a total of ten age groups. The period were also grouped by five year intervals, making six periods (1980 to 1984, 1985 to 1989, 1990 to 1994, 1995 to 1999, 2000 to 2004 and 2005 to 2009) and the birth cohorts started at 1900 and finished in 1979, making a total of 15 cohorts.

The main problem with estimating the parameters of the APC affect is the exact linear relationship between the age, period and cohort factors, which impedes estimation of the complete model. Various methodologies have been proposed to resolve this problem; however, no consensus exists in the literature. It was decided to estimate the parameters of the APC effect using estimable functions: deviations, curves and drift.[4,6,7,15]

The estimable functions limit the analysis of the effects to their linear combinations and curves. The curves are estimable functions of the parameters and remain constant regardless of the parameterization used.[4,6,7,15] The linear trend of the effects is divided into two components: the first is the linear effect of age and the other is the so-called drift, the linear effect of the cohort period.[4,6,7,15] The longitudinal tendency of age is equal to the sum of age and the gradient of period. in which and are the linear trend of age and of period respectively. Drift represents the linear trend of the logarithm of the rates specific to age. It is equal to the sum of the gradients of period and cohort.in which and are the linear trends for period and cohort, respectively.[4,6,7,15]

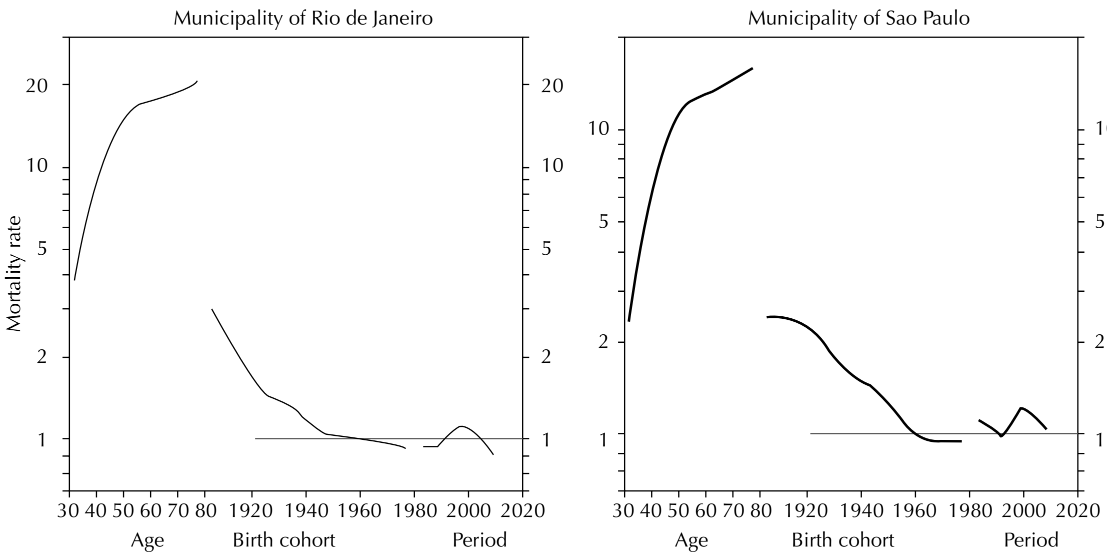

Figure 2. Results of the Age-period-cohort model, adjusted for cervical cancer mortality in the municipalities of Rio de Janeiro, and Sao Paulo, in Southeastern Brazil, 1980 to 2009.

For this methodology, a cohort and a period were chosen as reference. The specific rates for age and cohort/period of reference will be the RR (relative risk) of each cohort compared to the reference cohort and of each period compared to the reference period. It is advisable to choose central cohorts, as they was more complete than the first and last birth cohorts.[4,6,7,15] In this article, the 196-1964 cohort was used as the reference. The RR of the birth cohorts were adjusted for age and period effect and the RR of the period for birth cohort and age effect. These measures of association and their respective confidence intervals (95%CI) were calculated using Epi 1.1.18[a] (R statistic program, version 2.7.2).

The quality of fit was assessed using deviance statistics, defined as two times the logarithm of the estimated likelihood function of the model. The contribution of the effects was assessed by comparing the deviance of the model with the specific effect compared to the complete model (age-period-cohort). Results with $p \leq 0.05$ were considered significant. The tests were carried out using the R statistic program version 2.7.2, through the Epi 1.1.18 library,[a] as shown in Figures 1 and 2.

Figure 1 shows mortality rates by birth cohort for each age group. Figure 2 shows the effects of age, period and birth cohort based on the complete model. To the left, the mortality rates per 100,000 women by age are shown. The figure to the right of that shows the RR of the periods, adjusted for birth cohort and age effect and RR of birth cohorts adjusted for age and period in which death occurred.

RESULTS

Between 1980 and 2009 there were 9,995 deaths from cancer of the uterus in women aged over 30 in the municipality of Rio de Janeiro (MRJ), and 14,158 in the municipality of Sao Paulo (MSP). Deaths from cervical cancer were predominant in both cities (49.7% in MRJ and 51.9% in MSP).

The mortality rate from cervical cancer in MRJ was 10.76/100,000 women, and from cancer of the uterine body, 2.93/100,000 and for cancer of the uterus, part unspecified, 6.98/100,000 women. In MSP these figures were 11.45/100,000, 3.92/100,000 and 2.98/100,000 women respectively.

After redistributing the deaths classified as being from cancer of the uterus, part unspecified, mean mortality rates of 15.90/100,000 women from cervical cancer and 5.13/100,000 from cancer of the uterine body in MRJ and 15.87/100,000 and 5.75/100,000 women, respectively, in MSP.

The highest mortality rates in the two cities from this neoplasia were observed between 1980 and 1984, the rates declined between 1985 and 1989, although they rose again in the period 1990 and 1994. From 1995 to 1999 onwards there was a decrease in the mortality rates, a trend which continued until 2005 to 2009. This five-year-period had the lowest levels in the series studied (Table 1).

[a] Carstensen B, Plummer M, Hills M, Laara E. A package for statistical analysis in epidemiology. Vienna: Institute for Statistics and Mathematics; 2001 [cited 2010 Oct 19]. Available from: http://cran.r-project.org/web/packages/Epi/index.html

Table 1. Mortality from cervical cancer (per 100,000 women), in the municipalities of Rio de Janeiro and Sao Paulo, Southeastern Brazil, 1980 to 2009.

Age group (years)	Rio de Janeiro					
	1980 to 1984	1985 to 1989	1990 to 1994	1995 to 1999	2000 to 2004	2005 to 2009
30 to 34	3.60	4.24	3.60	3.31	3.46	3.21
35 to 39	6.91	6.21	9.29	7.40	5.00	6.02
40 to 44	11.20	8.37	9.31	10.40	9.54	9.64
45 to 49	17.99	13.05	16.51	14.14	16.15	12.78
50 to 54	19.53	21.63	22.25	18.40	17.87	12.78
55 to 59	20.40	26.02	23.66	21.13	17.57	15.09
60 to 64	29.38	22.14	25.25	29.05	21.82	17.28
65 to 69	34.64	28.57	31.99	24.60	25.43	22.03
70 to 74	26.76	18.51	18.37	16.70	17.01	17.62
75 +	31.25	23.41	21.05	30.71	22.02	15.21
Rate[a]	17.16	15.03	16.23	15.29	13.78	11.70
Age group (years)	Sao Paulo					
	1980 to 1984	1985 to 1989	1990 to 1994	1995 to 1999	2000 to 2004	2005 to 2009
30 to 34	2.98	3.18	2.58	2.38	2.25	2.37
35 to 39	6.43	5.27	4.69	5.21	4.58	3.79
40 to 44	12.80	9.54	9.03	9.77	7.93	8.10
45 to 49	15.32	14.33	17.45	14.44	12.65	10.32
50 to 54	22.61	18.80	21.05	19.67	16.46	12.23
55 to 59	30.55	23.43	25.04	23.20	21.54	16.94
60 to 64	35.26	28.26	22.88	20.83	22.84	16.31
65 to 69	36.41	30.51	30.76	31.25	25.56	20.21
70 to 74	25.78	24.80	24.67	28.65	22.41	25.55
75 +	24.45	24.87	24.68	29.74	22.83	20.30
Rate[a]	18,43	15,58	15,69	15,36	13,44	11,68

Source: Mortality Information System (SIM/DATASUS), Ministério da Saúde
Rate standardized using the direct method, with a reference population of the world population proposed by Segi and each modified by Doll et al[5] and corrected using proportional redistribution of the deaths classified as from cancer of the uterus, part unspecified.

The highest mortality rates were in women born between 1900 and 1940, over 20.0 deaths per 100,000 women aged up to 50-54 years old, in both cities. The mortality rates decreased in the younger age groups in each birth cohort, these being under 10.0 deaths per 100,000 in women born after the 1950s and in the age group 40 to 44 (Figure 1).

There was an overall decrease in cervical cancer mortality rates in both cities in the EAPC. The EAPC between 1980 and 1994 was -1.20% (95%CI -2.20;-0.09) and -2.58% (95%CI -3.41;-1.76) in MRJ between 1995 and 2009. In Sao Paulo, this was -1.46% (95%CI -2.30;-0.61) and -3.30% (95%CI -4.30;-2.29), respectively. Variations in the age groups showed that the MSP had a greater number of age groups with a statistically significant decrease, compared with MRJ (Table 2).

Both age-cohort and age-period models showed better fit to the data than the models containing just age and age-drift. The complete model was significantly better than that with only two factors AP ($p < 0.0001$) and AC ($p < 0.0001$). The AC model had as null hypothesis the lack of influence of period effect on mortality rates. And the AP model had as null hypothesis the lack of influence of the birth cohort effect (Table 3)

In both cities, there was a progressive increase in cervical cancer mortality rates with age (Figure 2).

In MRJ, a reduced risk of death compared to the reference period (1990 to 1994) was observed between 1985 and 1989 (RR = 0.93; 95%CI 0.89;0.97). There was an increased risk in the 1990s, with the highest value between 1995 and 1999 (RR = 1.12; 95%CI 1.04;1.20), which again decreased in the 2000s, and the lowest value was between 2005 and 2009 (RR = 0.86; 95%CI 0.83;0.92). The period between 1985 and 1989 had RR = 1.04 (95%CI 1.01;1.08) in MSP; there was increased risk in the 1990s, reaching a peak between

Table 2. Estimated annual percentage variation (EAPC) of cervical cancer mortality rates, in the municipalities of Rio de Janeiro, and Sao Paulo, in Southeastern Brazil, 1980 to 2009.

Age group (years)	Rio de Janeiro			
	1980 to 1994		1995 to 2009	
	EAPC%	95%CI	EAPC%	95%CI
30 to 34	1.73	-3.90;7.70	-0.29	-3.98;3.54
35 to 39	1.55	-3.00;6.30	-4.85	-9.76;0.33
40 to 44	-14.09	-54.34;61.64	-1.08	-3.07;0.96
45 to 49	-0.99	-4.77;2.93	0.46	-1.74;2.70
50 to 54	0.12	-2.46;2.77	-0.30	-3.82;3.35
55 to 59	1.44	-1.69;4.67	-0.82	-2.80;1.20
60 to 64	-1.82	-3.90;0.30	-5.39[a]	-7.15;-3.60
65 to 69	-1.58	-5.41;2.41	-1.67	-5.16;1.95
70 to 74	-2.85	-6.69;1.14	-3.10	-6.19;0.09
75 +	-3.60[a]	-5.13;-2.05-	-7.36[a]	-9.21;-5.48
Annual	-1.20[a]	-2.29;-0.09	-2.58[a]	-3.41;-1.76
Age group (years)	**Sao Paulo**			
	1980 to 1994		1995 to 2009	
	EAPC%	95%CI	EAPC%	95%CI
30 to 34	-1.03	-4.48;2.55	0.51	-2.78;3.90
35 to 39	-3.19	-7.34;1.14	-3.51[a]	-6.62;-0.29
40 to 44	-3.40[a]	-5.21;-1.55	-1.64	-3.67;0.43
45 to 49	2.24	-1.68;6.33	-2.87[a]	-5.33;-0.35
50 to 54	-0.81	-3.53;1.99	-4.14[a]	-5.67;-2.59
55 to 59	-2.39[a]	-4.60;-0.13	-2.11	-4.33;0.16
60 to 64	-3.86[a]	-5.77;-1.91	-2.12	-4.40;0.22
65 to 69	-1.76	-3.57;0.08	-3.83[a]	-6.12;-1.48
70 to 74	-0.66	-3.36;2.11	-4.83[a]	-7.41;-2.19
75 +	0.15	-2.80;3.19	-4.61[a]	-7.09;-2.06
Annual	-1.46[a]	2.30;-0.61	-3.30[a]	-4.30;-2.29

[a] EAPC: Statistically different from zero (two-tailed Student t test p ≤ 0.05)

1995 and 1999 (RR = 1.22; 95%CI 1.15;1.31), which then fell and continued to do so until 2009 (RR =1.02; 95%CI 0.97;1.07) (Figure 2).

Analysis of mortality in birth cohorts shows an accentuated tendency for risk of death to decrease in successive birth cohorts. There was a high risk of death from this neoplasia for women in both cities between 1900 and 1940. The 1900-1940 birth cohort had an RR = 3.30 (95%CI 2.78;3.86) in MRJ and RR = 2.40 (95%CI 2.05;2.80) in MSP. In both cities, there was a reduction in the rate for the 1930 to 1934 cohort (RR = 1.47; 95%CI 1.33;1.62) in MRJ and in MSP (RR = 1.57; 95%CI 1.45;1.72). After this decade, there was a progressive decrease in the risk of death, becoming < 1 in women born after the reference birth cohort (1960 to 1964); the lowest value was seen in women born in the 1975 to 1979 cohort. In MRJ, the RR was 0.89 (95%CI 0.81;0.96) and in MSP, was 0.85 (95%CI 0.78;0.95) (Figure 2).

Table 3. Adjustments to the models of age-period-cohort effects, for mortality from cervical cancer in the municipalities of Rio de Janeiro, and Sao Paulo, in Southeastern Brazil, 1980 to 2009.

Models	Rio de Janeiro		
	Degrees of freedom	Deviance residual	p (>|Chi|)
Age	54	330.4	
Age-*drift*[a]	53	170.8	< 0.00001
Age-cohort	49	142.4	< 0.00001
Age-period-cohort	45	90.2	< 0.00001
Age-period	49	135.2	< 0.00001
Age-*drift*[b]	53	170.8	< 0.00001
	Sao Paulo		
Age	54	441.9	
Age-*drift*[a]	53	209.8	< 0.00001
Age-cohort	49	193.3	< 0.0001
Age-period-cohort	45	145.9	< 0.00001
Age-period	49	162.3	< 0.00001
Age-*drift*[b]	53	209.8	< 0.00001

[a] Linear trend of the logarithm of the specific rates for Age over time is equal to the sum of the gradients for do tempo period and cohort $(\beta_L + \gamma_L)$, when β_L and γ_L are the linear trend for period and cohort, respectively.
[b] Longitudinal trend of Age is equal to the sum of Age and the gradient of period $(\alpha_L + \beta_L)$, when α_L and β_L are the linear trends of Age and period, respectively.

DISCUSSION

This study showed a significant difference in mortality from cervical cancer in both cities during the period in question, a significant period effect (national program for controlling cervical cancer) in reducing the risk of death. Lower RRs were observed after the 2000s, above all in women born after the 1960s.

Evaluating the risk of death from cervical cancer according to birth cohort showed that women born between 190 and 1920 had a high risk of death from this neoplasia. Birth cohorts after 1930 a progressively reduced risk of death, with a protective effect (RR < 1) for women born after 1960.

Between 1900 and 1920, cancer was seen as an incurable disease and there were no secondary preventative practices. This may explain the higher risk of death when compared with more recent birth cohorts.[1,20]

Among women in the 1930 to 1940 birth cohort, the introduction of measures to care for and prevent cancer may have had some influence on mortality rates. In the 1940s, pioneering work among health care professionals started to bring the practice of cytology and colposcopy to Brazil. These preventative and curative measures only reached a small group of the population, as at that time public health care resources prioritized the prevention and treatment of infectious diseases.[1,20]

The protective effect observed in women born after the 1960s may be related to intensified efforts to prevent and control this neoplasia with the establishing of the PNCCC at the end of the 1990s. This program increased the number of screening tests carried out annually by the Brazilian Unified Health System (SUS) by 81% between 1995 and 2003.[20]

There was an increase in the risk of death from this neoplasia during the 1990s, peaking between 1995 and 1999 in both MRJ and MSP, which then declined after 2000 and continued to decline until 2009.

The increased cervical cancer mortality rate in the 1990s may be related to low levels of coverage for the cytology tests at the beginning of the decade. In 1994, 37% of Brazilian women aged 35 to 49 had never had a smear test, in the Southeast the figure was 32%.[b] After the NCCCP was established in 1998, availability and access to these tests increased. Data from the National Research by Household Survey (PNAD) between 2003[c] and 2008[d] estimated coverage of 68.7% and 84.5% for protective gynecology in women aged over 25, respectively.

Decreasing mortality rates for this neoplasia related to the effect of the program for prevention and control of cervical cancer (period effect), indicated in this study, are similar to those of other studies carried out in the United Kingdom (1950-1997),[16] Switzerland (1953-1995)[2] and in the state to Minas Gerais, Southeast, (1980-2005).[1] The authors of these studies unanimously interpret the results of these studies as best explained by the establishment of a program of screening for cancer than as a birth cohort effect.

These results do not agree with those observed in Shandong, China (1970-1992),[10] and in Spain (1951-1991),[11] as the reduction in mortality rates was related to cohort effect in function of lowered exposure to risk factors related to this type of cancer. This hypothesis is coherent, considering that in China, brothels were closed, prostitution banned and the single child per couple policy instituted. In the same way, in Spain, before 1975 the low mortality rates found there were associated with becoming sexually active at a later age, a reduced number of sexual partners, delayed widespread use of hormonal contraceptives as well as the fact that adultery was criminalized until 1976. Campaigns to combat cervical cancer were regionalized and, in the period studied, only covered a small part of the female population.[10,11]

One of the limitations of this study was the quality of information, bearing in mind the large number of deaths classified as "cancer of the uterus, part unspecified", especially in the first years of the series studied. An attempt was made to correct this problem by redistributing these deaths according to the proportion of certificates registered for each category by age and year of death.

Another limitation concerns the APC models, which are still in development. The results obtained vary according to the assumptions used in constructing the models. In the last decade, articles have been published discussing methodological aspects in the specifications of the models and in resolving the problem of not identifying the complete model.[8,a]

The Poisson model assumes the equality of mean and variance, difficult to achieve in practice, and variance is generally greater than the mean. This phenomenon is known as overdispersion and, when not detected and corrected, leads to an incorrect estimation of standard deviation and, consequently, an incorrect assessment of the significance of the parameters. In the analyses in this study, the Poisson models were adjusted because the adjusted results for this distribution did not differ from those obtained from the negative binomial.

This study showed the importance of establishing and consolidating the NCCC Pin reducing the risk of death from cervical cancer, even in women with greater exposure to risk factors for this neoplasia. There was a protective effect (RR < 1) for women born after the 1960s, who were influenced by the sexual and cultural revolution which began in this decade (cohort effect) and underwent changes in lifestyle which increased their exposure to risk factors associated with this type of cancer.[20,21] The possible increased risk of infection with the HPV virus did not have a greater repercussion on mortality due to the existence of effective protective measures.

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[b] Ministério da Saúde. Instituto Nacional de Câncer. Viva Mulher – Programa Nacional de Controle do Câncer do Colo Uterino. Brasília (DF); 1996.

[c] Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional por Amostra de Domicílios (PNAD) 2003 – Acesso e utilização dos serviços de saúde. Brasília (DF); 2011 [cited 2010 Oct 20]. Available from: http://www.ibge.gov.br/home/estatistica/populacao/trabalhoerendimento/pnad2003/saude/saude2003.pdf

[d] Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional por Amostra de Domicílios (PNAD) 2008 – Suplemento Saúde. Brasília (DF); 2011 [cited 2010 Oct 20]. Available from: http://www.ibge.gov.br/home/estatistica/populacao/panorama_saude_brasil_2003_2008/default.shtm

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