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Recent decline in cancer mortality in Catalonia (Spain). A joinpoint regression analysis

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Abstract

The aim of this paper was to analyse recent changes in cancer mortality in Catalonia (Spain) between 1975 and 1998 using joinpoint regression models. Mortality data were obtained from the Mortality Registry of Catalonia. For each sex, age-standardised (standard world population) mortality rates were computed by the direct method, and joinpoint analysis was used to identify the best fitting points where a statistically significant change in the rates had occurred. In men, the overall cancer mortality (except skin non-melanoma) was highest in 1991 and decreased thereafter. Lung cancer was the main cause of cancer mortality, with an increase until 1989, and a subsequent levelling off (−0.8% annual between 1989 and 1998). Colorectal cancer was the second cause of cancer death, both in men and women, with a levelling-off of the rates since 1991 and 1989, respectively. In women, the mortality rate decreased for total cancer (except skin non-melanoma) since 1991 (−0.9% annually). Breast cancer increased until 1975, levelled-off and begun to decline since 1992 (−3.8% annual). Lung cancer increased since 1988 (+2.1%) and became the third cancer cause of death among women in 1998. These changes are mainly due to the decline of smoking prevalence in males, but not in females, and to the introduction of new diagnostic techniques and improved therapies for female breast cancer. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Mortality; Cancer; Time trends; Joinpoint regression; Tobacco; Smoking; Screening; Early detection; Catalonia, Spain

1. Introduction

Since the end of the 1980s, a decline in cancer mortality in Europe and the USA has been observed [1,2]. In the European Union, the trends analysed until 1996 show that, in males, lung cancer and colorectal mortality declined in the last decade, together with the steady decline in gastric cancer mortality. In women, lung cancer mortality has increased, but breast cancer, colorectal cancer, and uterine cancer mortality are decreasing [3].

A quite different pattern was observed in Catalonia (north east of Spain) until 1990, where the analysis of the mortality trends showed an increase in lung cancer, mouth and pharynx, intestines and melanoma in males, and increases in the mortality from breast cancer, ovary, colorectal, pancreas and melanoma in women [4], similar to those observed for the whole of Spain [5]. In men, cancers that have mainly contributed to these trends are those linked to smoking, that has had a somewhat different pattern compared with other European countries [6,7].

Most previous analyses of mortality were based on the modelling of mortality rates within a unique period of time (i.e. 1955–1990), which provides the average annual percentage of change assuming that rates increase or decrease at a constant rate over time, although the validity of this assumption has not been assessed [8]. In addition, age-period-cohort models have also been used to evaluate whether the changes observed were attributable to a period or a cohort effect [8]. The visual inspection of the plots of mortality rates has helped to describe the changes in the patterns, although

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no statistical procedure was used to identify the calendar years when changes occur.

The joinpoint regression model, recently developed [2,9] is useful to identify and describe the occurrence of changes in distinct periods of time in trend data. Thus, the aim of this paper was to analyse the recent changes in cancer mortality in Catalonia (Spain) between 1975 and 1998, using joinpoint regression models.

2. Patients and methods

Mortality data were obtained from the Mortality Registry of Catalonia maintained by the Ministry of Health of Catalonia. All cancer deaths of residents in Catalonia between 1975 and 1998 were included. The period of study included a change in the International Classification of Diseases (ICD), from the 8th to the 9th revision. Thus, all the deaths were coded using the 9th revision.

For each sex, truncated rates (35–64 years) and overall age-standardised (world population) mortality rates from the main cancer sites (Tables 1 and 2) were computed by the direct method, and are expressed as rates/100 000 men or women.

The joinpoint regression model was used to describe changes in trend data. This type of non-linear regression model has been named in the literature also as piecewise regression, segmented regression, broken line regression, or multi-phase regression with the continuity constraint [9]. In joinpoint analysis, the best fitting points (the "joinpoints") where the rate changes significantly (increase or decrease) are chosen [2,9]. The analysis starts with the minimum number of joinpoints (e.g. 0 joinpoints, which is a straight line) and tests whether one or more joinpoints are statistically significant and must be added to the model (up to four joinponts). The tests of significance use a Monte Carlo permutation method. In the final model each joinpoint (if any) informs of a statistically significant change in trend, and an annual percent of change is computed by each of those trends by means of generalised linear models assuming a Poisson distribution [8]. Significant changes include changes in direction or in the rate of increase or decrease. The annual percent of change is tested to determine if it is different from the null hypothesis that the annual percent change is 0% [2]. The computation of mortality rates and their standard errors was implemented in S-PLUS (S-PLUS 2000, MathSoft, Inc. 1999). The joinpoint analyses were performed using the

Table 1
Age-standardised cancer mortality rates (1975–1976 and 1997–1998) and joinpoint analysis (1975–1998): males, all ages, Catalonia (Spain)

Cancer site (ICD-9)	Age-standardised mortality rates[a]		Annual percent of change 1975–1998	Joinpoint analysis (1975–1998)							
	1975–1976	1997–1998		Trend 1		Trend 2		Trend 3		Trend 4	
				Years	APC[b]	Years	APC[b]	Years	APC[b]	Years	APC[b]
All sites (except non-melanoma skin cancer)	150.9	171.8	0.7[c]	1975–1981	0.5	1981–1992	1.6[c]	1992–1996	-2.5[c]	1996–1998	1.2
Smoking-related cancers	61.9	84.0	1.5[c]	1975–1990	2.8[c]	1990–1998	−1.1[c]				
Oral cavity and pharynx (140–149)	3.6	7.0	3.4[c]	1975–1998	3.4[c]						
Oesophagus (150)	5.3	5.0	0.3	1975–1998	0.						
Stomach (151)	20.5	10.4	−2.9[c]	1975–1981	−4.3[c]	1981–1998	−2.6[c]				
Colorectal (153, 154, 159)	13.3	18.5	1.9[c]	1975–1982	0.2	1982–1991	3.5[c]	1991–1998	−0.1		
Liver (155)	9.8	8.9	0.1	1975–1983	0.3	1983–1987	−6.0	1987–1990	9.9	1990–1998	−1.5
Gallbladder (156)	1.2	1.4	1.4[c]	1975–1977	−16.7	1977–1987	7.9[c]	1987–1991	−7.4	1991–1998	1.9
Pancreas (157)	3.9	6.5	2.3[c]	1975–1987	3.9[c]	1987–1998	0.8				
Larynx (161)	7.9	5.2	−1.7[c]	1975–1991	−1.3[c]	1991–1998	−3.4[c]				
Lung (162)	32.8	48.8	1.8[c]	1975–1982	2.3[c]	1982–1989	4.0[c]	1989–1998	−0.8[c]		
Melanoma (172)	0.4	1.1	5.0[c]	1975–1986	10.3[c]	1986–1998	2.1				
Prostate (185)	12.9	14.2	0.4[c]	1975–1998	0.4[c]						
Urinary bladder (188)	6.7	8.6	1.1[c]	1975–1992	2.3[c]	1992–1998	−3.3				
Kidney (189)	2.00	3.1	2.4[c]	1975–1990	3.9[c]	1992–1998	−0.4				
Brain (191–192)	5.6	4.3	−1.6[c]	1975–1998	−1.6[c]						
Thyroid (193)	0.1	0.3	1.8	1975–1998	1.8						
Hodgkin's disease (201)	1.5	0.9	−2.9[c]	1975–1998	−2.9[c]						
Non-Hodgkin's lymphoma (200–202)	1.8	3.8	3.4[c]	1975–1991	5.6[c]	1991–1998	−1.9				
Myeloma (203)	1.0	1.9	2.8[c]	1975–1990	4.9[c]	1991–1998	−0.9				
Leukaemias (204–208)	5.3	4.9	−0.2	1975–1991	0.9[c]	1991–1998	−3.3				

[a] Rates are per 100 000 inhabitants and are age-adjusted to the world population.
[b] APC, annual percent of change.
[c] The APC is statistically significantly different from 0 ($P < 0.05$).

Table 2
Age-standardised cancer mortality rates (1975–1976 and 1997–1998) and joinpoint analysis (1975–1998): females, all ages, Catalonia (Spain)

Cancer site (ICD-9)	Age-standardised mortality rates[a]		Annual percent of change 1975–1998	Joinpoint analysis (1975–1998)					
	1975–1976	1997–1998		Trend 1		Trend 2		Trend 3	
				Years	APC[b]	Years	APC[b]	Years	APC[b]
All sites (except non-melanoma skin cancer)	90.53	78.0	−0.4[c]	1975–1980	−2.2[c]	1980–1991	0.4	1991–1998	−1.8[c]
Smoking-related cancers	10.80	11.5	0.2	1975–1981	−1.2	1981–1998	0.5		
Oral cavity and pharynx (140–149)	0.7	0.8	1.8[c]	1975–1998	1.8[c]				
Oesophagus (150)	0.7	0.5	−2.3[c]	1975–1998	−2.3[c]				
Stomach (151)	11.1	4.3	−3.7[c]	1975–1980	−7.2[c]	1980–1992	::2.5[c]	1992–1998	−5.2[c]
Colorectal (153, 154, 159)	9.8	11.1	0.8[c]	1975–1988	1.7[c]	1988–1998	−0.5		
Liver (155)	7.3	3.3	−3.6[c]	1975–1986	−5.2[c]	1986–1998	−2.0[c]		
Gallbladder (156)	1.4	1.6	−0.1	1975–1998	−0.1				
Pancreas (157)	2.5	3.3	1.5[c]	1975–1998	1.5[c]				
Larynx (161)	0.3	0.1	−4.5[c]	1975–1998	−4.5[c]				
Lung (162)	4.1	4.4	−0.1	1975–1988	−1.7[c]	1988–1998	2.1[c]		
Melanoma (172)	0.3	0.8	3.5[c]	1975–1987	6.8[c]	1987–1998	1.0		
Breast (174)	15.1	16.8	1.0[c]	1975–1992	2.1[c]	1992–1998	−3.8[c]		
Uterus NOS (179)	7.6	0.8	−9.2[c]	1975–1981	−6.2[c]	1981–1998	−10.2[c]		
Cervix (180)	1.2	1.7	1.9[c]	1975–1981	0.4	1981–1987	7.5[c]	1987–1998	−1.3
Uterine corpus (182)	8.3	1.8	−8.1[c]	1975–1979	−7.7[c]	1979–1982	−45.7[c]	1982–1998	4.4[c]
Uterus, cervix and corpus (179–182)	9.6	4.3	−3.4[c]	1975–1982	−4.8[c]	1982–1998	−2.9[c]		
Ovary (183)	2.2	4.1	2.8[c]	1975–1985	6.8[c]	1985–1995	1.6	1995–1998	−5.4
Urinary bladder (188)	1.3	1.1	−0.8[c]	1975–1998	−0.8[c]				
Kidney (189)	1.3	1.2	0.3	1975–1987	−1.8	1987–1998	2.6[c]		
Brain (191, 192)	3.5	2.6	−1.6[c]	1975–1998	−1.6[c]				
Thyroid (193)	0.3	0.4	0.3	1975–1998	0.3				
Hodgkin's disease (201)	0.5	0.3	−3.5[c]	1975–1998	−3.5[c]				
Non-Hodgkin's lymphoma (200–202)	1.0	2.6	4.2[c]	1975–1990	7.3[c]	1990–1998	−1.1		
Myeloma (203)	0.5	1.6	3.4[c]	1975–1998	3.4[c]				
Leukaemias (204–208)	4.1	3.2	−0.9[c]	1975–1983	−2.5	1983–1987	5.3	1987–1998	−2.9[c]

NOS, not otherwise specified.
[a] Rates are per 100 000 inhabitants and are age-adjusted to the world population.
[b] APC, annual percent of change.
[c] The APC is statistically significantly different from 0 ($P<0.05$).

'Joinpoint' software from the Surveillance Research Program of the US National Cancer Institute (available at http://www-dccps.ims.nci.nih.gov/SRAB).

3. Results

Age-standardised and truncated (35–64 years) mortality rates from all cancers, lung, colorectal, stomach, prostate, urinary bladder, breast, uterus, and ovary are presented in Figs. 1–3. Tables 1 and 2 show the joinpoints, that is, the points where the rate changes significantly, and the annual percentage of change for each trend, for the main cancer sites in males and females, respectively.

In males, mortality from all cancers (except non-melanoma skin cancer) significantly increased until 1992 (annual increase 1.6%), followed by a significant steady decrease of −2.5% for 1992–1996. Cancer deaths for women decreased prior to 1980, levelled off until 1991 and then declined after 1991 (−1.8% annually; $P<0.05$). As shown in Fig. 1, the pattern of decline was more marked when the truncated rates were analysed. In males, the leading cancer cause of death was lung cancer, with an age-standardised rate of 48.8/100 000 in 1997–1998 (annual percentage change of 1.8%; $P<0.05$). As shown in Fig. 2, a sharp increase occurred between 1982 and 1989 (4.0%), followed by a slight, but statistically significant decrease from 1989 onwards (−0.8% per year).

In women, lung cancer became in 1998 the third cause of cancer death (4.4/100 000), before stomach, uterus and ovary cancer, with breast and colorectal cancer mortality rates representing the leading causes of death. Although no trend for lung cancer in females during the whole period (1975–1998) was apparent (−0.1%), the recent trend since 1988 show an annual statistical significant increase of 2.1% (Table 2). The truncated rates were higher, both in males and females, with a similar pattern to that described (Figs. 2 and 3). Breast cancer was the main cause of cancer death in women in 1997–1998 (Table 2). After a steady increase between 1975 and 1992 (annual increase of 2.1%, more apparent according to the truncated rates, Fig. 3), the rates level-

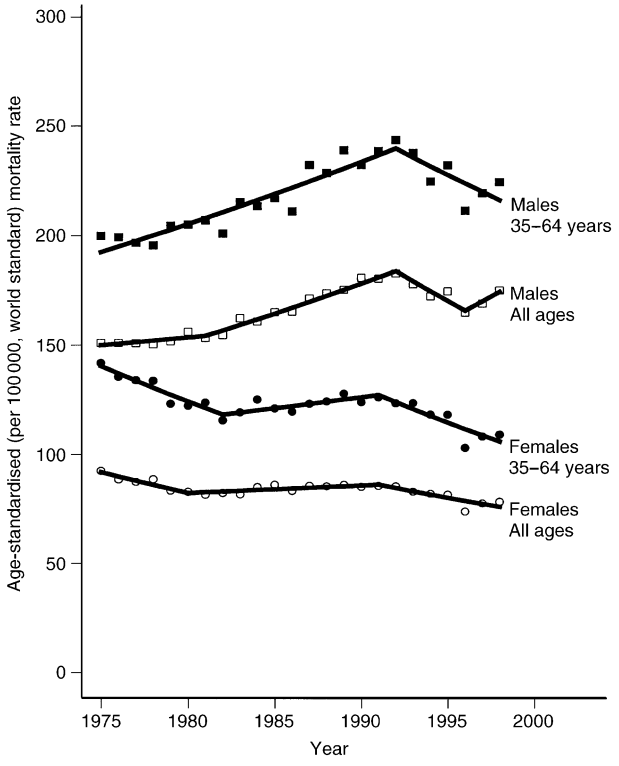

Fig. 1. Trends in age-standardised (per 100 000 world standard) mortality rates for cancers (all sites except non-melanoma skin cancer) in Catalonia (Spain), 1975–1998.

led off and steadily decreased between 1992 and 1998, with a statistically significant drop of 3.8% per year.

Colorectal cancer was the second leading cause of cancer death in males and females, as shown in Figs. 2 and 3. Recent trends (since 1991 in males and since 1988 in females) show a levelling off of the mortality rates, which is more apparent in females, following the steady increases observed previously. This pattern was even more marked when the truncated rates were analysed (Figs. 2 and 3).

In males, prostate cancer became the third leading cause of cancer mortality in 1997–1998 (age-adjusted rate of 14.2/100 000), before stomach cancer (10.4/100 000). This situation is as a consequence of the slight increase of 0.4% per year between 1975 and 1998 (no joinpoint) in prostate cancer mortality together with the significant annual decrease in stomach cancer mortality (−4.3% 1975 and 1981, and −2.6% until 1998). In females, stomach cancer mortality was the fifth leading cause of cancer death (age-adjusted mortality rate of 4.33/100 000, after uterus, cervix and corpus, with a rate of 4.34/100 000) and decreased an annual average of −3.7%, with sharp decreases between 1975 and 1980 (−7.2% per year) and 1992–1998 (−5.2% per year).

Finally, the mortality rates for smoking-related cancers were also computed (oral cavity and pharynx, oesophagus, pancreas, larynx, lung, urinary bladder, and kidney). As shown in Table 1, a favourable trend (−1.1% per year, $P<0.05$) between 1990 and 1998 is apparent in males. In females, a non-significant steady increase of 0.5% per year since 1981 is present.

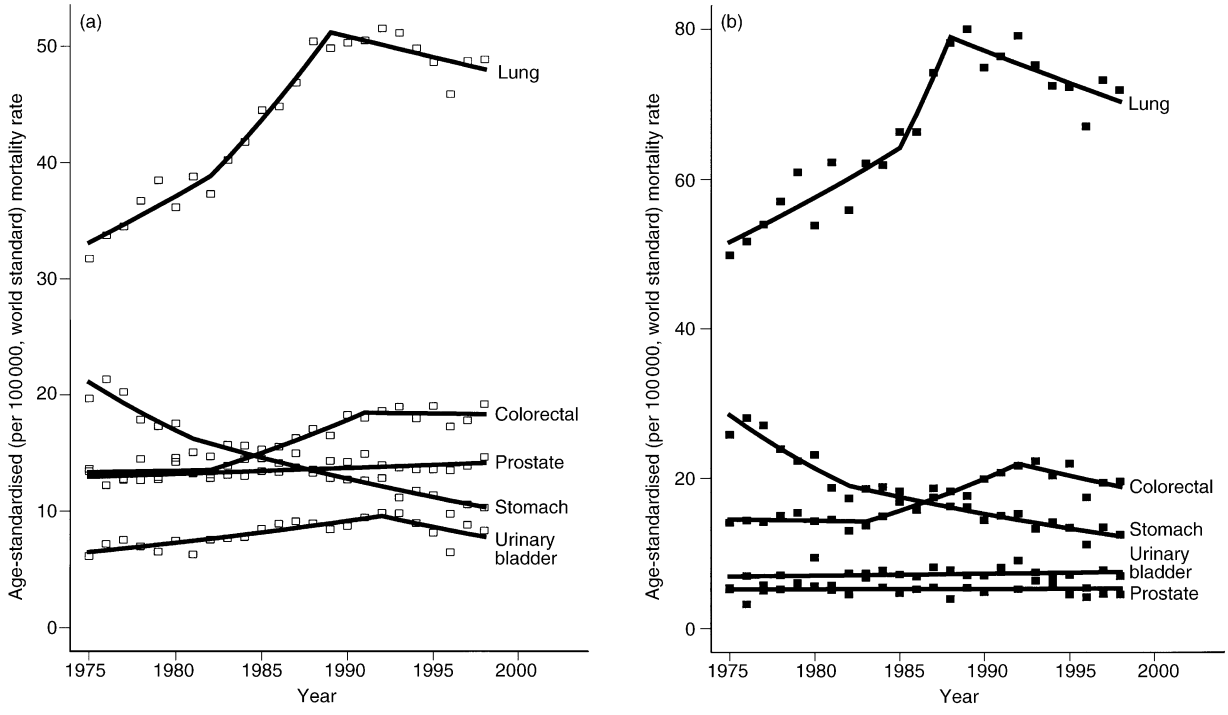

Fig. 2. Trends in age-standardised (per 100 000 world standard) mortality rates for selected cancers in Catalonia (Spain). Males (a) all ages and (b) 35–64 years.

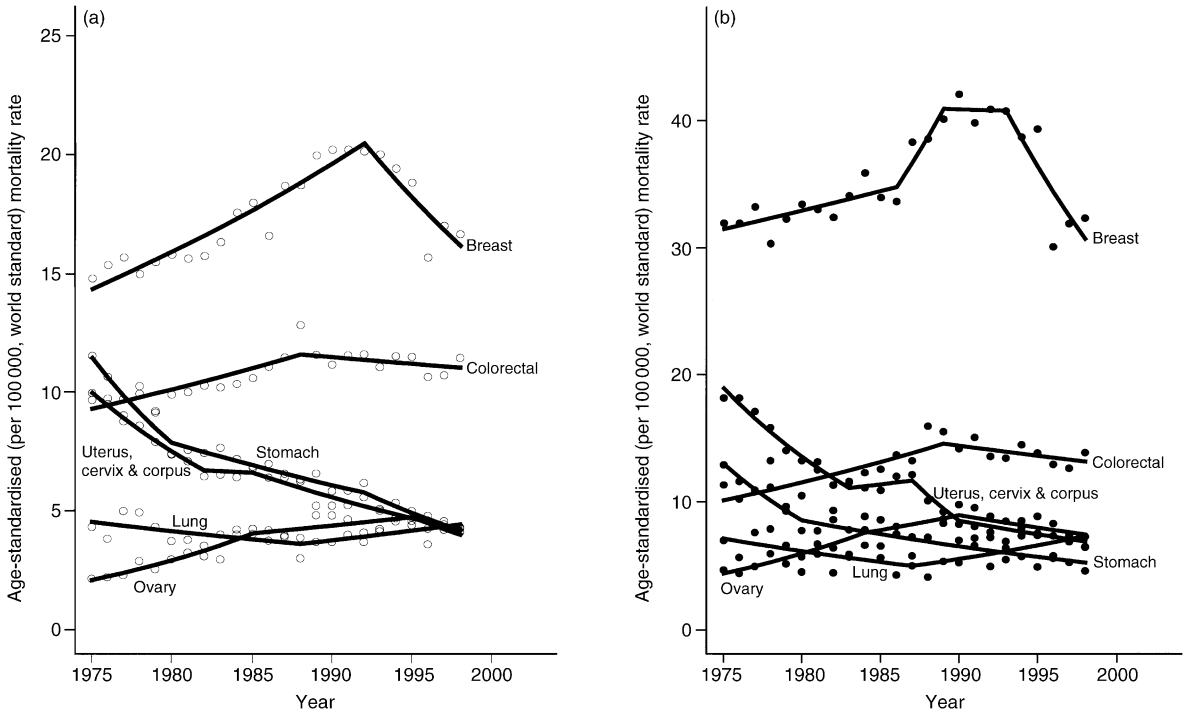

Fig. 3. Trends in age-standardised (per 100 000 world standard) mortality rates for selected cancers in Catalonia (Spain). Females (a) all ages and (b) 35–64 years old.

4. Discussion

Joinpoint analyses allowed the identification of the beginning of the decline of cancer mortality in both sexes since 1991–1992 in Catalonia (Spain). This levelling-off and subsequent decline is similar to that observed in the European Union and the United States since 1988 [1,2]. Although a delay in observing the changes of the mortality pattern was already suggested in previous studies [4,5], this report confirms the beginning of the control of cancer mortality in our country.

This overall decline in cancer mortality is mostly related to the levelling-off and significant steady decrease in lung cancer mortality and other smoking-related cancers in males since 1990, to the decline since 1991 in breast cancer mortality among females, and to the levelling-off of colorectal cancer mortality in both males and females. The persistent fall in stomach cancer mortality rates—that follows a decline in incidence—has also contributed to the overall recent favourable trend. Taking into account the increase in cancer incidence observed from 1980 onwards [10], this recent declining trend in cancer mortality could be partly attributed to an increase in survival in several cancer sites, as consistently observed in Catalonia and Spain [11]. The increase in survival may have two non-excluding explanations. Firstly, early diagnosis and improved treatments increase the time between diagnosis and death from cancer, and secondly, more people are living *with* a diagnosis of cancer and will die later from other competing causes, but not from their cancer.

The decline in mortality from lung and other smoking-related cancers in males reflects the downward trends in smoking over the last few decades in our country. Trends in smoking prevalence in Catalonia in the last 15 years indicate a decline in the habit in males, but an increase in females over the same period, specifically those of younger ages [6]. Age-specific smoking initiation rates in Catalonia were very low for females before the 1970s and have not converged with males rates until recently [12]. Lung cancer mortality in females has increased since 1988, and there are also increasing incidence rates [13], reflecting the pattern of initiation and the upwards trends in smoking prevalence since the beginning of the 1970s [6,7]. This increase in the mortality rates has occurred with substantial delay with respect to most European countries [14], and the differential pattern of the tobacco epidemic in females may explain these data (age at starting smoking, tobacco type, intensity and duration of habit [12,15,16,31]). This analysis suggests that the smoking epidemic and its impact on incidence and mortality will be a main public health problem in our country in the near future.

While the control of breast cancer mortality is, in part, attributable to improved screening and early diagnosis [17], its impact in Catalonia is still limited, given that the first population-based programmes started in

the mid-1990s [10]. The decline in breast cancer mortality may be attributed to improved survival as a consequence of the general adoption of hormonal therapy and polychemotherapy [3,18]. Other factors, such as a greater awareness amongst women and accessibility to health services might have contributed to the decline in breast cancer mortality [19].

The trend in stomach cancer mortality has been attributed to the effects of a more affluent diet and improved food storage and conservation. Better hygiene, with a lower prevalence of *Helicobacter pylori* infection, may be also involved in the decline of stomach cancer [20]. A favourable effect of exogenous hormones in colorectal cancer risk may contribute to the larger decline observed in females [21,22]. All these changes have been slower to occur in Catalonia and other Southern and Eastern countries, and may be influenced by improved diagnosis and treatment [23].

The rise observed in prostate cancer mortality is similar to that observed in several European countries and lower than that of the US [3,24,31]. An increase in prostate cancer incidence is also apparent in Catalonia [10], which might be influenced by an increase in surveillance and early diagnosis [25].

Death certification data may be affected by potential sources of error, including problems of reliability and validity. The acceptable validity of the underlying cause of death from death certificates in our country is reassuring as regards information bias [26,27], as well as the similarity of the pattern observed for the truncated rates, which are less affected by errors in death certification [28]. Finally, uterine cancer has been analysed without distinguishing cervix, corpus and unspecified uterine cancer deaths, given the recognised problems to accurately classify them from death certificates alone [29,30].

The use of the joinpoint method of analysis has allowed a detailed and accurate description of the pattern of cancer mortality in recent years, since it identifies the calendar years in which statistically significant changes in the trends occurred, and the annual percentage of change within the periods identified. This offers a clearer picture of the actual trends in mortality over long periods of time rather than data using only one trend statistic [2]. The joinpoint regression and other similar methods have been applied to age-adjusted cancer mortality and incidence rates for different cancer sites by sex and race, and for truncated rates. The method is applicable to analyse survival rates and to identify trends for age-specific mortality or incidence rates, together with age-period-cohort models, since in joinpoint regression analysis some cohort effects may remain hidden.

In conclusion, the most favourable indication from this analysis of cancer mortality in Catalonia is the overall levelling of rates, which reflects the beginning of a decline in lung cancer and tobacco-related cancers rates in males since 1989, the declining of breast cancer mortality in females since 1992 and the persistent decline in stomach cancer in both sexes. Of great concern, given their public health implications and potential for prevention, is the spread of the lung cancer and tobacco-related cancer epidemic in females.

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