

Time trend and age-period-cohort effects on gastric cancer incidence in Zaragoza and Navarre, Spain

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Abstract

Study objective—To describe time trends in gastric cancer incidence in Zaragoza and Navarre, and to investigate time period and birth cohort as determinants of such trends.

Design—Cases from two registries were grouped into five year intervals and the following were calculated: age specific and sex specific incidence rates, age adjusted incidence rates, cumulative rates, and the male to female ratio. Log linear models including age, period of diagnosis, and birth cohort were fitted.

Setting—The Zaragoza Cancer Registry covers the province of Zaragoza, which has a population of 824 776 (403 755 men and 421 021 women). The Navarre Cancer Registry covers the province of Navarre which has 512 512 inhabitants (254 786 men and 257 726 women). In both cases population figures were based on the 1986 census.

Patients—These comprised incident cases of gastric cancer reported to the Zaragoza Cancer Registry in 1963–87 and to the Navarre Cancer Registry in 1973–87.

Main results—Navarre registered higher adjusted and cumulative rates than Zaragoza for both sexes. In both provinces, there were relative declines in the rates for men and women of 3% and 4% respectively per year. In Zaragoza, the risk of developing stomach cancer fell in generations born between 1888 and 1933, and rose in subsequent birth cohorts in both sexes, while in Navarre the cohort effect showed an approximately linear decrease in risk for both sexes. Both provinces recorded increases in risk associated with cohorts born between 1933 and 1943.

Conclusions—The incidence rates of gastric cancer fell in both Zaragoza and Navarre. The reason for the greater incidence of gastric cancer in Navarre remains unknown. Trends in rates seem to be mainly linked to birth cohort. Increases in risk in generations born after 1933 may be ascribable to nutritional deficiencies in the early years of life.

(*J Epidemiol Community Health* 1997;51:412–417)

The decline in gastric cancer incidence and mortality is a worldwide phenomenon coinciding with the second half of this century.^{1,2}

Nevertheless, it is still one of the most frequent cancers in the world and occurs twice as frequently in men than in women.³

Gastric cancer exhibits noticeable international differences. European population based registries with the highest and lowest gastric cancer incidence rates for both sexes are St Petersburg, Russia (52.8 cases per 100 000 person-years for men and 25.3 for women) and Tarn, France (8.3 for men and 3.4 for women), respectively.⁴ In Spain, gastric cancer not only registers high levels of incidence and mortality (above the European Community average^{4,5}) but in 1985 was the second leading cause of cancer deaths in men and the third in women.⁶ As yet, no complete explanation has been forthcoming as to the important geographical differences that exist between and within countries or the factors associated with the development of this tumour.

Study of the effects of age, time period, and birth cohort may be helpful in gaining further insight into the causes of stomach cancer. This type of analysis has been carried out on the basis of incidence and mortality data in different countries. The existence of follow up data for a minimum period of 15 years at the Zaragoza and Navarre Cancer Registries has made it possible for such a study to be undertaken in Spain. Our study aimed to describe the time trends for gastric cancer incidence in Zaragoza and Navarre and to investigate time period and birth cohort as determinants of such trends.

Methods

CANCER REGISTRIES

The longest established cancer registries in Spain are those of Zaragoza (1960) and Navarre (1973), which together constitute the sole sources of incidence data going back more than 15 years. The Zaragoza Cancer Registry covers the province of Zaragoza which, based on the 1986 census, has a population of 824 776 (403 755 males and 421 021 females), while the Cancer Registry of Navarre covers the Autonomous Region of Navarre (in essence, a region comprising a single province), with 512 512 inhabitants (254 786 males and 257 726 females). The geographical area covered by these two registries lies in the north of the Iberian Peninsula. Zaragoza is bordered to the west by the Autonomous Region of Navarre.

This study is based on incident cases of gastric cancer reported to the Zaragoza Cancer Registry in 1963–87, and the Navarre Cancer

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Accepted for publication
November 1996

Table 1 Number of cases, age adjusted incidence rates per 100 000 person years (European (E) and World (W) standard populations), and cumulative rate per 100 for the population aged 0–74 years in Zaragoza (1963–87) and Navarre (1973–87), Spain

	Men				Women				M:F
	Cases	AR(E)	AR(W)	CR	Cases	AR(E)	AR(W)	CR	
Zaragoza									
1963–67	761	53.93	36.59	4.47	598	34.13	22.14	2.61	1.58
1968–72	781	50.22	33.11	3.92	574	28.20	18.00	2.01	1.78
1973–77	726	41.62	27.44	3.27	561	24.15	15.12	1.63	1.72
1978–82	585	30.09	19.61	2.12	437	16.27	10.12	1.01	1.85
1983–87	666	31.34	21.03	2.44	423	14.54	9.52	1.04	2.16
Navarre									
1973–77	531	53.12	35.34	4.07	355	27.86	18.12	2.04	1.91
1978–82	536	47.31	31.98	3.83	313	21.20	13.66	1.45	2.23
1983–87	477	38.58	25.68	2.83	295	18.00	11.83	1.26	2.14

AR(E) European age adjusted incidence rate; AR(W) world age adjusted incidence rate; CR cumulative rate; M:F male to female ratio.

Registry in 1973–87. At the time the study was carried out, the last complete year available was 1987. Data on gastric cancer correspond to rubric 151 of the *International Classification of Diseases (9th rev)*, and were extracted from the registers on a case by case basis. Data gathering methods employed by the two registries are: Zaragoza, mixed (active and passive); Navarre, active. A more detailed description of both registries is given elsewhere.⁴⁷ Population estimates were calculated from all available censuses and municipal rolls for the study period using a log linear polynomial model.⁸

STATISTICAL METHODS

Age specific and sex specific incidence rates were calculated by grouping cases into five year intervals in both registries. Incidence rates were age adjusted by the direct method to the European and world standard populations, and, as an alternative to standardisation, cumulative rates for 0–74 years were also calculated. Relative risk was computed for male versus female patients.

To investigate the risk associated with specific generations, the number of cases in each group and period was assumed to constitute a variable with a Poisson distribution, and log linear models including age, period of diagnosis, and birth cohort were then fitted to the rates for each registry in both sexes. We originally studied the Zaragoza and Navarre registries jointly, using age-period-cohort-registry models including all possible interaction terms. However, in view of the existence of interactions between the registry term and the other variables, it was decided that a separate analysis would be presented for each registry.

Analysis was restricted to the population aged under 85 years, and the youngest group included in the model was the first group over the age of 14 years found to have at least five cases of gastric cancer in each quinquennium.

We first tested whether any age specific rates exhibited a degree of variability greater than that permitted by a Poisson distribution (over dispersion of rates). In such cases, the variance estimators from the Poisson model could lead to some factors proving statistically significant without really being so. Hence, where this

KEY POINTS

- In both Zaragoza and Navarre the incidence of gastric cancer fell between 1963 and 1987.
- The rates observed in young women may indicate a levelling off in incidence in the most recent generations.

proved to be the case, we proceeded to use a corrected model (gamma-Poisson model) which took over dispersion into account.⁹

The fact that a model which simultaneously considers age, period, and cohort has no single specific solution (non-identifiability problem), means that additional constraints have to be imposed.^{10 11 12} We opted for one of the solutions described in published reports, whereby the overall slope of the period effect is assumed to be zero.^{13 14} The rationale for this approach is that cohort has a stronger association with incidence than period.¹⁵ Furthermore, exposure to risk factors associated with this tumour seems to be determined to a great extent by birth cohort.^{16 18} Cohort and period of diagnosis values were averaged to unity.

Results

Table 1 shows the following: the absolute number of cases of gastric cancer diagnosed in Zaragoza (1963–87) and Navarre (1973–87) for men and women; age adjusted incidence rates per 100 000 person-years (European and world standard populations); cumulative rates; and the male to female ratio. Figure 1 depicts age adjusted gastric cancer incidence rates (European standard population) for Zaragoza and Navarre in both sexes.

Stomach cancer incidence fell in Zaragoza and Navarre in both sexes over the time periods studied. In Zaragoza, 3519 cases of stomach cancer were diagnosed in men and 2593 in women in the period 1963–87. Furthermore, male and female rates respectively fell from 53.93 and 34.13 per 100 000 person-years in 1963–67 (European standard population) to 31.34 and 14.54 in 1983–87. In Navarre, 1544 and 963 cases respectively were diagnosed in men and women in 1973–87. Adjusted and

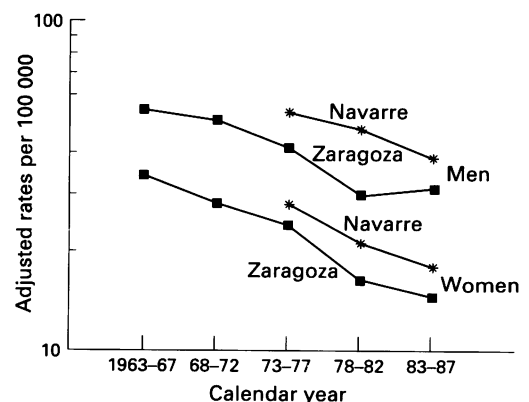


Figure 1 Age adjusted gastric cancer incidence rates by sex for Zaragoza and Navarre.

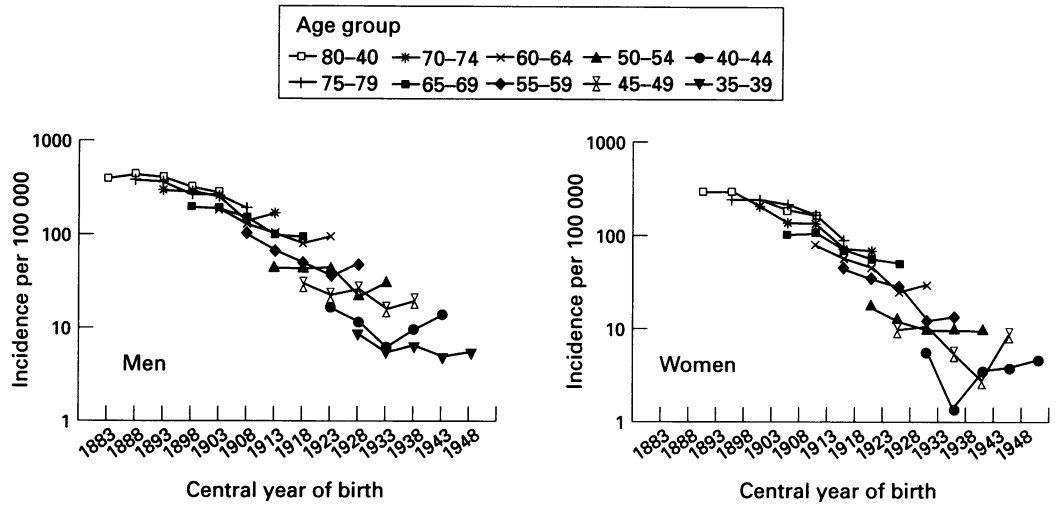


Figure 2 Age specific gastric cancer incidence rates by central year of birth and sex in Zaragoza.

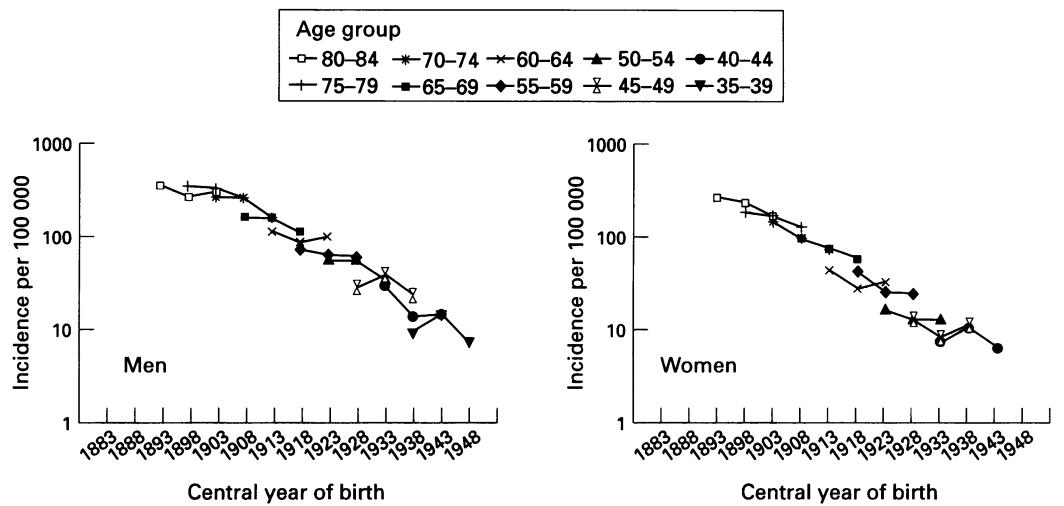


Figure 3 Age specific gastric cancer incidence rates by central year of birth and sex in Navarre.

cumulative rates for Navarre were higher than those for Zaragoza for both sexes. Indeed in men, the 1983–87 adjusted rates were almost as high as those reported for Zaragoza 10 years earlier. Both provinces showed overall relative declines in rates of 3% per year in men and 4% per year in women. However, as will be observed in figure 1, there was a greater than expected fall off in male and female cases registered in Zaragoza between 1978 and 1982. The overall male to female ratios were 1.9 in Zaragoza, with an almost constant upward rise throughout the study period, and 2.1 in Navarre.

Figures 2 and 3 plot age specific incidence rates for gastric cancer by median year of birth for male and female patients in Zaragoza and Navarre. In Zaragoza, rates fell for most age groups in both sexes during the penultimate five year period, with a subsequent rise thereafter in most age groups. In Navarre, while male trends were downward overall, for women aged under 65, the trend ultimately levelled off.

Table 2 shows the goodness of fit of various Poisson models. The results from the two registries differed. In Zaragoza, the age + cohort model proved significantly better than

age + drift model for men and women alike. Where men alone were concerned, however, the model which best fitted the data was age + period + cohort. In Navarre, age + drift models were found to adequately represent the data for both men and women.

Figure 4 shows the cohort and period effects resulting from the age + period + cohort models when the period slope is assumed to be equal

Table 2 Goodness of fit for different age, period, and cohort models of gastric cancer in Zaragoza and Navarre in both sexes

Models	Men		Women	
	Deviance	df	Deviance	df
Zaragoza				
I Age	208.2	40	214.4	36
II Age + drift	57.9	39	46.6	35
III Age + period	45.9	36	42.9	32
IV Age + cohort	36.3	27	24.6	24
V Age + period + cohort	24.3	24	21.6	21
Overdispersion corrected	Yes		Yes	
Navarre				
I Age	28.7	20	37.3	18
II Age + drift	15.2	19	8.1	17
III Age + period	14.3	18	8.0	16
IV Age + cohort	8.9	9	4.9	8
V Age + period + cohort	8.1	8	4.8	7
Overdispersion corrected	Yes		No	

df = degrees of freedom.

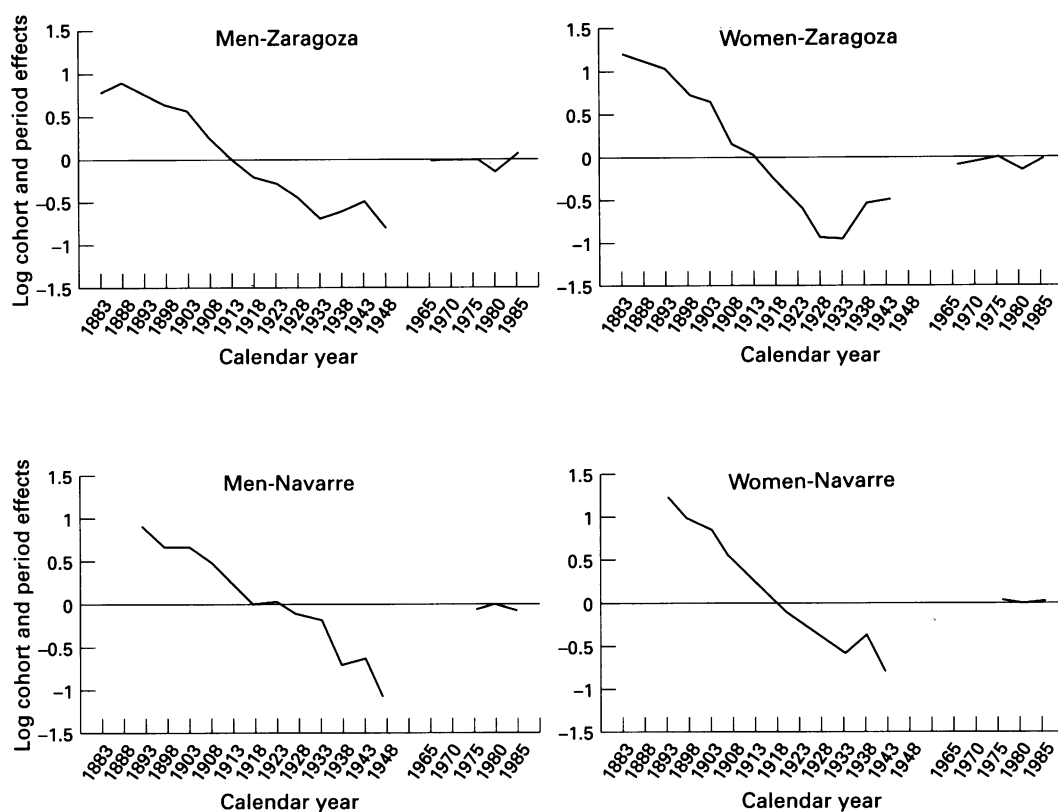


Figure 4 Cohort and period effect on gastric cancer incidence by registry and sex. An overall period slope of zero was assumed.

to zero. Although the inclusion of the three factors is not necessary in all cases to explain the variability in the rates, the cohort and period effects of this model are depicted for greater ease of comparison between registries and sexes.

Taking the mean rate for all cohorts as reference, in Zaragoza the risk of developing stomach cancer declined in generations born between 1888 and 1933 and rose in subsequent birth cohorts in both sexes, though more noticeably so in women. In Navarre, the cohort effect showed an approximately linear decrease (on a logarithmic scale) in the risk of gastric cancer in both sexes for all generations studied, with fluctuations associated with certain birth cohorts. The patterns in Zaragoza and Navarre showed a peak in increased risk coinciding with the 1943 birth cohort in men and the 1938 birth cohort in women. The period effect in Zaragoza was affected by the 1978–82 decline in both sexes, which marked a departure from the general trend and was appreciable from observation of the adjusted and specific rates. The period effect in Navarre proved stable.

Net drift was $-0.141/\text{year}$ for men and -0.188 for women in Zaragoza, amounting to a fall of 2.86% per year for men and one of 3.86% for women. In Navarre, net drift was $-0.165/\text{year}$ in men and $-0.202/\text{year}$ in women, which translates as respective falls of 3.36% and 4.12% per year in men and women.

Discussion

The results show that in both Zaragoza and Navarre the incidence rate of gastric cancer

decreased. This decrease was more pronounced in women, leading to a rise in the male to female ratio over the study period. The trend in rates mainly seems to be related to birth cohort, as is borne out by the results from Zaragoza (the registry for which a longer follow up period is available). In Navarre, the rates observed in young women may indicate a levelling off in incidence in the most recent generations, something which remains to be confirmed in years to come.

The importance of studying the cohort effect resides in the fact that cohorts represent the most natural way of aggregating individuals, since the prevalence of aetiological factors linked to environment and/or lifestyle is to a great extent determined by year of birth. The use of age-period-cohort models implies the need to include additional assumptions. In this study the slope of the period effect was assumed to be equal to zero. Any improvement in the quality of registry data over time⁷ would be reflected in the model as an upward period effect. In this respect therefore, the above assumption tends to be conservative, in that the decline in incidence among the generations studied could be equal to or greater than that presented in this paper. This model shows that the risk of developing gastric cancer has declined in Zaragoza and Navarre, a phenomenon which, in overall terms, translates as a decrease in the rates of 3% per year in men and 4% in women. Despite this general trend, however, the downward movement is seen to halt in both sexes among post-1933 cohorts in Zaragoza, in line with mortality observations for this tumour nationwide.¹⁹

The substantial decline in gastric cancer in recent decades suggests that, in the main, environmental rather than genetic factors are implicated in its aetiology.¹⁶ Gastric cancer aetiology has been associated with dietary habits during the first years of life^{16,20} and *Helicobacter pylori* infection.^{21,22} The rise in risk registered in Zaragoza for the most recent study cohorts—namely, those born during the Spanish Civil War and postwar period—may be linked to the dramatic situation prevailing in Spain at the time. Widespread scarcity had a considerable impact on diet and there was probably an increased prevalence of infection with *Helicobacter pylori*. In this respect and notwithstanding the fact that the downward trend is linear, in Navarre the cohort effect indeed shows specific rises in risk in both sexes among the war and postwar generations.

Trends in the appearance of gastric cancer have been variously described on the basis of histological type²³ and subsite.¹⁷ While incidence of and mortality from adenocarcinoma of the gastric cardia have increased over recent decades, those for adenocarcinoma of the distal stomach have fallen.^{23,24,25} Such disparity as well as the different epidemiologic characteristics, suggest that we are confronted with two aetiologically different entities. Incidence patterns in Zaragoza and Navarre could not, however, be analysed by anatomic subsite, since 4th digit coding had not been widely enough applied to data at these cancer registries.

With respect to the period effect, the most noteworthy aspect is the fall observed in the 1978–82 period in Zaragoza. One underlying cause affecting data quality is incomplete case finding. In 1980, case finding, which until then had been passive, underwent a change in Zaragoza. Thenceforth, the role of voluntary reporters became limited to concrete rural areas, while active case searching and arrangements with hospital registries grew in importance. This new approach, though still not fully operational in the years immediately following its introduction, could have given rise to the subregister which seems to be present in the penultimate five year period. The day to day running and methodology of the Navarre Cancer Registry remained basically unchanged throughout the study period.

The incidence found in Navarre was higher than that of Zaragoza. The Navarre:Zaragoza incidence rates ratio ranged from 1.23 to 1.57 in men and from 1.15 to 1.3 in women for the period 1973–87. The better quality indices of the Navarre registry may point to the existence of a subregister in Zaragoza. Thus, the Zaragoza figures for all cases with histological confirmation were 67.0% in men and 50.8% in women, as against 86.2% and 76.9% respectively for Navarre,⁷ and the proportion of diagnoses ascertained via death certificates in Zaragoza totalled 19.8% in men and 29.6% in women versus 10.1% and 19.1% respectively in Navarre.⁷ Despite these differences, the existence of a real difference in tumour incidence as between these two provinces cannot be ruled out. Geographical differences have been linked to environmental factors more common in rural

settings, such as high consumption of sausage meats (meats which tend, moreover, to be preserved using traditional methods). In this respect, it should be stressed that Navarre has a larger rural population (40% of the population live in towns with under 5000 inhabitants, and only 36% live in the provincial capital, Pamplona),⁴ whereas in the province of Zaragoza, 75% of the population live in the capital.²⁶

Gastric cancer mortality rates for Navarre are likewise higher than those for Zaragoza, and both are higher than elsewhere in Spain. Spanish age adjusted mortality rates (standard European population) for the periods 1972–76 and 1982–86 respectively were 38.81 and 25.03 per 100 000 person-years in men and 21.22 and 12.44 in women.¹⁹ In spite of the differences between mortality and incidence data, the decline in gastric cancer incidence in Zaragoza and Navarre parallels the decline in gastric cancer mortality nationwide.¹⁹ The fact that these trends are the same may indicate that, overall, there have been no major changes in survival or case registration.

The Spanish cancer registries reporting the highest gastric cancer rates are those of Navarre, Zaragoza, and the Basque Country.⁴ The rates for Zaragoza and Navarre are high compared with those for the European Union (EU). Expressed in concrete terms, Navarre's rates rank only behind those quoted for the following registries: Vila Nova de Gaia (Portugal); Florence, Lombardy Region (Varese Province), Parma Province and Romagna (Italy); and the Basque Country (Spain). In women, the Navarre registry rates are solely exceeded by those of the above Portuguese and Italian registries.⁴ On the other hand, the decline in incidence rates in Spain is similar to that observed for the remaining EU member states.¹

This study describes the decline in gastric cancer incidence for both sexes as observed in Zaragoza and Navarre over recent decades. The higher incidence of gastric cancer in Navarre may be due to greater exposure to risk factors for stomach cancer, the better quality of the data on its register, or a combination of the two. Age-period-cohort analyses furnish evidence of increased risk in certain birth cohorts, possibly associated with rises in exposure to risk factors. Bearing in mind that other studies have suggested a possible future levelling off in rates in developed countries,^{17,27} a longer period of observation is required for ascertainment of the trend—downward at present—in the incidence of this tumour in years to come.

Funding: this study was supported by the Health Research Fund of the Spanish Ministry of Health (Fondo de Investigacion Sanitaria, grant 94/150).
Conflicts of interest: none.

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