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Childhood and Adolescent Cancer in Spain: Mortality Time Trends 1956–1990

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Using log-linear Poisson modelling, trends in childhood cancer mortality among the population under 20 years of age in Spain are described over the 35-year period from 1956 to 1990. Overall cancer mortality and seven specific sites were considered: all leukaemias, Hodgkin's disease, non-Hodgkin's lymphomas, malignant brain tumours, kidney cancer, malignant bone neoplasms, and a broad category of ill-defined tumours. An age–period–cohort model was used to analyse the influence of age, period of death and birth cohort. Recent trends were estimated by restricting analysis to the last three 5-year periods. In general, mortality began to decline at the beginning of the 1970s, with reductions of 36% in males and 45% in females being registered between 1966–1970 and 1986–1990. The use of age–period–cohort models revealed an initially rising period effect attributable to diagnostic advances. The decline in mortality in post-1965 generations and the final downturn in the period effect are both most certainly a consequence of the remarkable progress achieved in the treatment of such tumours. During the final 15 years, there was a relative decline in mortality of approximately 20% every 5 years. However, in the case of malignant renal tumours in males and malignant bone tumours and non-Hodgkin's lymphomas in both sexes the situation remained stable.

Key words: childhood mortality, mortality trends, Poisson models, age–period–cohort models
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INTRODUCTION

CANCER IN children is fortunately rare. However, it constitutes the second leading cause of child death after the first year of life [1] and in 1990 accounted for 35 175.5 potential years of life lost in Spain, which translated as 2.1% of total potential years of life lost and 7.6% of those due to cancer. Studies on incidence published to date indicate a trend that is stable or slightly upward over time [2–14]. Despite such stability, mortality has undergone a considerable decline in recent decades owing to major advances in treatment [4, 5, 12, 14–18].

In spite of the relative homogeneity in incidence rates worldwide [2–4, 19], comparison of the pertinent mortality rates in European Community (EC) countries indicates a clear north–south pattern [15]. Spain exhibits a high mortality rate for childhood and adolescent cancer (CAC), and in the EC ranks second after Portugal as regards males and third, after Portugal and Italy, as regards females [15].

Traditionally, trends in mortality have been studied by using summary measures (adjusted rates) for each period of observation. In the context of a prospective study, however, birth cohorts constitute a more natural method of aggregating individuals. Age–period–cohort (APC) models simultaneously study variability in rates *vis-à-vis* these three factors [20–24]. In such models, cohort and period effects reflect the influence of factors usually related to time on a different basis. For example, environmental exposures would be more easily observed as birth cohort effects, while changes in mortality determined by modifications in diagnosis or certification practices could be related to the calendar time of death [21, 24].

This paper analyses trends in CAC mortality in Spain over the period 1956–1990. The goals as regards CAC as a whole and those sites with greatest mortality were as follows: (1) to ascertain the general trend for each sex, (2) to study the moment at which a shift in the trend occurred, (3) to investigate the influence of age, period of death and birth cohort on the trend observed in specific rates, (4) to quantify the decrease in mortality and the number of deaths avoided during the 1980s, by using data from the last three 5-year periods.

MATERIALS AND METHODS

We considered total cancer mortality, six specific sites—leukaemias, Hodgkin's disease, non-Hodgkin's lymphomas, malignant brain tumours, malignant bone neoplasms and kidney cancer—and a broad category of secondary tumours or ill-

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defined tumours. During the study period, four different revisions of the International Classification of Diseases were in use and, as a guide, Table 1 sets out the specific tumour-site codes used by the respective ICD revisions. For ease of reference, the remaining tables and figures are based on the ICD-9th coding. Since the ICD 6th and 7th versions do not distinguish between brain and other nervous system tumours, brain tumours are analysed only for the last four quinquennia.

Cancer mortality rates

Annual age-specific cancer death rates for each sex and age group (<1, 1–4, 5–9, 10–14 and 14–19) were computed on the basis of death certification numbers published annually by Spain's National Institute of Statistics. Population estimates were calculated from all available censuses and municipal population registers for the study period using a logistic polynomial model [25]. Rates were adjusted for age using the European population as standard. As an alternative to standardisation [26], cumulative rates from 0 to 19 years were computed.

Changes in trend

Graph-based observation of the trend in specific rates evinced a general rising–falling pattern common to both sexes for all ages and sites. Accordingly, annual cumulative rates were modelled by means of a parabolically-shaped log-linear Poisson model using "year" and "year*year" as the explanatory variables. The inflection point or moment at which a shift takes place in the trend corresponds to the year in which the first derivative of the model equals zero.

Age, period and cohort modelling

Age- and sex-specific mortality rates were then calculated for the seven 5-year periods (from 1956–1960 until 1986–1990). We used a log-linear Poisson model with age, period of death and cohort as possible predictor variables. In this analysis, we combined all deaths in children under 5 years of age in a single group. Both cohorts and periods were defined according to their corresponding midpoints. We first tested whether 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. Thus, where this proved to be the case, we proceeded to use a corrected model (gamma-Poisson model) which took over-dispersion into account [27,28].

Predictor variables were sequentially incorporated into the model. Age was taken first, in view of the fact that for these causes incidence and mortality change remarkably with age. Each variable's contribution was evaluated using the log-likelihood ratio test.

When the final model includes all three factors, there can be no single specific solution owing to the fact that the three variables are inter-related (identifiability problem). In practical terms, this means that it is not possible to quantify the slope of the linear component of each of the effects without imposing an additional condition on the model. However, the sum of the period and cohort slopes—denominated net drift [21–24]—is estimable without the need for any additional condition. In our case, the rising–falling trend in the rates led to overall net drift being small in magnitude. This allowed for two extreme situations to be represented which resulted from alternatively attributing the net drift to the period and cohort effects, respectively [23]. These twin assumptions serve to trace out a sort of confidence bound which would contain the true estimators.

Recent trends

An overall linear trend over time was calculated for the last three consecutive periods of the study (1976–1980, 1981–1985 and 1986–1990) using a log-linear Poisson model. Taking 1976–1980 as reference, we estimated the number of avoided deaths in the two subsequent 5-year periods on the basis of the number expected.

Table 1. Disease codings as used by different ICD revisions

Site	6th revision 1956–1960	7th revision 1961–1967	8th revision 1968–1979	9th revision 1980–1990
Total malignant tumours	140–204	140–204	140–207	140–208
Leukaemias	204	204	204–207	204–208
Hodgkin's lymphoma	201	201	201	201
Non-Hodgkin's lymphomas	200+202	200+202	200+202	200+202
Malignant brain tumours	—	—	191	191
Malignant renal tumours	180	180	189	189
Malignant bone tumours	196	196	170	170
Ill-defined malignant tumours	198–199	198–199	195–199	195–199

RESULTS

Cancer mortality rates

Shown in Tables 2 and 3 are the number of deaths, average age at death, age- and period-specific rates, standardised and cumulative rates for all sites considered, for males and females, respectively. The adjusted childhood cancer mortality rates for the first and last 5-year periods were 61.93 and 55.55 per million in males and 49.82 and 38.01 per million in females. This amounts to a decline of 10% and 23% for each sex with respect to the first 5-year period, although given the increase in mortality observed in the initial periods, the fall-off observed as against the period of highest mortality (1966–1970) was actually 36% in boys and 45% in girls. The greater reduction among females led to a rise in the sex ratio, from 1.24 at the outset of the study to 1.46 in the final 5-year period.

The decline in mortality was not homogeneous across all sites. Thus, whereas a decrease of over 50% was seen in Hodgkin's lymphomas and ill-defined tumours between 1966–1970 and 1986–1990 and in brain tumours between 1971–75 and 1986–1990, non-Hodgkin's lymphomas and malignant bone tumours recorded a stable situation in males, while showing a reduction in mortality among females.

In general, the trend observed for all age groups was "rising–falling". The sole exceptions were Hodgkin's disease and ill-defined tumours in females, where the relevant specific rates presented a downward trend throughout the entire period. The magnitude of the decline was generally greater among the youngest subjects. Consequently, the highest specific rates for children's tumours as a whole, which in the first period corresponded to the under 1-year-olds, shows a progressive shift towards older groups.

Table 2. Mortality due to malignant tumours. Boys and young adults (from 0 to 19 years of age). Number of deaths. Average age at death. Specific rates and adjusted rates per 1 000 000 person-years. Cumulative risk per 100 000. Spain, 1956–1990

Period of death	No. of cases	Average age	Age-specific rates <1	1–4	5–9	10–14	15–19	Standardised rate	Cumulative risk
Total malignant tumours (ICD-9: 140–208)									
1956–1960	1635	8.7	137.10	69.38	56.20	48.28	57.32	61.93	122.3
1961–1965	2112	8.7	141.16	89.88	70.50	50.00	75.86	75.02	148.1
1966–1970	2622	8.7	184.72	96.60	82.45	60.14	87.01	86.93	171.8
1971–1975	2721	9.5	91.38	91.29	89.59	67.52	90.78	85.02	169.5
1976–1980	2675	10.0	80.42	83.02	85.25	68.32	88.77	81.25	162.3
1981–1985	2342	10.4	46.28	77.46	78.00	61.37	79.00	72.36	144.7
1986–1990	1672	11.3	48.23	53.86	53.24	48.85	67.79	55.55	111.2
Leukaemias (ICD-9: 204–208)									
1956–1960	713	8.1	54.14	36.58	25.46	18.66	21.78	26.97	52.98
1961–1965	932	8.3	49.82	46.64	31.86	22.78	28.05	33.00	64.96
1966–1970	1036	8.1	60.57	46.61	35.21	23.42	26.52	34.18	67.25
1971–1975	992	9.3	23.60	35.34	36.17	25.83	28.03	30.83	61.49
1976–1980	986	10.1	23.16	29.23	32.92	26.52	32.06	29.81	59.74
1981–1985	887	10.0	14.69	27.49	35.54	24.74	24.28	27.29	54.73
1986–1990	646	11.3	10.92	17.95	23.74	21.28	23.80	21.18	42.68
Hodgkin's lymphomas (ICD-9: 201)									
1956–1960	95	11.8	0.70	1.20	4.22	4.47	4.91	3.59	7.36
1961–1965	112	13.1	0.64	0.97	2.77	5.44	7.49	4.04	8.30
1966–1970	119	11.2	5.45	1.23	4.69	3.06	6.26	3.95	8.04
1971–1975	92	13.3	0.00	0.90	2.01	3.25	5.88	2.89	5.93
1976–1980	58	12.4	0.00	0.47	1.96	2.03	2.64	1.70	3.51
1981–1985	50	13.4	0.00	0.35	1.33	1.53	2.84	1.45	2.99
1986–1990	31	15.9	0.00	0.00	0.28	0.73	2.68	0.89	1.85
Non-Hodgkin's lymphomas (ICD-9: 200+202)									
1956–1960	60	8.9	0.70	3.09	2.86	1.54	1.97	2.26	4.49
1961–1965	126	9.0	1.28	6.13	5.40	2.72	4.46	4.46	8.88
1966–1970	168	9.2	5.45	5.98	6.46	4.52	5.22	5.55	5.53
1971–1975	234	9.5	3.63	8.72	8.39	5.24	7.79	7.30	14.56
1976–1980	262	10.4	3.22	6.84	8.90	8.84	7.80	7.85	15.82
1981–1985	209	10.0	2.94	6.74	8.49	5.42	5.92	6.44	12.90
1986–1990	202	11.5	1.82	6.34	6.46	6.65	8.05	6.61	13.30
Malignant brain tumours (ICD-9: 191)									
1971–1975	447	8.8	21.79	14.14	16.90	12.23	10.39	13.86	27.59
1976–1980	460	9.2	11.58	14.30	19.06	12.66	9.93	13.85	27.70
1981–1985	376	9.5	4.41	16.08	12.86	11.90	8.29	11.77	23.39
1986–1990	191	10.6	6.37	5.49	7.73	6.65	5.60	6.39	12.82
Malignant renal tumours (ICD-9: 189)									
1956–1960	55	3.3	16.87	3.43	1.05	0.46	0.16	2.10	3.90
1961–1965	99	3.8	18.52	8.23	1.52	0.43	0.80	3.50	6.52
1966–1970	91	4.4	15.14	6.44	1.65	0.67	0.89	3.03	5.69
1971–1975	88	5.9	5.45	5.56	3.43	1.00	0.68	2.76	5.32
1976–1980	70	5.7	7.08	4.35	2.31	0.84	0.50	2.23	4.27
1981–1985	45	7.3	0.73	2.59	2.55	0.35	0.59	1.46	2.86
1986–1990	41	8.0	0.91	2.75	1.97	1.09	0.47	1.51	2.95
Malignant bone tumours (ICD-9: 170)									
1956–1960	76	12.0	2.11	2.23	1.36	2.78	5.40	2.91	5.87
1961–1965	79	10.7	5.11	1.78	2.35	2.01	4.62	2.84	5.71
1966–1970	114	12.8	2.42	0.92	2.91	3.99	7.60	3.84	7.86
1971–1975	166	13.1	1.21	1.65	3.31	6.24	10.25	5.21	10.68
1976–1980	177	13.4	0.00	1.55	3.81	5.85	10.69	5.26	10.80
1981–1985	200	14.5	0.00	1.21	3.03	5.65	14.21	5.79	11.93
1986–1990	129	14.2	0.91	1.27	2.11	4.11	8.52	3.89	7.96
Ill-defined malignant tumours (ICD-9: 195–199)									
1956–1960	232	8.3	28.83	8.07	8.29	6.02	8.19	8.80	17.36
1961–1965	269	9.2	27.47	8.55	7.34	5.87	12.59	9.63	19.07
1966–1970	313	9.4	30.89	8.13	8.61	6.12	14.16	10.47	20.78
1971–1975	193	8.9	15.73	6.77	4.49	4.74	6.29	6.11	12.04
1976–1980	178	9.9	10.29	5.91	4.51	3.23	7.29	5.50	10.90
1981–1985	121	11.1	3.67	4.32	2.67	2.47	5.69	3.77	7.51
1986–1990	109	10.7	8.19	4.44	2.25	3.02	4.43	3.77	7.45

Table 3. Mortality due to malignant tumours. Girls and young adults (from 0 to 19 years of age). Number of deaths. Average age at death. Specific rates and adjusted rates per 1 000 000 person-years. Cumulative risk per 100 000. Spain, 1956–1990

Period of death	No. of cases	Average age	Age-specific rates <1	1–4	5–9	10–14	15–19	Standardised rate	Cumulative risk
Total malignant tumours (ICD-9: 140–208)									
1956–1960	1271	8.5	114.18	61.82	41.28	35.67	46.82	49.82	98.0
1961–1965	1523	8.6	102.65	72.24	48.77	42.10	52.00	56.09	110.5
1966–1970	1986	8.2	143.87	89.75	60.94	50.88	57.47	68.61	134.8
1971–1975	1926	9.0	79.02	81.89	59.45	53.00	56.87	63.30	125.2
1976–1980	1869	9.5	72.96	72.53	56.70	53.66	56.06	60.20	119.5
1981–1985	1579	10.4	44.54	56.59	49.01	47.85	55.08	51.62	103.0
1986–1990	1089	11.3	29.92	36.06	36.83	37.23	43.63	38.01	76.2
Leukaemias (ICD-9: 204–208)									
1956–1960	547	7.9	42.72	31.98	18.84	14.62	16.26	21.42	41.92
1961–1965	717	7.9	47.99	38.56	25.25	18.28	19.28	26.32	51.61
1966–1970	781	7.7	43.10	43.26	24.77	19.65	17.73	26.93	52.68
1971–1975	708	8.5	26.76	29.83	27.86	17.54	16.94	23.11	45.76
1976–1980	669	9.5	21.82	23.90	23.95	19.06	18.77	21.39	42.62
1981–1985	577	10.1	10.94	22.97	18.52	19.09	17.25	18.92	37.71
1986–1990	442	11.3	11.58	12.09	15.89	17.40	16.21	15.26	30.74
Hodgkin's lymphomas (ICD-9: 201)									
1956–1960	50	12.1	0.74	1.07	1.88	1.45	3.61	1.95	3.98
1961–1965	54	12.4	0.67	0.51	1.88	2.55	3.24	2.00	4.10
1966–1970	51	11.3	1.90	1.13	1.19	2.09	2.60	1.77	3.58
1971–1975	35	14.5	0.00	0.16	0.62	1.05	2.96	1.15	2.38
1976–1980	36	14.3	0.68	0.16	0.61	0.88	2.87	1.13	2.31
1981–1985	32	15.9	0.00	0.00	0.13	0.99	2.83	0.95	1.98
1986–1990	23	16.2	0.00	0.00	0.15	0.51	2.19	0.69	1.43
Non-Hodgkin's lymphomas (ICD: 200+202)									
1956–1960	30	10.6	0.00	1.43	1.10	0.64	1.81	1.17	2.35
1961–1965	53	8.8	0.00	3.37	1.73	1.50	1.78	1.95	3.85
1966–1970	99	8.5	2.54	4.99	3.84	2.37	2.75	3.40	6.73
1971–1975	107	8.6	3.82	6.35	1.74	3.53	2.82	3.57	6.97
1976–1980	82	10.4	2.73	2.31	2.57	2.63	2.87	2.61	5.23
1981–1985	78	10.4	3.91	1.65	3.22	2.23	2.59	2.52	5.07
1986–1990	68	11.1	2.90	1.79	2.23	2.94	2.32	2.36	4.75
Malignant brain tumours (ICD-9: 191)									
1971–1975	367	9.1	14.66	13.17	13.56	10.60	10.02	11.97	23.82
1976–1980	373	9.0	15.68	14.18	13.20	11.03	8.87	11.98	23.78
1981–1985	297	9.8	5.47	10.29	12.99	8.31	8.13	9.68	19.38
1986–1990	145	10.5	0.97	6.49	5.79	4.73	4.75	5.17	10.34
Malignant renal tumours (ICD-9: 189)									
1956–1960	55	4.6	14.73	2.86	1.88	0.64	0.49	2.17	4.13
1961–1965	64	4.5	8.67	5.39	2.02	0.30	0.49	2.34	4.42
1966–1970	94	4.5	10.77	7.72	2.91	0.56	0.46	3.25	6.13
1971–1975	67	5.5	2.55	6.19	1.74	0.79	0.56	2.25	4.27
1976–1980	70	5.7	3.41	5.77	2.57	0.63	0.52	2.36	4.51
1981–1985	55	7.7	3.13	2.20	3.34	0.87	0.74	1.85	3.67
1986–1990	36	8.5	2.90	1.57	1.93	1.02	0.61	1.37	2.70
Malignant bone tumours (ICD-9: 170)									
1956–1960	61	11.9	2.21	1.43	1.57	2.41	4.11	2.39	4.83
1961–1965	72	11.1	4.67	1.68	1.59	2.70	4.21	2.68	5.39
1966–1970	92	12.2	1.90	1.61	1.46	5.16	4.74	3.20	6.51
1971–1975	112	12.5	0.00	2.06	1.99	5.63	5.65	3.66	7.46
1976–1980	118	12.7	1.36	0.82	1.96	7.65	4.43	3.65	7.49
1981–1985	135	14.6	0.00	0.74	1.67	5.21	9.36	4.08	8.42
1986–1990	88	13.7	0.00	0.22	2.23	4.35	4.63	2.76	5.69
Ill-defined malignant tumours (ICD-9: 195–199)									
1956–1960	204	8.1	25.78	10.36	5.49	4.50	7.89	8.03	15.66
1961–1965	202	8.1	18.00	11.11	4.62	4.80	7.29	7.48	14.60
1966–1970	234	8.1	31.06	8.36	5.83	4.74	8.41	8.14	15.94
1971–1975	141	9.3	9.56	5.40	3.11	4.32	4.80	4.67	9.23
1976–1980	139	8.7	8.86	6.10	3.79	3.76	3.65	4.54	8.92
1981–1985	94	8.6	7.81	4.41	2.96	2.11	2.47	3.22	6.31
1986–1990	71	10.8	3.86	2.91	1.93	2.30	2.80	2.55	5.07

Over the course of the study period, not only was there a decline in childhood cancer mortality, but the average age at death rose by 2.5 years in both sexes. This rise was especially important in the case of renal tumours and Hodgkin's disease (at around 4 years of age).

Changes in trend

Shown in Table 4 are the inflection points or peaks for each site. The reduction in cancer mortality among under 20-year-olds appeared from 1972 in males and 1971 in females. This shift in the trend occurred earlier in the case of leukaemias, Hodgkin's disease, renal and ill-defined tumours. At the other end of the spectrum lie non-Hodgkin's lymphomas and bone tumours.

For the whole range of tumours, the younger the age, the earlier the decline, with a decline occurring from 1963 in the under 1-year-olds, 1970 in the 1–4 age group, 1972 in the 5–9 age group, 1974 in the 10–14 age group and 1973 in the 15–19 age group.

Age, period and cohort modelling

The remaining sections of Table 4 set out the results of modelling, namely, the existence or absence of over-dispersion, deviances and degrees of freedom of the different adjusted models and the final model chosen in each case.

With the exception of the overall CAC, in both sexes as well as leukaemias in females, a two-factor model was sufficient for the purpose of explaining the trend observed in the rates.

Figure 1 depicts the cohort and/or period effects of the final model, with the 1970 cohort (1965–1974) and the 1971–1974 period taken as references. Any interpretation of the cohort effect must take into account the fact that the first and last cohorts are estimated on the basis of one specific rate (incomplete cohorts), thus rendering the estimators of effect somewhat less reliable.

For CAC as a whole, both effects (cohort and period) were significant. With respect to the birth cohort, mortality in both sexes began to fall progressively as from 1965. The period effect showed an initial climb until the 1966–1970 period, giving way to an ensuing decline which became more pronounced in the last 5-year period.

Haematological tumours showed a heterogeneous trend. Hodgkin's disease showed a decline in birth-cohort mortality from the 1950s cohorts onwards. This decline became more marked in the last two cohorts, yet it should be borne in mind that, in respect of these cohorts, no rate was available for the 15–19 age group, the included age range at which mortality due to this cause is greatest. While the period effect in leukaemias was significant in females, its magnitude proved less than the cohort effect, which displayed a similar trend in both sexes, with a pronounced reduction dating from 1965. Non-Hodgkin's lymphomas exhibit a very pronounced period effect for the initial quinquennia under study. Among females, there was a clear, recent fall in mortality by period of death not observable in males.

Table 4. Mortality due to malignant tumours. Children and young adults (from 0 to 19 years of age). Year of maximum mortality. "Age–period–cohort" models: existence of over-dispersion, deviance and degrees of freedom of two- and three-factor models, and final model selected. Spain, 1956–1990

Tumour	Inflection point	Over-dispersion	Degrees of freedom of the models: Deviance age	Age + period	Age + cohort	Age + period + cohort	Final model
Total malignant tumours (ICD-9: 140–208)							
Males	1972	YES*	108 (24)	33 (18)	27 (15)	9 (10)	A+P+C
Females	1971	YES*	277 (24)	85 (18)	53 (15)	10 (10)	A+P+C
Leukaemias (ICD-9: 204–208)							
Males	1970	YES*	51 (24)	31 (18)	11 (15)	9 (10)	A+C
Females	1968	YES*	120 (24)	67 (18)	20 (15)	10 (10)	A+P+C
Hodgkin's lymphomas (ICD-9: 201)†							
Males	1962	YES*	63 (18)	13 (12)	7 (10)	5 (5)	A+C
Females	1956	NO	47 (18)	23 (12)	11 (10)	2 (5)	A+C
Non-Hodgkin's lymphomas (ICD-9: 200+202)							
Males	1979	YES*	109 (24)	16 (18)	28 (15)	10 (10)	A+P
Females	1975	YES*	52 (24)	20 (18)	28 (15)	10 (10)	A+P
Malignant brain tumours (ICD-9: 191)‡							
Males	1975	NO	113 (12)	10 (9)	24 (6)	2 (4)	A+P
Females	1974	NO	103 (24)	6 (9)	19 (6)	2 (4)	A+P
Malignant renal tumours (ICD-9: 189)							
Males	1969	YES*	26 (24)	19 (18)	12 (15)	8 (10)	A
Females	1970	NO	54 (24)	35 (18)	15 (15)	5 (10)	A+C
Malignant bone tumours (ICD-9: 170)							
Males	1979	YES*	50 (24)	27 (18)	13 (15)	9 (10)	A+C
Females	1977	YES*	33 (24)	28 (18)	11 (15)	10 (10)	A+C
Ill-defined malignant tumours (ICD-9: 195–199)							
Males	1962	NO	219 (24)	18 (18)	29 (15)	6 (10)	A+P
Females	1955	YES*	133 (24)	13 (18)	20 (15)	10 (10)	A+P

*In this case, the relevant figure is the difference between the deviances of the nested models, and not the absolute value of the deviance. †The 0–4 years age group has been excluded owing to a lack of cases. ‡Only the last four quinquennia have been included.

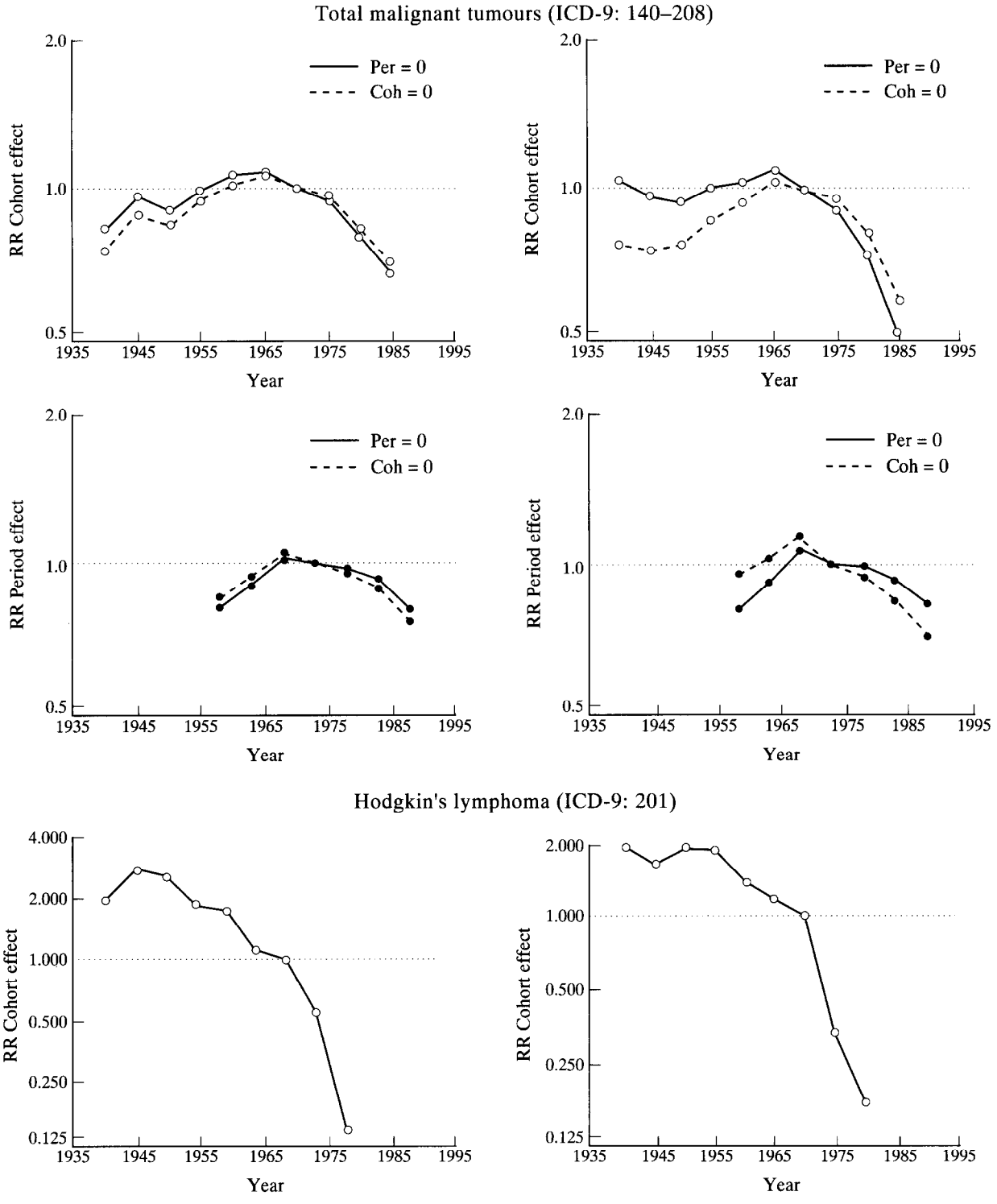

Figure 1. Continued opposite.

Malignant brain tumours showed statistical significance only for the period effect, which was a downward trend from the mid 1970s, with a visibly more pronounced decrease for the last quinquennium.

Both in malignant renal tumours in females and malignant bone tumours in both sexes, a statistically significant cohort effect was observed. For males, the last point plotted for malignant bone tumours should not be considered since it only includes boys under 4 years of age, among whom these tumours are very infrequent. In renal tumours in males, neither of the effects attained statistical significance, owing to the heterogeneous trend in age-specific mortality.

As from the 1966–1970 quinquennium, ill-defined tumours exhibited a substantial reduction relative to the period of observation. The cohort effect was not significant.

The age effect—not shown in the figure—is in line with the differences observed between the specific rates (Tables 2 and 3). In general, three distinct patterns were observed: in a first group of tumours, including leukaemias, malignant brain tumours and malignant renal tumours, mortality declined with age. For other

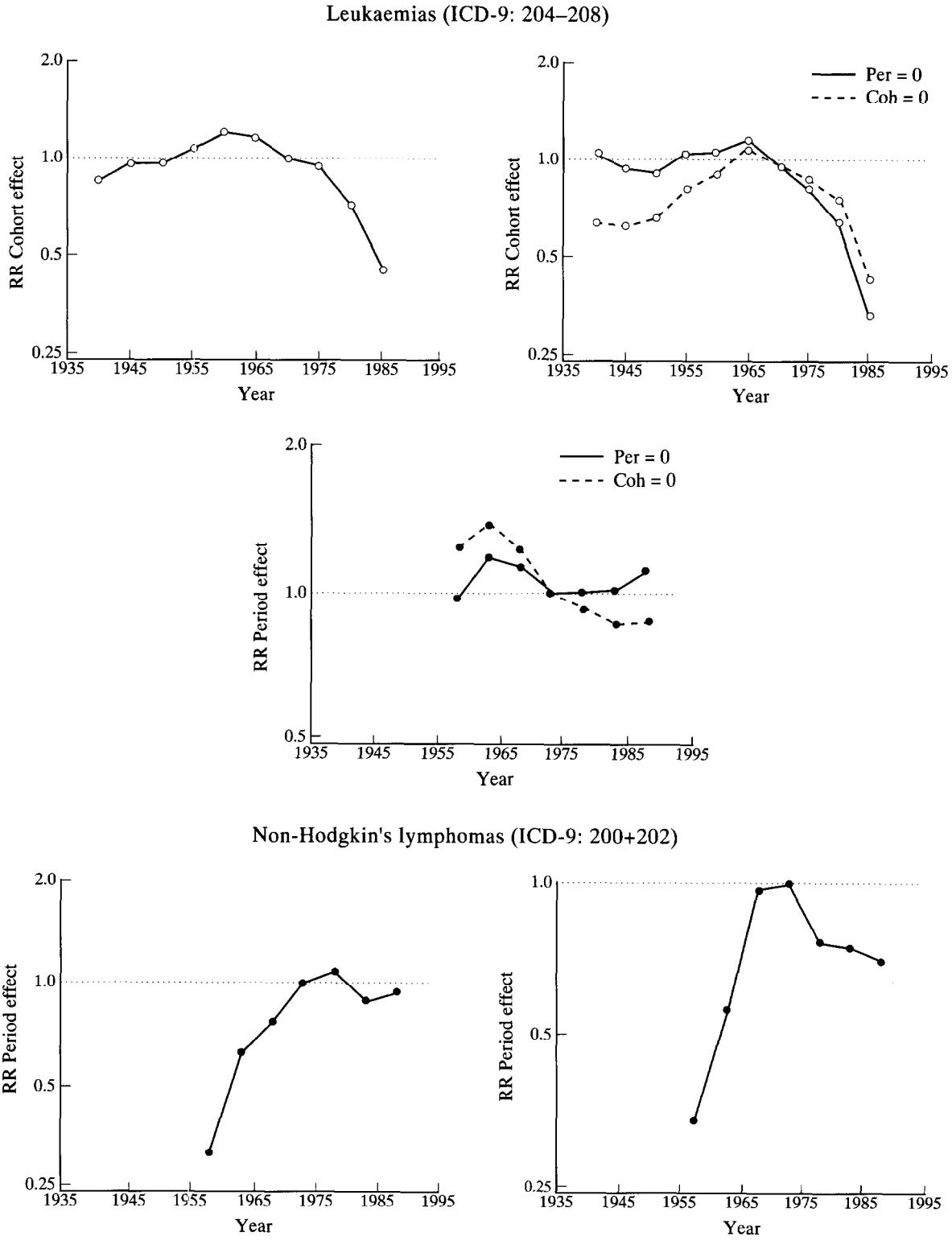

Figure 1. Continued.

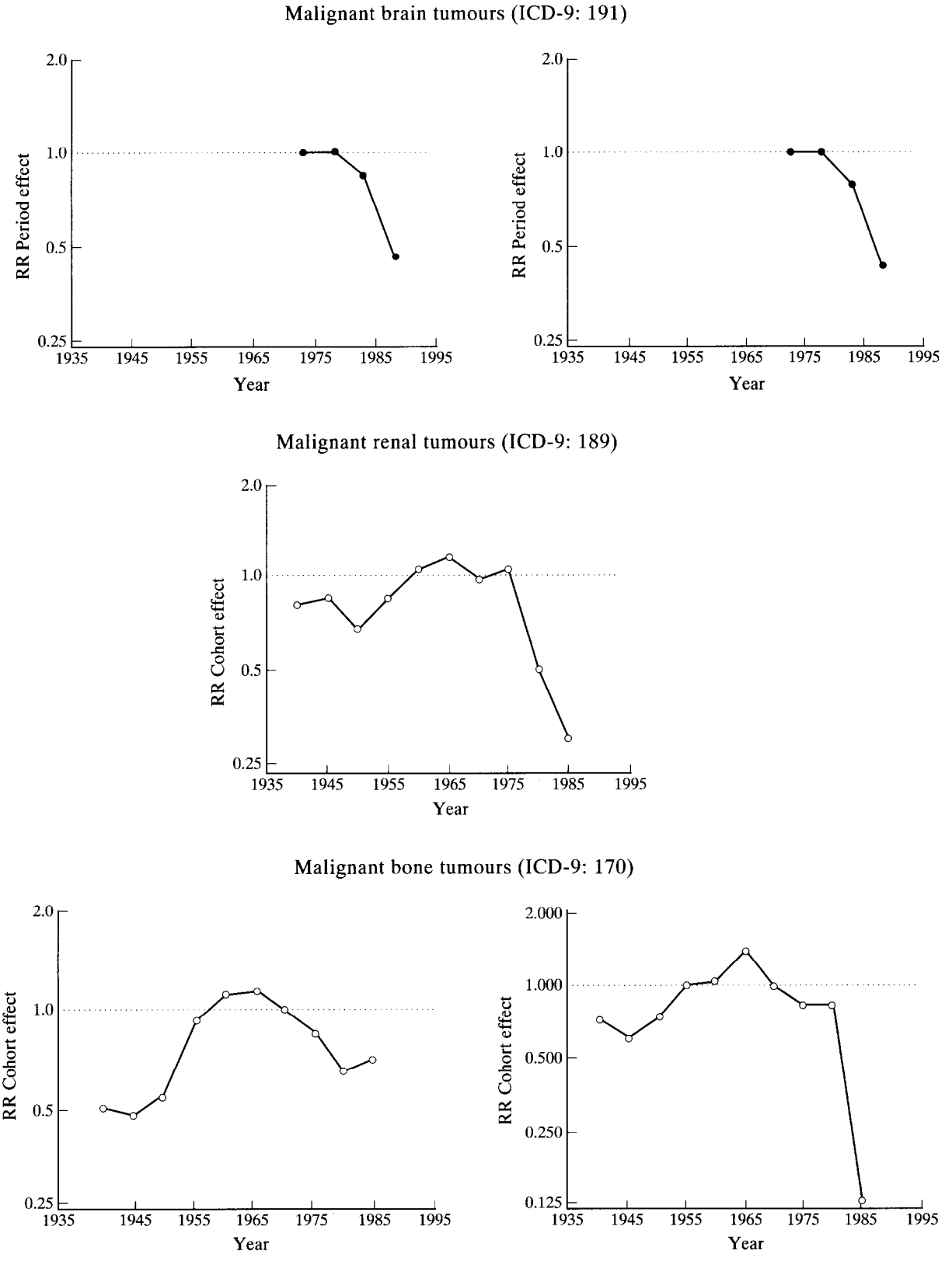

Figure 1. Continued.

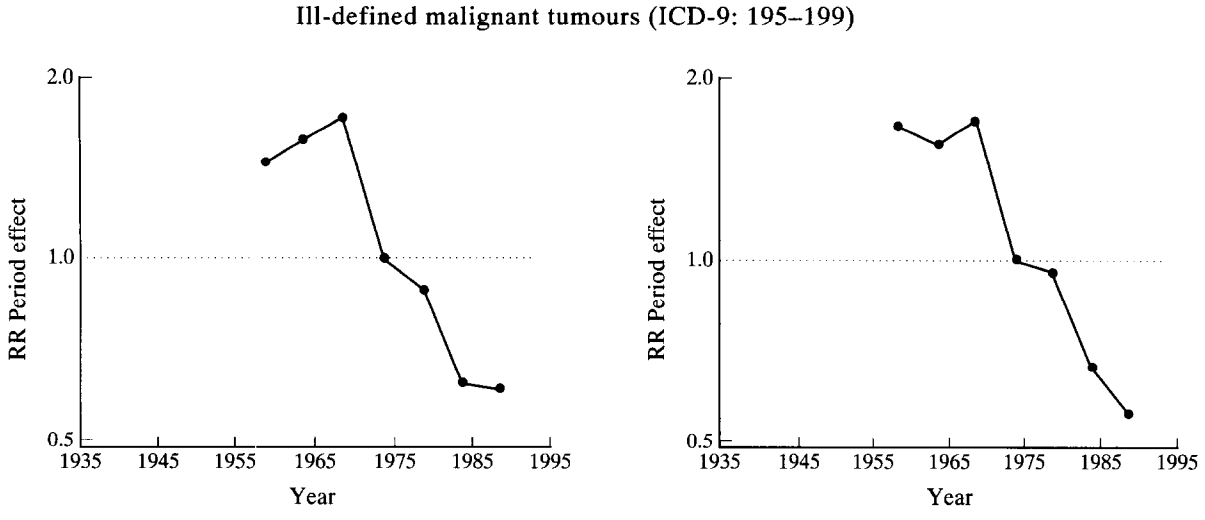

Figure 1. Mortality due to malignant tumours in males (left) and females (right) aged 0–19 years: cohort and/or period effects. Spain, 1956–1990. Solid line represents the results given by the model which attributes the overall net drift to the cohort effect, and the broken line, the results from the model attributing net drift to the period effect, where the final model was a three-factor model.

tumours (Hodgkin's disease and bone tumours), mortality rose with age. Finally, for all types of CAC and ill-defined tumours, age-specific mortality described a "U", there being two peaks corresponding to the extreme age groups. Non-Hodgkin's lymphomas failed to fit any of these three patterns, registering a fairly stable age-specific mortality in females but peaking in the 5–9 age group in males.

Recent trends

Table 5 shows 5-yearly rate ratios (RR) based on the last 15 study years, the relevant confidence intervals, the number of deaths avoided in the last two periods (reference rate, 1976–1980) and the percentage which these deaths represent over the total number of deaths observed for the decade in question (1981–1990). The RR values quantify the relative mortality for each 5-year period compared with the preceding period. RR for the total of malignant tumours was similar for both sexes (0.83 in males and 0.80 in females), amounting to a reduction of 20% every 5 years. As regards specific sites, the greatest recent decline was seen in tumours of the brain (a reduction of 30% every 5 years) and Hodgkin's disease, although in females the decline was not statistically significant. The rates for non-Hodgkin's lymphomas and bone tumours in both sexes were stable, as was the rate for renal tumours in males.

The decline observed in the final years of the study served to avoid 1022 deaths in males and 810 in females. Avoided leukaemia- and brain tumour-induced deaths, respectively, accounted for 30% and 29% of total avoided deaths. In the case of bone tumours, mortality rates for both sexes were higher during the 1981–1985 period than for the preceding 5-year period, with observed deaths thus exceeding expected deaths.

DISCUSSION

CAC-induced mortality in Spain continues to show a downward trend, begun in the early 1970s, exhibiting a slight lag against other European countries [4, 15]. In the interim, mortality rates have fallen by 40%. The reduction in mortality is more pronounced among females. Gender-related differences appear to be especially important in Spain, since it displays the highest sex ratio in Europe [15]. The trend observed over the last 15 study years is particularly favourable, with relative falls of approximately 20% every 5 years. This decline has made it possible to avoid 1832 CAC-related deaths in the last decade, despite the fact that children's tumours continue to rank as the second leading cause of death among the 1–20 age range [29]. The results reported for CAC as a whole are basically determined by the decline in mortality due to leukaemias and brain tumours, these two sites having the highest recorded mortality rates.

Leukaemia-induced mortality in Spain started to fall in the late 1960s/early 1970s, lagging somewhat with respect to the remaining EC countries [15]. In Spain, the reduction translates as a progressive decline in the risk of dying from leukaemias in post-1965 generations. The reduction in leukaemia-induced mortality emphasises the effectiveness of the treatment guidelines introduced in the 1960s [15]. Indeed, among children's tumours, it is leukaemia for which the most favourable survival, both abroad [5, 12, 30–32] and locally [33] is reported. In Spain, survival at 5 years of cases diagnosed in the period 1980–1985 stands at 54% for leukaemias overall and 60% for Acute Lymphatic Leukaemia (the most frequent type) [33].

Malignant brain tumours had the most pronounced decline in the last 15 years of the study. Overall analysis of all malignant tumours of the nervous system (ICD-9: 191 and 192) points to a rise in the number of diagnosed cases up to the 1970s (data not shown). The impossibility of including the first three quinquennia for the study of brain tumours conceals this initial increase, attributable mainly to advances in diagnostic techniques [13, 14, 34, 35]. Therapeutic achievements would only partly explain the period effect found. A reduction in adult mortality due to these tumours has also been observed in our country during the final decade owing to changes in coding criteria [36], and this factor's influence cannot be discounted here. Inter-country comparisons prove difficult, owing to the wide differences in the coding of tumours as malignant or benign [15]. In Spain, survival at 5 years currently stands at 55% [33].

The constant decline in mortality due to Hodgkin's lymphoma is in accordance with that observed for other countries [15]. At all events, the age groups selected are not suitable for studying this tumour, since the first peak in incidence in Spain lies between 25 and 35 years [37]. Present survival exceeds 80% [5, 12, 30–33], with the Spanish figure being 88% [33]. The difficulty encountered by age–period–cohort models in discrimi-

Table 5. Mortality due to malignant tumours. Children and young adults (from 0 to 19 years of age). Five-yearly rate ratio and avoided deaths in the decade 1981–1990. Spain, 1976–1990

Tumour	RR every 5 years	95% CI	Avoided deaths 1981–1985	Avoided deaths 1986–1990	Avoided deaths/ observed deaths (%)
Total malignant tumours (ICD-9: 140–208)					
Males	0.83	0.80–0.86	280	742	25.5
Females	0.80	0.77–0.84	238	572	30.3
Leukaemias (ICD-9: 204–208)					
Males	0.85	0.80–0.90	81	246	21.3
Females	0.85	0.79–0.92	73	152	22.1
Hodgkin's lymphomas (ICD-9: 201)					
Males	0.74	0.56–0.97	8	25	40.8
Females	0.79	0.57–1.09	5	13	32.4
Non-Hodgkin's lymphomas (ICD-9: 200+202)					
Males	0.91	0.81–1.03	49	37	21.0
Females	0.95	0.78–1.16	3	7	6.2
Malignant brain tumours (ICD-9: 191)					
Males	0.70	0.63–0.77	71	215	50.4
Females	0.68	0.61–0.76	64	182	55.7
Malignant renal tumours (ICD-9: 189)					
Males	0.82	0.64–1.04	20	15	41.0
Females	0.78	0.62–0.98	10	20	32.7
Malignant bone tumours (ICD-9: 170)					
Males	0.87	0.76–1.00	−20*	45	7.9
Females	0.88	0.75–1.04	−16*	26	4.7
Ill-defined malignant tumours (ICD-9: 195–199)					
Males	0.82	0.70–0.95	53	52	45.6
Females	0.75	0.63–0.89	40	50	54.7

*Observed deaths are greater than avoided deaths. RR = rate ratios.

nating between a period and a cohort effect where the trend is constant over time [20, 38] would explain why both models (A+C and A+P, see Table 4) are equally valid for males.

Non-Hodgkin's lymphomas present an initially upward period effect attributable to the rise in the number of cases diagnosed. In the last 15 study years, there was no significant decline in mortality due to these tumours, despite the rises in survival reported during this same period [12, 30–33]. In Italy too, a levelling-off in mortality was witnessed in the latter years of the study, this being the neoplasm exhibiting the smallest decline in mortality in that country [5, 16]. At a European level, incidence of non-Hodgkin's lymphomas is higher in the Mediterranean countries [19] and, in the case of Spain, Zaragoza register incidence rates are the highest in Europe for males and the second highest for females [4]. In Spain, survival at 5 years stands at 56% [33].

Most malignant renal tumours correspond to Wilms' tumours [6, 19]. The mortality time trend is very heterogeneous in the different age groups, which explains why neither the period nor the cohort effect proved statistically significant in males. Furthermore, no decline in renal cancer-related mortality among males was seen over the final 15 study years. In Europe, mortality declined as from the first half of the 1960s [15]. Survival has increased over the last few decades [5, 12, 30–32], with the Spanish figure currently standing at 75% at 5 years [33].

The most frequent types of malignant bone tumours are osteosarcomas and Ewing's sarcomas [3, 19]. Whereas osteosarcoma registers a peak in adolescence [19], that for Ewing's sarcoma occurs somewhat earlier [3]. The cohort effect encountered was similar in size for both sexes. Mortality declined as from the 1965 generation, albeit very gradually. In the last years of the study, the trend was not significant. The real trend over these years was actually "rising–falling" (Tables 2 and 3)—the slope found in the model failing to describe the situation adequately—while the adjusted rates evince a substantial reduction during the final 5-year period. Survival improved considerably [12, 30–32] yet, despite this, over comparable periods, in Italy and Spain survival fell short of that observed for the U.S.A. [5, 12, 33]. With respect to incidence, the Zaragoza register shows males as having the highest rates in Europe, while females rank at an intermediate level [4].

Ill-defined malignant tumours has been included as an indirect measure of trends in certification quality in Spain. Cases coded under the "ill-defined" rubric have declined sharply over time, which translates as a marked downswing in the period effect. Such a fall in the ill-defined category logically influences the trend in the remaining sites, with true declines thereby becoming attenuated.

Age–period–cohort models have been widely used to describe trends in cancer incidence and mortality among adults [38–41]. In mortality studies, specific rates encompass incident cases at any given age, along with surviving cases diagnosed at earlier ages. In the case of children's tumours, this element accentuates the differences between the first age group (which can only contain incident cases) and the rest [15]. However, the cohort effect summarises the experience of individuals of the same generation, irrespective of the age at which they may die. Moreover, for many risk factors, there is an association between

the birth generation on the one hand and exposure opportunity and intensity on the other. In fact, the cohort effect has proved to be more important than the period effect for almost all tumour sites [38–41]. It is traditionally maintained that the period effect principally reflects changes in case certification, diagnostic techniques and treatment procedures. In order for this to be truly so, these factors must have a similar influence across all age groups [21, 24].

In conclusion, advances in diagnosis and improved case certification could be responsible for the initial rise in the period effect observed for children's tumours overall and for non-Hodgkin lymphomas. The declines in both effects (period and cohort) can be most certainly ascribed to therapeutic advances. The fact that for many sites this reduction is perceived as a cohort effect confirms that effectiveness of treatment differs with age (generally proving most favourable among the youngest children). This "age*period" interaction is actually a cohort effect, since generation-set determines age of access to treatment. Lastly, while the trend observed in the final years promises a hopeful future, stress must nevertheless be laid upon the need to implement the most effective treatment guidelines for all those tumours exhibiting less favourable trends, bone tumours and non-Hodgkin's lymphomas in particular—compared to the other European countries, Spain exhibits relatively high incidence rates for both these tumours [4].

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