Pergamon

European Journal of Cancer Vol. 33, No. 4, pp. 616–623, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00525-4

Original Paper

Childhood Cancer Incidence in Zaragoza and Navarre (Spain): 1973–1987

M. Pollán,[1] G. López-Abente,[1] E. Ardanaz,[2] P. Moreo,[3] C. Moreno,[2] A. Vergara[3] and N. Aragonés[1]

[1]Cancer Epidemiology Unit, National Center for Epidemiology, Carlos III Institute of Health, Sinesio Delgado 6, 28029 Madrid; [2]Cancer Registry of Navarre, Navarre Public Health Institute, Leyre 15, 31003 Pamplona; and [3]Cancer Registry of Zaragoza, Zaragoza Provincial Health Authority, Ramón y Cajal, 68, 50004 Zaragoza, Spain

Patterns and trends in childhood cancer incidence for Navarre and Zaragoza registries were studied over the 15-year period, 1973–1987. Overall cancer rates and rates for 10 specific types of cancer were analysed using a log-linear Poisson model or, alternatively, a gamma-Poisson model whenever overdispersion was present, with age, sex, registry and period being used as predictor variables. Childhood cancer was 30% more frequent in boys than in girls, and, except for lymphomas and bone tumours, incidence decreased remarkably with age. Adjusted rates were high in comparison with other European countries, particularly in the case of non-Hodgkin's lymphomas. Cancer rates proved somewhat higher in Navarre, but this difference attained statistical significance solely in the case of central nervous system tumours (rate ratio = 1.75; 95% confidence interval 1.21–2.54). A significant rise in overall incidence was observed (11% 5-yearly increase) due mainly to the upward trend in central nervous system tumours. While the rise in these tumours coincides with the period which witnessed the spread of computerised tomography in Spain, the trend nevertheless held steady over the last 5-year period, when access to this diagnostic technique had already become generalised nationwide. © **1997 Elsevier Science Ltd. All rights reserved.**

Eur J Cancer, Vol. 33, No. 4, pp. 616–623, 1997

INTRODUCTION

THERE IS a very low frequency of cancer in children under the age of 15 years. Cases in this age group account for 1% of total malignant neoplasms [1]. However, the specific characteristics of childhood tumours render it essential for these to be regarded as a group apart.

Differences vis-à-vis adult cancer go beyond the purely clinical (histology, presentation, prognosis or survival) and include important discrepancies in the respective epidemiological characteristics. Hence, with the exception of Burkitt's lymphoma, geographical variations are far less marked [1–3], as seems to be the case with changes over time [4–8]. Furthermore, the principal known risk factors (tobacco, alcohol and profession) could only act indirectly on tumour genesis, whereas genetic factors play a more relevant role [1, 8–10].

Two Spanish cancer registries have been providing information on incidence for over 15 years now. The Zaragoza Cancer Registry, set up in 1960, was the first registry of its kind in Spain. This registry's catchment area is the Province of Zaragoza, situated in north-east Spain with a population of 832 855 (Figure 1). The Navarre Cancer Registry, dating from 1970, currently covers a population of 517 344. Navarre also lies in the north of the country, adjacent to Zaragoza (Figure 1). According to 1981 census figures, the breakdown for the childhood population under 15 years of age was: Zaragoza, 96 017 boys and 90 457 girls; Navarre, 62 496 boys and 59 248 girls.

This paper studies patterns and trends in childhood cancer incidence in Navarre and Zaragoza, the respective catchment areas for Spain's two longest-serving cancer registries. Specific goals were: (1) to describe childhood incidence by specific site and sex in both registries; (2) to analyse the in-

Correspondence to M. Pollán.
Received 29 May 1996; revised 11 Nov. 1996; accepted 18 Dec. 1996.

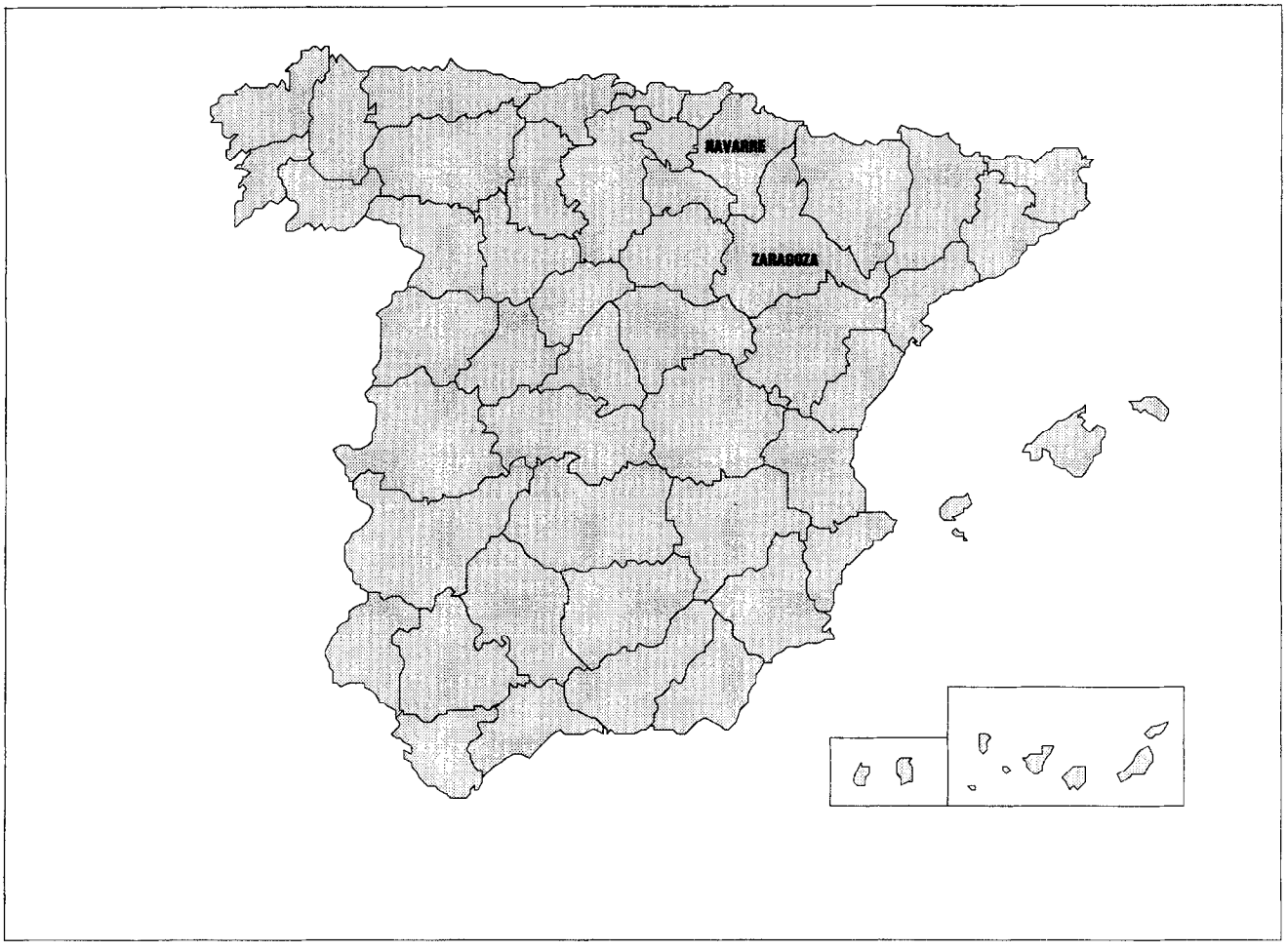

Figure 1. Geographical position of Zaragoza and Navarre in Spain.

fluence of age, sex and registry on observed rates; and (3) to investigate and quantify any time trends detected.

MATERIALS AND METHODS

All cases diagnosed between 1973 and the last available year, 1987, in children aged under 15 years in Zaragoza and Navarre were included in the analysis. Diagnostic groups were based on the International Classification of Diseases for Oncology (ICD-O), in accordance with the classification scheme developed for childhood cancer [11, 12]. Non-Hodgkin's, Burkitt's and unspecified lymphomas (groups II b, c d of the Birch–Marsden classification) were grouped under the heading of non-Hodgkin's lymphoma. With respect to central nervous system tumours (CNS), benign and uncertain neoplasms were excluded.

Age-specific rates for each sex and age group (0–4, 5–9 and 10–14 years) were computed in both registries. Population estimates were calculated from all available censuses and municipal population registers for the study period, using a logistic polynomial model [13]. To allow for differences in childhood age distribution, overall rates were age-adjusted by using the world standard childhood population [14].

A more detailed analysis was carried out for diagnostic groups having more than 25 cases. Specific rates were computed for every quinquennium and log-linear Poisson models were fitted, with age, sex, registry and period being taken as explanatory variables. We first tested whether specific rates exhibited a degree of variability greater than that permitted by a Poisson distribution (overdispersion of rates). In such cases, the Poisson model would erroneously produce narrower variance estimators. Thus, where this proved to be the case, we proceeded to use a corrected model (gamma-Poisson model) which took overdispersion into account [15, 16]. Explanatory terms were sequentially introduced in the following order: age, sex, registry and period; and differences in rates attributable to these variables were tested by using the log-likelihood ration test [17]. Since it was of particular interest to ascertain whether temporal trends were similar for the two registries, both sexes and all age groups, a check was run on these interaction terms. For comparison purposes, we also tested all remaining two-way interaction terms, including registry. Maximum likelihood estimates of rate ratios for the explanatory variables and their corresponding 95% confidence intervals were calculated. However, owing to a lack of sympathetic nervous system tumours and renal neoplasms in the 10–14 age group, we had no option but to exclude these from the analysis for both sites.

Finally, using a log-linear age-cohort-period model [18], we tested for changes in incidence among different birth-cohorts, simultaneously allowing for the effects of sex and registry.

Table 1. *Childhood cancer in Zaragoza and Navarre,* 1973–1987. *Number of cases, average annual incidence and adjusted rates per million*

		Zaragoza				Navarre				Both registries	
Tumour	Sex	No	Crude	Adjusted*	95% CI†	No‡	Crude	Adjusted*	95% CI†	Adjusted*	95% CI†
All malignant tumours	M	204	142.4	148.0	128.7–169.3	148*	157.6	164.3	139.4–192.4	154.5	139.0–171.1
	F	134	99.4	105.5	88.9–124.3	108*	121.2	127.8	105.4–153.6	114.4	100.8–129.3
All leukaemias	M	65	45.4	49.0	38.2–61.9	45	47.9	51.9	38.4–68.7	50.2	41.6–60.1
	F	52	38.6	40.1	30.1–52.3	31	34.8	37.5	25.9–52.6	39.1	31.3–48.2
Lymphocytic leukaemias	M	40	27.9	30.1	21.8–40.5	29	30.9	32.5	22.0–46.3	31.0	24.4–39.0
	F	36	26.7	28.7	20.3–39.2	25	28.1	30.6	20.2–44.5	29.4	22.8–37.5
Other leukaemias	M	25	17.5	19.0	12.5–27.6	16	17.0	19.4	11.5–30.6	19.1	14.0–25.6
	F	16	11.9	11.4	6.5–18.7	6	6.7	6.9	2.6–14.9	9.6	6.0–14.6
Hodgkin's disease	M	11	7.7	7.5	3.7–13.5	8	8.5	7.5	3.0–15.4	7.5	4.4–11.9
	F	5	3.7	3.1	0.9–7.8	4	4.5	4.3	1.1–11.2	3.6	1.6–7.1
Non-Hodgkin's lymphomas	M	30	20.9	20.0	13.4–28.8	20	21.3	20.8	12.6–32.3	20.3	15.0–26.9
	F	14	10.4	10.7	5.9–17.8	10	11.2	12.5	6.2–22.2	11.4	7.4–16.7
CNS neoplasms	M	34	23.7	24.8	17.4–34.5	37	39.4	38.8	27.3–53.6	30.4	23.8 38.2
	F	18	13.3	13.4	7.9–21.1	23	25.8	24.3	15.2–36.9	17.7	12.6–24.2
Neuroblastoma	M	11	7.7	9.1	4.8–15.5	9	9.6	11.4	5.6–20.5	10.0	6.4–14.9
	F	13	9.6	12.5	7.2–20.0	8	9.0	11.0	5.2–20.3	11.9	7.8–17.3
Retinoblastoma	M	2	1.4	1.8	0.3–5.6	4	4.3	5.3	1.7–12.4	3.2	1.3–6.4
	F	3	2.2	2.8	0.7–7.4	2	2.2	2.6	0.4–8.7	2.7	1.0–5.9
Renal tumours	M	10	7.0	7.4	3.6–13.3	2	2.1	2.7	0.4–8.5	5.5	2.9–9.4
	F	6	4.4	5.2	2.1–10.7	8	9.0	10.7	5.0–20.0	7.4	4.3–11.9
Hepatic tumours	M	10	7.0	7.3	3.5–13.2	4	4.3	4.7	1.3–11.5	6.2	3.5–10.3
	F	1	0.7	0.9	0.0–4.5	0	0.0	0.0	0.0–4.1	0.6	0.0–2.7
Malignant bone tumours	M	9	6.3	5.4	2.3–10.8	7	7.5	7.2	2.8–15.0	6.1	3.4–10.2
	F	8	5.9	5.6	2.4–11.3	7	7.9	7.2	2.7–15.3	6.3	3.4–10.5
Soft-tissue sarcoma	M	16	11.2	11.3	6.5–18.3	8	8.5	9.4	4.2–17.9	10.5	6.8–15.5
	F	9	6.7	7.3	3.5–13.5	6	6.7	6.8	2.5–14.7	7.1	4.0–11.5
Gonadal neoplasms	M	1	0.7	0.6	0.0–3.7	1	1.1	1.4	0.1–6.6	0.9	0.1–3.2
	F	4	3.0	3.2	0.9–7.9	2	2.2	2.8	0.5–9.0	3.0	1.2–6.3
Malignant epithelial neoplasms	M	3	2.1	2.1	0.4–6.1	2	2.1	1.9	0.2–7.3	2.0	0.6–4.8
	F	1	0.7	0.7	0.0–4.0	3	3.4	2.9	0.5–9.1	1.6	0.4–4.3
Unspecified malignant neoplasms	M	2	1.4	1.8	0.3–5.6	0	0.0	0.0	0.0–3.9	1.1	0.2–3.4
	F	0	0.0	0.0	0.0–2.7	3	3.4	3.6	0.8–10.2	1.4	0.3–4.1

*Adjusted rates using the world standard childhood population. †95% confidence interval. ‡Two cases not listed specifically include histiocytosis X and other reticuloendothelial neoplasms.
M, male; F, female; CNS, central nervous system.

RESULTS

In the period 1973–1987, 338 childhood cancer cases were registered in Zaragoza and 256 in Navarre. Crude and adjusted rates for the entire period are shown in Table 1. The term "neuroblastoma" replaces the rubric "sympathetic nervous system" tumours in the tables, since all those involved were neuroblastomas. Almost one-third of all cases were leukaemias, and haematological tumours (leukaemias and lymphomas) together accounted for 50% of the total number of cancer cases. Among solid tumours, the most frequent were those of the central nervous system (CNS). As seen in Table 1, cancer rates were generally somewhat higher in Navarre, and the overall male-to-female ratio was similar in both registries, standing at around 1.3–1.4. This sex ratio was higher for non-lymphocytic leukaemias, Hodgkin's and non-Hodgkin's lymphomas and CNS neoplasms.

Owing to the low number of cases, retinoblastomas, hepatic tumours, gonadal neoplasms, malignant epithelial neoplasms and unspecified malignant neoplasms were excluded from subsequent analysis. Table 2 shows age-specific rates for the remaining groups and statistical significance for age, sex and registry variables when they are sequentially included in the model, as yielded by the log-likelihood ratio test. In general, rates decreased with age, with this pheonomenon being stronger for neuroblastomas. Indeed, for this type as well as for malignant renal tumours, there was only one case in the 10–14 year age group, thus determining the group's exclusion from the model. The exceptions to the rule were Hodgkin's disease and malignant bone tumours, both displaying a rising trend with age, and CNS with no clear unique pattern.

Table 3 shows the standardised 5-yearly rates for the two registries. The statistically significant trend seen for overall cancer rates was chiefly due to the pronounced increase in CNS tumours, non-Hodgkin's lymphomas seemed to increase during the two first quinquennia, but the overall trend was not significant.

Overdispersion of rates was present in four sites, namely: other leukaemias, Hodgkin's disease, non-Hodgkin's lymphomas and renal tumours. Modelling was carried out by taking the "age + sex + registry + period" as baseline. In no case did replacing the period variable (linear time trend) by a factor (non-linear time trend) improve the model (data not shown). None of the interactions considered proved to be statistically significant. Thus, the absence of interactions means that there are no significant differences in trend with respect to the other variables, and that sex and age distributions are roughly similar in both registries.

Effect estimators for sex, age, registry and time are shown in Table 4. Rate ratios for age confirm the aforementioned downward trend. Taking the first group as reference, cancer incidence fell by 30% in the 5–9 years age group, and by almost 50% in the eldest group. Neuroblastomas were mostly diagnosed in children under 5 years of age, and the incidence of renal tumours in 5–9-year old children was half that of the reference group. In contrast, Hodgkin's disease and bone tumours showed a sharp increase with age, as expected.

Childhood cancer was 30% less frequent in girls (Table 4). Differences between the sexes were more marked in the case of lymphomas (Hodgkin's and non-Hodgkin's), where the incidence was half that of the boys. While the same was true for non-lymphocytic leukaemias, lymphocytic leukaemias appeared with the same frequency in both sexes. For solid tumours, these differences were less marked, and in the case of neuroblastomas and malignant bone tumours, girls showed a non-significant excess of risk.

Table 2. Childhood cancer in Zaragoza and Navarre. Number of cases and age-specific rates per million by sex. Statistical significance of age, sex and registry factors

Tumour	Sex	0–4 years		5–9 years		10–14 years		*P*-values		
		No	Rate	No	Rate	No	Rate	Age	Sex*	Registry†
All malignant tumours	M	137	190.9	134	162.4	81	97.8	<0.01	<0.01	0.10
	F	108	160.2	63	81.3	71	89.8			
All leukaemias	M	54	75.3	39	47.3	17	20.5	<0.01	0.12	0.91
	F	37	54.9	23	29.7	23	29.1			
Lymphocytic leukaemias	M	31	43.2	28	33.9	10	12.1	<0.01	0.72	0.68
	F	30	44.5	21	27.1	10	12.7			
Other leukaemias	M	23	32.1	11	13.3	7	8.4	0.12	0.14	0.46
	F	7	10.4	2	2.6	13	16.4			
Hodgkin's disease	M	3	4.2	7	8.5	9	10.9	0.42	0.31	0.86
	F	1	1.5	2	2.6	6	7.6			
Non-Hodgkin's lymphomas	M	9	12.5	29	35.1	12	14.5	0.15	0.04	0.76
	F	11	16.3	7	9.0	6	7.6			
CNS neoplasms	M	23	32.1	32	38.8	16	19.3	0.52	0.01	<0.01
	F	10	14.8	12	15.5	19	24.0			
Neuroblastomas	M	14	19.5	5	6.1	1	1.2	<0.01‡	0.61	0.73
	F	18	26.7	3	3.9	0	0.0			
Renal tumours	M	6	8.4	5	6.1	1	1.2	0.12†	0.48	0.88
	F	10	14.8	4	5.2	0	0.0			
Malignant bone tumours	M	2	2.8	4	4.8	10	12.1	0.01	0.98	0.53
	F	3	4.4	3	3.9	9	11.4			
Soft-tissue sarcomas	M	9	12.5	9	10.9	6	7.2	0.28	0.21	0.62
	F	7	10.4	4	5.2	4	5.1			

*Taking age into account. †Taking age and sex into account. ‡10–14 year age group excluded from analysis. CNS, central nervous system.

Table 3. Childhood cancer in Zaragoza and Navarre. Number of cases and average annual standardised incidence per million by period of diagnosis

Tumour	Sex	1973–1977		1978–1982		1983–1987		Trend*
		No	Rate	No	Rate	No	Rate	*P*-value
All malignant tumours	M	123	155.5	113	147.4	116	173.9	0.04
	F	76	103.7	74	103.6	92	147.4	
All leukaemias	M	39	49.4	34	46.0	37	61.3	0.93
	F	35	48.0	23	31.6	25	39.7	
Lymphocytic leukaemias	M	21	25.4	23	31.2	25	41.6	0.61
	F	26	36.0	16	22.5	19	31.9	
Other leukaemias	M	18	24.0	11	14.8	12	19.8	0.72
	F	9	12.0	7	9.1	6	7.9	
Hodgkin's disease	M	12	14.0	3	3.3	4	5.4	0.48
	F	4	4.6	1	1.7	4	4.8	
Non-Hodgkin's lymphomas	M	16	19.3	18	21.9	16	21.2	0.58
	F	6	8.6	10	13.8	8	12.5	
CNS neoplasms	M	13	16.4	28	34.8	30	44.4	<0.01
	F	8	10.5	14	17.2	19	27.5	
Neuroblastomas	M	8	11.5	8	11.7	4	6.6	0.65†
	F	6	8.8	6	10.1	9	19.2	
Renal tumours	M	6	8.1	3	4.4	3	3.9	0.87†
	F	5	7.5	3	4.6	6	11.1	
Malignant bone tumours	M	6	6.6	5	5.9	5	6.4	0.70
	F	2	2.4	9	12.0	4	4.5	
Soft-tissue sarcomas	M	14	17.6	5	6.9	5	6.9	0.16
	F	6	8.2	3	5.1	6	8.2	

*Taking into account age, sex and registry. †10–14 year age group excluded from analysis. CNS, central nervous system.

Table 4. Childhood cancer incidence in Zaragoza and Navarre. Rate ratios and 95% confidence intervals from the Poisson models

Tumour	RR† by age group			RR* Females versus males	RR* Navarre versus Zaragoza	Relative† 5-yearly trend
	0–4	5–9	10–14			
All malignant tumours	1	0.70	0.53	0.73	1.15	1.11
		0.58–0.84	0.43–0.64	0.62–0.86	0.98–1.35	1.00–1.22
All leukaemias	1	0.60	0.38	0.80	0.98	0.99
		0.43–0.83	0.26–0.55	0.60–1.06	0.74–1.31	0.83–1.18
Lymphocytic leukaemias	1	0.70	0.28	0.94	1.08	1.06
		0.48–1.02	0.17–0.46	0.66–1.32	0.76–1.52	0.85–1.31
Other leukaemias	1	0.34	0.65	0.52	0.76	0.92
		0.12–0.95	0.26–1.67	0.23–1.18	0.34–1.70	0.56–1.50
Hodgkin's disease	1	1.98	3.58	0.51	1.04	0.74
		0.29–13.64	0.55–23.22	0.12–2.22	0.24–4.51	0.30–1.83
Non-Hodgkin's lymphomas	1	1.39	0.73	0.53	1.10	1.11
		0.70–2.76	0.34–1.56	0.29–0.96	0.62–1.97	0.78–1.58
CNS neoplasms	1	1.15	0.87	0.61	1.75	1.58
		0.73–1.80	0.54–1.40	0.42–0.90	1.21–2.54	1.25–2.00
Neuroblastomas	1	0.22		1.18	1.12	1.09
		0.10–0.47		0.63–2.19	0.60–2.09	0.74–1.60
Renal tumours	1	0.49		1.39	0.94	1.05
		0.19–1.23		0.56–3.47	0.37–2.37	0.60–1.84
Malignant bone tumours	1	1.22	3.22	0.99	1.25	1.09
		0.39–3.84	1.20–8.62	0.49–2.00	0.62–2.54	0.71–1.68
Soft-tissue sarcomas	1	0.72	0.55	0.66	0.85	0.76
		0.35–1.50	0.25–1.21	0.35–1.26	0.44–1.63	0.51–1.13

*Rate ratio. †Five-yearly rate ratio relative to preceding period. CNS, central nervous system.

The slight excess in incidence in Navarre (Table 4) was almost completely due to CNS neoplasms, which were 75% more frequent than in Zaragoza. The remaining sites yielded similar rates in the two registries.

Childhood cancer incidence rose by 11% for every 5 years of the study period (Table 4), which translated into an annual increase of 2%. For specific sites, CNS tumours alone exhibited a statistically significant increase of 58% for

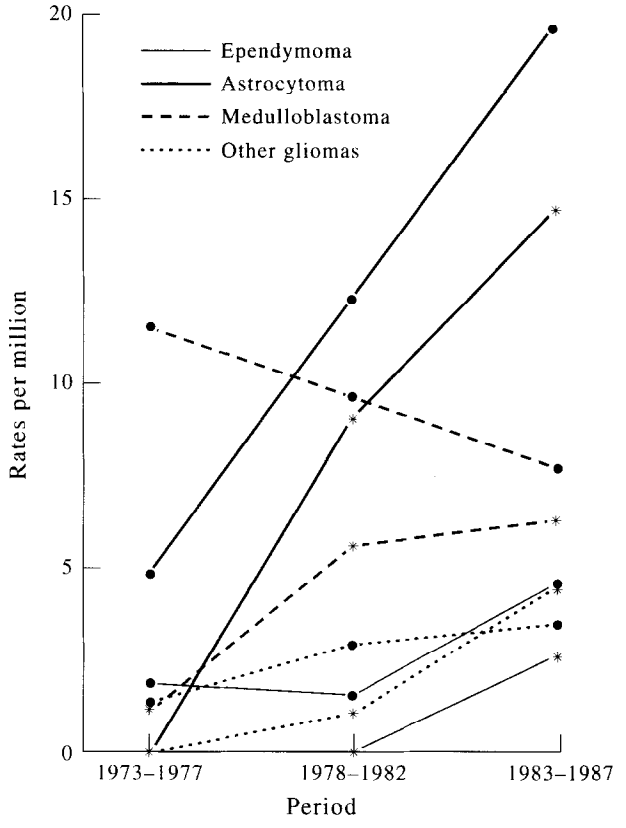

Figure 2. Central nervous system tumour incidence rates by histological type in Navarre (•) and Zaragoza (*).

every 5 years (9.6% p.a.). Non-Hodgkin's lymphomas, neuroblastomas and malignant bone tumours recorded a non-significant upward trend (less than 2% p.a.). The opposite was true of Hodgkin's and soft-tissue sarcomas which decreased by approximately 6% annually.

Given that registry-related differences and the presence of a statistical significant trend were both restricted to CNS, a comparison of these tumours by histological type is shown in Figure 2, in which adjusted rates for each registry are plotted over time. It can be seen that differences between Navarre and Zaragoza were not confined to a single histological group. However, one can reasonably assume that the aforementioned upward trend was mainly due to the increased incidence of astrocytomas reported in both registries.

One would have expected a cohort effect to be present only for those sites with some evidence of a time trend. In our case, both overall cancer and CNS tumours showed a constant rise with time not linked to any particular period or cohort. As the age-period-cohort analysis failed to detect significant cohort effects for any site, these results have not been presented.

DISCUSSION

In Navarre and Zaragoza, overall childhood cancer incidence, particularly in boys, ranks among the highest in Europe [2, 4, 5, 7, 14]. Similar rates appear in Italy and certain Scandinavian countries (Sweden and Finland). The incidence is equal in magnitude to that reported in the U.S.A. [19]. Cases among children under the age of 5 years account for approximately 40% of the total. M incidence has been described as being 20% higher [8], a phenomenon which is more pronounced in Spain. In general, while relative distribution of the different types of tumours is similar to that found in other countries [1], the proportion of lymphomas is somewhat greater due to the high incidence of non-Hodgkin's lymphomas. Over the 15-year study period, childhood cancer incidence exhibited a rising trend, owing in most part to an increase in CNS tumours.

The relative rarity of childhood cancer means that large population groups must be studied over lengthy periods of time in order to obtain incidence rates that are at all reliable [3]. The respective child populations covered by the two registries (around 150 000 children) limits the viability of separate studies. In this regard, we judged it acceptable for the information on Navarre and Zaragoza to be combined in the same model, given that they are neighbouring provinces and alike in many ways. Nonetheless, information has been quoted by province and the variable registry has been retained in the analysis to allow for comparisons between these two geographical areas.

Accuracy in denominators is essential in order to explain variability of rates in terms of change in incidence. Given that population figures are not available at the midpoint of every stratum, we used a logistic polynomial model to estimate these. This saturated model took observed demographic trends into account, precluding the assumption of a constant rate of change.

On interpreting incidence patterns and time trends, attention must be paid to the quality of the data. In Navarre, the percentage of cases diagnosed by death certificate in the three 5-year periods were 9%, 2% and 3%, respectively, and 90% of cases were histologically confirmed. In Zaragoza, the percentage of cases diagnosed by death certificate in the first and last quinquennia were 10% and 1%, respectively, and histological confirmation rose from 85% to 97%. However, in 1979 and 1980, half of all cases registered in Zaragoza were on a death certificate basis. This was due to a change of the reporting system which was passive until 1979 and active from this date. This possible under-registration might explain the appreciable downturn observed during the second 5-year period for most of the sites studied (see Table 3).

Log-linear Poisson regression models have only recently been applied to analysis of childhood cancer incidence [20–22]. Regression models allow effect estimates to be obtained for the different factors that influence variability in rates, removing the confounding effect stemming from their interrelationship. Furthermore, in the case of diseases with very low incidence (the case in point), Poisson models have proved to have theoretical and practical advantages over other approaches [23]. However, Poisson distribution assumes that variance in the rate is equal to the mean rate divided by person-years. It is important, particularly in the case of very low rates, to check whether this strong assumption in fact holds, and to use a corrected model if overdispersion is present [15]. Otherwise, statistical significance may be found purely because estimates of variance yielded by the Poisson model are erroneously small. Then again, the power to detect small effects depends on the size of the population and the underlying incidence rate. In our case, this implies that some differences between sexes, registries, periods and age groups would not be detected. For this reason, we decided not to remove any of these variables

from the final model. Even though confidence intervals may be wide, rate ratios serve to quantify the aforementioned differences.

Other authors have suggested the convenience of using "age-period-cohort" models when studying trends in childhood cancer [20]. The birth cohort represents the natural way of aggregating individuals and better detecting the influence of variations in those environmental factors having greatest impact during the prenatal period. Access to only three 5-year periods limits the potential of such models in our case, ruling out the possibility of detecting significant cohort effects for any tumour. For meaningful conclusions to be drawn, this analysis would have to be repeated with a longer follow-up time. To our knowledge, the only study on childhood cancer incidence using "age-period cohort" models involved the Connecticut registry, covered data for the period 1935–1979, and found no birth-cohort-related differences in incidence [22].

The incidence rates for leukaemias were similar for both registries and in agreement with figures reported for other European countries [14]. Two-thirds correspond to acute lymphocytic leukaemias (among lymphocytic leukaemias, all but two cases were acute), with a similar incidence for both sexes, in contrast to other leukaemias where frequency was higher in males. Incidence of lymphocytic leukaemias in the developed countries exhibits a peak between ages 2–4 years [1, 4, 5]. Some studies based on European and U.S. registries have shown a rise in incidence for leukaemias in general and acute lymphocytic leukaemias in particular [3, 6, 20, 22, 24], which has been attributed to a possible increase in the prevalence of infectious agents implicated in the disease's aetiology [25]. Nevertheless, in Navarre and Zaragoza, leukaemia incidence can be regarded as stable over the 15-year study period.

The incidence of Hodgkin's disease was high compared with the rest of Europe [2, 14] and disease frequency was 2-fold higher in boys. The relative trend found suggests a fall-off over time. This decline is evident in Navarre, but less so in Zaragoza. In Spain the first peak in incidence of this tumour is seen beyond the age range under review [26]. International patterns of Hodgkin's disease in children coincide with the distribution of infectious agents such as Epstein–Barr virus, poliomyelitis and tuberculosis. This, together with the observation of space-time clusters, has lent force to the hypothesis of an infectious aetiology for this tumour [8].

Non-Hodgkin's lymphomas are particularly frequent in Mediterranean countries [1, 2]. On the basis of the rates reported in this paper, Spain has the highest incidence in Europe for both boys and girls [14]. Unlike adults, confusion between Hodgkin's and non-Hodgkin's lymphomas is infrequent among children, so that this phenomenon can be ruled out as an explanation for the rates observed [27]. Of the lymphomas diagnosed: 76% corresponded to lymphatic and reticulocytic sarcomas; 19% to Burkitt's lymphomas and 4% were unspecified. A peak in incidence was seen between the ages of 5 and 9 years, with frequency among boys being twice that of girls. Furthermore, the relative trend observed (1.11 per quinquennium), while not statistically significant, does suggest an increase in the frequency of these tumours in this country. The same conclusion can be drawn from the observation of the Zaragoza incidence rates. Rises in incidence have been reported in Australia [28] and the U.S.A. [6].

The rates of CNS neoplasms observed for boys in Navarre are among the highest in Europe [14]. The relative frequency of the histological types is different to that found among adults, suggesting possible aetiological differences [29]. A number of authors warn as to the difficulty of establishing comparisons between different geographical areas, owing to marked divergences in diagnostic techniques [1] and the absence of a clear limit between benign and malignant tumours for certain histological types [3, 14]. It is, however, possible that these factors do not totally explain the rate ratio of 1.75 for Navarre versus Zaragoza, especially when one bears in mind that the availability of diagnostic procedures is similar across both provinces. CNS tumours have been diagnosed with growing frequency over recent decades [3, 21, 22, 30, 31], although in some countries rates have been observed to level off or fall from the age of 70 years [3, 4, 22]. Computerised axial tomography (CAT) was introduced in Spain in 1977 and, therefore, widely available in the 1980s [32].

Neuroblastoma accounted for 7% of childhood cancer in both provinces, a percentage similar to that reported for other registries [1, 33]. Although the most frequent tumour in children under one year old, it is nevertheless seldom seen among those over the age of 5 years [1, 4, 5, 8, 22]. While France exhibits the highest rates in Europe [5], Navarre and Zaragoza rank at an intermediate position. There are under-reporting problems hindering comparison, since mass postnatal screening results in a considerable increase in the number of cases diagnosed [1]. Descriptions of increased incidence in this tumour in different countries have always been attributed to improved case detection [21, 22, 34]. The 5-yearly rates for the registries studied showed a trend in the opposite direction, although in no case was this statistically significant.

Of the renal tumours, most (84%) were nephroblastomas, and the incidence resembled that of other European countries [14]. In Zaragoza, the frequency was higher among boys, while in Navarre the opposite applied. Although it was initially thought that incidence of nephroblastomas were constant worldwide, substantial variations have been found [3]. The incidence fell to half in the 5–9 age group, and was very low thereafter. Sweden is the only country reporting a pre-1975 increase in these tumours [35].

The incidence of bone tumours was similar to that found in the rest of Europe [14], with Navarre rates being 25% higher than those for Zaragoza. A little over half the cases diagnosed correspond to Ewing's sarcomas (55%), and the remainder to osteosarcomas. Incidence rates were similar across the sexes and showed a clear rise with age. As with Hodgkin's disease, the age range chosen places limitations on the analysis of these tumours.

Rates for soft-tissue sarcomas in Zaragoza, in boys in particular, rank among the highest in Europe (alongside France and Switzerland) [14]. The two most common histological types were rhabdomyosarcomas (51%) and fibrosarcomas (23%). For this group of tumours, incidence declined with age, and frequency was somewhat higher among boys. The 5-yearly rates observed and the relative trend plotted by the Poisson model both suggest a fall-off in incidence, albeit not statistically significant. In Italy, in contrast, a rise in incidence has been reported [7].

Among the remaining tumours, mention should be made of the high incidence of hepatic tumours among males in

Zaragoza. Half of these tumours were hepatoblastomas and the remainder hepatocarcinomas. Elsewhere in Europe, the highest incidence rates are registered by Slovenia for hepatoblastoma (2.6 per million), and Norway for hepatocarcinoma (1.8 per million). This high incidence in Zaragoza is concentrated in the last quinquennium (1983–1987), in which seven out of the total of 10 cases were diagnosed.

The population covered by the two registries accounts for only 3% of Spain's child population. Accordingly, it must be asked logically to what extent the results discussed here represent the situation at a national level. The rates reported by other, more recently created, Spanish cancer registries are similar to those found in this study [26]. Furthermore, both the sex ratio and the relative proportion of the different tumours agree with data provided by the National Childhood Cancer Registry (Registro Nacional de Tumoures Infantiles), which gathers information on cases diagnosed in 40 Spanish hospitals [36]. The sole point of difference worthy of note is the high proportion of CNS tumours in Navarre: 23.4% versus a figure of 17.7% quoted by the above source [36].

In conclusion, taking childhood cancer incidence reported in these two registries as reference, one out of every 440 boys and one out of every 590 girls in Spain develops cancer of one type or another before the age of 15 years. Incidence rates are particularly high for lymphomas, and especially so in the case of non-Hodgkin's lymphomas. The rise in CNS neoplasms coincides with the period which witnessed the spread of computerised tomography in Spain [32]. The trend held steady over the last 5-year period when access to this diagnostic technique had already become generalised nationwide. We are unaware of the underlying reason(s) for the high rate of CNS neoplasms in Navarre, affecting a wider age group than that strictly covered by this paper [26]. Hence, before any definitive conclusions can prudently be drawn, we feel that over the next few years, an in-depth follow-up in both registries of this tumour's incidence is needed.

1. Parkin M, Nectoux J, Stiller C, Draper G. L'incidence des cancers de l'enfant dans le monde. *Pediatrie* 1989, **44**, 725–736.
2. Levi F, La Vecchia C, Lucchini F, Negri E, Boyle P. Patterns of childhood cancer incidence and mortality in Europe. *Eur J Cancer* 1992, **28**, 2028–2049.
3. Breslow NE, Langholz B. Childhood cancer incidence: geographical and temporal variations. *Int J Cancer* 1983, **32**, 703–716.
4. De Nully Brown P, Hertz H, Olsen JH, Yssing M, Scheibel E, Jensen OM. Incidence of childhood cancer in Denmark 1943–1984. *Int J Epidemiol* 1984, **18**, 546–555.
5. Bernard JL, Bernard-Couteret E, Coste D, *et al.* Childhood cancer incidence in the south-east of France: a report of the Provence-Alpes-Côte d'Azur and Corsica regions pediatric cancer registry, 1984–1991. *Eur J Cancer* 1993, **29A**, 2284–2291.
6. Blever WA. What can be learned about childhood cancer from "Cancer Statistics Review 1973–1988". *Cancer* 1993, **71**, 3229–3236.
7. Mosso ML, Colombo R, Giordano L, Pastore G, Terracini B, Magnani C. Childhood cancer registry of the province of Torino, Italy. Survival, incidence and mortality over 20 years. *Cancer* 1992, **69**, 1300–1306.
8. Greenberg RS, Shuster JL. Epidemiology of cancer in children. *Epidemiol Rev* 1985, **7**, 22–48.
9. Knudson AG. Pediatric molecular oncology. Past as prologue to the futurc. *Cancer* 1993, **71**, 3320–3324.
10. Mili F, Khoury MJ, Flanders WD, Greenberg RS. Risk of childhood cancer for infants with birth defects. *Am J Epidemiol* 1993, **137**, 629–638.
11. World Health Organization. *ICD-O: International Classification of Diseases for Oncology*, 1st edn. Geneva, World Health Organization, 1976.
12. Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer* 1987, **40**, 620–624.
13. Aickin M, Dunn CN, Flood TJ. Estimation of population denominators for public health studies at the tract, gender and age-specific level. *Am J Public Health* 1991, **81**, 918–920.
14. Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL. *International Incidence of Childhood Cancer*. Lyon, IARC Scientific Publications No. 87, 1988, 17–22.
15. Breslow NE. Extra-Poisson variation in log-linear models. *Appl Statist* 1984, **33**, 38–44.
16. Bennet S. An extension of Williams' method for overdispersion models. *GLIM Newsletter* 1988, **17**, 12–18.
17. Breslow NE, Day NE. *Statistical Methods in Cancer Research*, Vol 2. *The Analysis of Cohort Studies. The Analysis of Cohort Studies*. Lyon, IARC Scientific Publications No. 82, 1987, 137–138.
18. Holford TR. Analysing the temporal effects of age, period and cohort. *Stat Methods Med Res* 1992, **1**, 317–337.
19. Bleyer WA. The impact of childhood cancer on the United States and the world. *CA Cancer J Clin* 1990, **40**, 355–367.
20. Blair V, Birch JM. Patterns and temporal trends in the incidence of malignant disease in children: I. Leukaemia and lymphoma. *Eur J Cancer* 1994, **30**, 1490–1498.
21. Blair V, Birch JM. Patterns and temporal trends in the incidence of malignant disease in children: II. Solid tumours of childhood. *Eur J Cancer* 1994, **30**, 1498–1511.
22. van Hoff J, Schymura MJ, McCrea Curne MG. Trends in the incidence of childhood and adolescent cancer in Connecticut, 1935–1979. *Med Pediatr Oncol* 1988, 16, 78–87.
23. Lovett AA, Bentham CG, Flowerdew R. Analysing geographical variations in mortality using Poisson regression: the example of ischaemic heart disease in England and Wales 1969–1973. *Soc Sci Med* 1986, **23**, 935–943.
24. Stiller CA, Draper GJ. Trends in childhood leukaemia in Britain 1968–1978. *Br J Cancer* 1982, **45**, 543–551.
25. Alexander FE. Viruses, clusters and clustering of childhood leukaemia: a new perspective? *Eur J Cancer* 1993, **29**, 1424–1443.
26. González J, Gorgojo L, Martin J, Villar F. *Cáncer en España*. Madrid, Ministerio de Sanidad y Consumo, 1993.
27. Franssila KO, Heiskala MK, Rapola J. Non-Hodgkin's lymphomas in childhood. *Cancer* 1987, **59**, 1837–1846.
28. McWhirter WR, Petroeschevsky AL. Incidence trends in childhood cancer in Queensland, 1973–1988. *Med J Aust* 1991, **154**, 453–455.
29. Stiller CA, Nectoux J. International incidence of childhood brain and spinal tumours. *Int J Epidemiol* 1994, **23**, 458–464.
30. Pollack IF. Brain tumours in children. *N Engl J Med* 1994, **331**, 1500–1507.
31. Lannering B, Marky I, Nordborg C. Brtain tumours in childhood and adolescence in west Sweden 1970–1984: epidemiology and survival. *Cancer* 1990, **66**, 604–609.
32. Lázaro P. *Evaluación de Servicio Sanitarios: La Alta Tecnología Médica en España*. Madrid, Fondo de Investigación Sanitaria, 1990.
33. Kaatsch P, Haaf G, Michaelis J. Childhood malignancies in Germany. Methods and results of a nationwide registry. *Eur J Cancer* 1995, **31**, 993–999.
34. Stiller CA. Trends in neuroblastoma in Great Britain: incidence and mortality, 1971–1990. *Eur J Cancer* 1993, **29A**, 1008–1012.
35. Ericsson JL-E, Karnström L, Mattsson B. Childhood cancer in Sweden, 1958–1974. I. Incidence and mortality. *Acta Pediatr Scand* 1978, **67**, 425–432.
36. Registro Nacional de Tumoures Infantiles. *Estadísticas Básicas 3 (1980–1990). Supervivencia 1980–1989*. Valencia, Generalitat Valenciana, 1992.

Acknowledgements—This study was supported by the Health Research Fund (FIS) of the Spanish Ministry of Health (Fondo de Investigación Sanitaria, Grant 94/0152).