Temporal trends in the incidence of childhood leukemia, lymphomas and solid tumors in north-west Italy, 1967-2001. A report of the Childhood Cancer Registry of Piedmont

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Background and Objectives. Several studies have been published on trends in childhood cancer incidence, with different patterns being reported. We present an analysis of cancer incidence trends in Piedmont (Italy) in 1967-2001 for the major categories of childhood malignant neoplasms.

Design and Methods. The population-based Childhood Cancer Registry of Piedmont has recorded incident cases of malignant neoplasm in children (age 0-14) since 1967. Procedures for data collection and coding have been uniform throughout the study period. We calculated incidence rates per million children per year by sex and age-group. Trends were estimated using Poisson regression analysis, adjusted for age and sex and presented as the annual percent change (APC).

Results. Significant increases were observed for all malignant neoplasms combined (3360 cases, APC:1.3%, 95% CI:1.0% to 1.6%), leukemia (APC: 1.0%, 95% CI: 0.4% to 1.6%), central nervous system (CNS) tumors (APC of 2.3%, 95% CI: 1.6% to 3.1%) and neuroblastoma (APC: 2.3%, 95% CI: 1.0% to 3.5%). Acute lymphoblastic leukemia (APC 1.2%, 95% CI: 0.2% to 2.3%), and Acute non-lymphoblastic leukemia (APC 1.7%, 95% CI–0.6%, 4.1) both increased over time. Differences by age groups were observed for some tumor types, such as for neuroblastoma in infants (4.8% increase per year), leukemia in children aged 1-4 years (1.2%) and CNS tumors in children aged 10-14 (3.4%).

Interpretations and Conclusions. Our data suggest an increasing incidence of childhood cancer in general, and specifically for leukemia, CNS tumors and neuroblastoma in Piedmont in 1967-2001. The observed trends are unlikely to be explained by random variation, changes in exhaustiveness or quality of data collection and registration.

Key words: childhood malignant neoplasm, childhood leukemia, incidence, time trend, cancer registry, epidemiology.

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In the last few decades several studies have examined temporal trends in the incidence of childhood cancer in various Western countries. These reports have focused mainly on leukemia[1-18] brain tumors,[2,4,7,8,15-17,19-28] and to a lesser extent on rarer childhood neoplasms.[2,4,6-8,15,17,19,20,25] The findings are not consistent, with differing patterns for different cancer sites and in different countries.

Several papers have reported an increase in childhood leukemia[1-6,10,15,17] or in some leukemia subtypes,[1,5,9-11,14] whereas others have found no significant trends or have reported stable rates.[7,12,13,16,18-20] A more complex pattern was reported by the SEER working group. Ries *et al.*[8] reported a significant annual percent increase for leukemia (all types combined) of 0.7% from 1975 to 2001; the increases primarily occurred during 1975-1986 (annual percent change: +1.5%), whereas in 1987-2001 the trend was weaker and not statistically significant (+0.3%). The patterns are more consistent for brain tumors[2,4,7,8,22,25] and for neuroblastoma[7,24,26] with most studies reporting significant increases over time. However, it is not clear whether improvements in diagnostic procedures account for the observed trends or whether a genuine increase in incidence has occurred.[3,7,15,19,20,23,26-28] Only a few studies have examined other types of childhood cancer and the findings have been inconsistent, possibly because of the small number of cases involved.

The Childhood Cancer Registry of Piedmont (CCRP) is the oldest and largest pediatric population-based Cancer Registry active in Italy. Data are available over a 35-year period, from 1967 to 2001. In a previous report[14] we described inci-

dence trends for leukemia until 1998, observing a statistically significant increase for acute lymphoblastic leukemia (ALL) of the pre-B subtype. There was a non-significant increase in the incidence of acute non-lymphoblastic leukemia (AnLL). In the current study we have updated our previous analysis of leukemia, and we have also examined trends for other types of childhood cancer in Piedmont from 1967 to 2001.

Design and Methods

Since 1967, the population-based Childhood Cancer Registry of Piedmont (CCRP) has been recording cancer incidence in children (age 0-14 years) resident in the Piedmont region. Cases are actively searched for by trained personnel in the archives of pediatric wards of all hospitals in the region. Data are also collected in the same way from non-pediatric wards that may treat children with cancer. Further case ascertainment is conducted through cross-checking with the Hospital Admission and Discharge Files (HADF), also including hospital stays in other Italian hospitals, the records of reimbursements for cancer treatments administered abroad, the Piedmont Cancer Registry and the database of the *Italian Association of Pediatric Hematology and Oncology* (AIEOP).[29] The registration information for each patient includes personal, medical and follow-up data. All diagnoses are coded using the ICD-O classification and then grouped according to the International Classification for Childhood Cancer (ICCC).[30] Data collection and coding procedures were homogeneous throughout the entire period of activity of the CCRP. For each registered child we checked the residence at diagnosis (as reported in the clinical records) at the corresponding Town Office (all Italian residents have to be listed in the roster of a town, and the information is promptly updated in the case of a change of address or change of status). Cases are included in the CCRP only after positive confirmation of residence in Piedmont at diagnosis. Further details of the methods employed by the Registry have been published elsewhere.[31]

Population figures were obtained from census data and inter-census estimates,[32] by calendar year, age and sex. Population censuses are conducted every 10 years by the Italian National Institute of Statistics (ISTAT); the relevant data for the present study were provided by censuses carried out in 1971, 1981, 1991 and 2001. Annual inter-census estimates have been provided since 1980 by the *Banca Dati Demografico Evolutiva* (BDDE) of the Piedmont Region, based on birth, death and migration figures and on the number of residents on December 31 of each year, according to the National Institute for Statistics (ISTAT) and Registrar Offices.[32] Figures for the 1970s were provided by IRES Piemonte using the same methods on an experimental basis. In Turin – the major city in the Region – we compared population estimates from census data and inter-census estimates[32] with the corresponding figures from the Town Office; the differences were not systematic and were in the range of -2.0% to 0.5%. The population of Piedmont is relatively stable with respect to population movements, but the childhood population decreased from approximately 800,000 in 1975-79 to approximately 500,000 in 1999-2001, due to a reduction in birth rates.[14]

Time trend analyses were based on annual incidence rates by age group (<1, 1-4, 5-9, 10-14 years) and sex. We also computed sex and age-standardized (based on the 1981 Italian population) incidence rates for the overall period 1967-2001. All rates were expressed per 1,000,000 children-years.

Time trends were assessed for all childhood cancers combined, and for the major categories of the ICCC. We also assessed time trends for selected minor categories that were of *a priori* interest and/or had a sufficiently large number of cases. Lymphomas were subdivided into two groups: Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Central nervous system (CNS) tumors were analyzed separately in the subgroups of ependymoma, astrocytoma and medulloblastoma. Intracranial primitive neuroectodermal tumors were grouped with medulloblastoma.

The analyses for leukemia were conducted following the same criteria as in our previous analysis.[14] In order to avoid possible bias due to improvements in diagnostic methods over the past two decades,[33] the analysis for ALL was restricted to data from 1977 (rather than 1967) onwards.

The trend in incidence rates over time was estimated as the annual percent change (APC) in the incidence rate using Poisson regression analysis, adjusted for age and gender. The APC is equal to 100 times (RR-1), where RR is the average relative risk for a given year over the preceding year. The level of statistical significance was set at 5% (two-tailed test). The analyses were conducted using STATA 8.0.

Results

Between 1967 and 2001, the CCRP registered 3,360 cases, of which 1,874 were males, with an annual incidence rate of 146.7 per million children (boys: 159.5; girls: 133.2) and a male to female ratio of 1.2. The numbers and rates of registrations, as well as the age-standardized rates, are shown in Table 1 for each

Table 1. Number of cases, sex and age-standardized incidence rates (per million person-years), sex ratio,% of microscopic verification (MV) and death certification only for the 12 main ICCC diagnostic categories and selected subgroups in the Childhood Cancer Registry of Piedmont, 1967-2001.

	<1 years		1-4 years		5-9 years		10-14 years		0-14 years		M/F ratio	MV (%)	DCO (%)
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No	Rate*			
Leukemia	51	38.4	506	90.6	343	45.2	221	27.6	1121	48.5	1.1	96.6	2.6
ALL§	14	15.8	317	84.4	193	36.6	117	19.8	641	40.0			
AnLL§	13	14.7	34	9.0	43	8.2	41	6.9	131	8.2			
Lymphomas	9	6.8	65	11.6	128	16.9	193	24.1	395	17.9	2.5	97.0	0.8
HD	2	1.5	14	2.5	42	5.5	98	12.2	156	7.2	1.9	99.4	0.0
NHL	1	0.8	29	5.2	60	7.9	60	7.5	150	6.8	2.9	98.0	1.4
Central nervous system tumors	29	21.9	201	36.0	295	38.9	228	28.5	753	33.4	1.2	76.8	1.6
Ependymoma	3	2.3	36	6.4	25	3.3	17	2.1	81	3.5	0.7	98.8	0.0
Astrocytoma	11	8.3	80	14.3	97	12.8	88	11.0	276	12.2	1.5	97.1	0.0
Medulloblastoma	6	4.5	30	5.4	65	8.6	35	4.4	136	6.1	1.8	97.8	0.0
Sympathetic nervous system tumors	76	57.3	124	22.2	37	4.9	17	2.1	254	10.4	1.2	94.9	0.0
Retinoblastoma	30	22.6	47	8.4	7	0.9	1	0.1	85	3.4	1.2	75.3	0.0
Renal tumors	27	20.3	95	17.0	34	4.5	5	0.6	161	6.7	0.8	95.7	0.7
Hepatic tumors	9	6.8	14	2.5	3	0.4	7	0.9	33	1.4	0.9	90.9	6.5
Bone tumors	1	0.8	9	1.6	48	6.3	121	15.1	179	8.3	0.9	92.2	4.6
Soft tissue sarcomas	23	17.3	54	9.7	53	7.0	65	8.1	195	8.5	1.2	96.4	0.6
Germinal cell tumors	17	12.8	24	4.3	18	2.4	27	3.4	86	3.7	0.6	95.4	1.3
Carcinomas	1	0.8	3	0.5	20	2.6	54	6.7	78	3.6	0.9	98.7	0.0
Other and unspecified tumors	5	3.8	9	1.6	2	0.3	4	0.5	20	0.8	1.4	25.0	15.0
All neoplasms	278	209.5	1151	206.0	988	130.1	943	117.8	3360	146.7	1.2	90.8	1.8

Age-standardized; §since 1977. MV, microscopic verification; DCO: death certification only.

cancer site and age-group. The most frequent major histological categories were leukemia (33.4% of total cases, 23.5% ALL), CNS tumors (22.4%, 8.2% astrocytoma) and lymphomas (11.8% with 4.6% HD and 4.5% NHL) (Table 1). Almost 90.8% of the tumors were microscopically confirmed, with an increase from 78.5% in 1967-71 to 96.1% in 1997-2001. The overall proportion of cancer registrations based on death certification only was 1.8%, decreasing from 7.4% in 1967-71, to 5.0% in 1972-76, 0.2% in 1977-81 and 0% afterwards.

Table 2 shows the APC for each diagnostic category and age-group, and Figure 1 shows the time trends in the age-standardized rates for selected cancer sites.

The incidence rate for all neoplasms combined increased by 1.3% per year (95% CI: 1.0% to 1.6%) from 122.6 cases per million children per year in 1967-71 to 195.2 in 1997-2001. The increase was statistically significant for both sexes and for all age-groups studied. No differences in time trends were observed by gender: the APC was 1.3% (95% CI: 0.8% to 1.8%) in both boys and girls. The increases were greater among children in the 10-14 year old age-group (APC: 2.0%, 95% CI: 1.3% to 2.7%), than among infants (APC: 1.5%, 95% CI: 0.3% to 2.6%) and 1-4 year old children (APC: 1.3%, 95% CI: 0.8% to 2.9%).

The incidence rate for leukemia (all types combined) increased on average by 1.0% per year (95% CI: 0.4% to 1.6%) during the study period. However, the increase was non-linear (Figure 1) with a marked increase in the incidence rates in the 1990s. The increase was mainly in the 1-4 year old age-group (from 94.3 cases per million in 1987-91 to 118.3 in 1992-96 and 107.3 in 1997-2001), in which the APC was 1.2% (95% CI: 0.4% to 2.1%). There was no significant variation in the incidence trend in other age classes (<1 year: APC not computed as there were too few cases; 5-9 years APC: 0.9%, 95% CI: -0.2% to 2.0%; 10-14 years APC: 0.9%, 95% CI: -0.5% to 2.3%).

In order to avoid spurious trends due to improved

Table 2. Time trends in childhood cancer incidence (average percent change [APC]) in the Childhood Cancer Registry of Piedmont, 1967-2001.

	APC (95% CI)				
	<1 year	*1-4 years*	*5-9 years*	*10-14 years*	*0-14 years*
Leukemia (all types)	-1.0 (-3.7; 1.6)	1.2 (0.4; 2.1)	0.9 (-0.2; 2.0)	0.9 (-0.5; 2.3)	1.0 (0.4; 1.6)
ALL§	*	1.8 (0.3; 3.3)	1.1 (-0.8; 3.0)	0.1 (-2.5; 2.8)	1.2 (0.2; 2.3)
AnLL§	*	0.7 (-3.7; 5.4)	-0.5 (-4.6; 3.7)	4.4 (0.0; 9.0)	1.7 (-0.6; 4.1)
Lymphomas	*	0.8 (-2.3; 2.5)	0.0 (-1.8; 1.7)	3.6 (2.0;5.2)	1.4 (-0.3; 3.0)
HD	*	-4.1 (-9.4; 1.4)	1.2 (-1.8; 4.4)	2.6 (0.0; 4.8)	1.4 (-0.3 ; 3.0)
NHL	*	-1.6 (-5.2; 2.1)	-2.2 (-4.7; 0.5)	1.1 (-1.6; 3.9)	0.8 (-2.4 ; 0.9)
CNS tumors	1.2 (-2.2; 4.9)	2.5 (1.2; 3.9)	1.5 (0.3; 2.6)	3.4 (2.0; 4.9)	2.3 (1.6 ; 3.1)
Ependymoma	*	8.6 (4.7;12.6)	5.2 (1.0; 9.6)	5.3 (-0.1;11.1)	6.5 (4.0; 9.0)
Astrocytoma	*	1.9 (-0.3; 4.1)	3.0 (1.0; 5.2)	7.0 (4.5; 9.6)	3.8 (2.5; 5.0)
Medulloblastoma	*	-0.6 (-4.0; 3.0)	1.6 (-0.8; 4.2)	2.9 (-0.7; 6.7)	1.3 (-0.4 ; 3.1)
SNS tumors	4.8 (2.5; 7.2)	1.4 (-0.3; 3.2)	0.6 (-2.6; 4.0)	0.4 (-4.5; 5.6)	2.3 (1.0 ; 3.5)
Retinoblastoma	4.8 (1.1; 8.7)	0.3 (-2.4; 3.2)	*	*	1.1 (-0.9; 3.3)
Renal tumors	-4.4 (-8.1; -0.5)	1.2 (-0.8; 3.2)	5.1 (1.5; 8.8)	*	1.1 (-0.4; 2.7)
Hepatic tumors	*	-0.5 (-5.6; 4.8)	*	*	0.0 (-3.3; 3.5)
Bone tumors	*	*	-1.5 (-4.3; 1.5)	-0.4 (-2.2; 1.6)	-0.7 (-2.3; 0.9)
Soft tissue sarcomas	1.5 (-2.5; 5.5)	1.4 (-1.2; 4.0)	0.2 (-2.6; 2.9)	2.7 (0.0; 5.4)	1.4 (0.0; 2.9)
Germinal cell tumors	*	4.0 (0.0; 8.3)	-2.6 (-7.3; 2.3)	4.4 (0.1; 8.8)	3.0 (0.8; 5.3)
Carcinomas	*	*	-4.8 (-9.5; 0.0)	1.7 (-1.2; 4.7)	0.4 (-1.9; 2.8)
All neoplasms	1.5 (0.3; 2.6)	1.3 (0.8; 1.9)	0.6 (0.0; 1.3)	2.0 (1.3; 2.7)	1.3 (1.0; 1.6)

**Time trends were not calculated because the number of cases was too small; §since 1977.*

diagnosis of leukemia cell types, we restricted these analyses to data collected from 1977 onwards, i.e. when the proportion of unspecified leukemia began to be negligible.[14] From 1977 to 2001, there was a significant increase of 1.2% per year (95% CI: 0.2% to 2.3%) in ALL, with the increase being similar in males and females. The increase was strongest in the 1-4 year old age-group which showed an APC of 1.8% (95% CI: 0.3% to 3.3%), whereas no significant trend was observed in the 5-14 year old age-group (APC: 0.9%, 95% CI: -0.7% to 2.4%).

The incidence of AnLL showed an increase (APC: 1.7%, 95% CI: -0.6% to 4.1%) which was of greater magnitude than the increase for ALL (Table 2), but was not statistically significant because of the smaller number of cases involved (Table 1). A non-significant increase in incidence rates was observed for HD (APC: 1.4%, 95% CI: -0.3% to 3.0%). However, different patterns were observed by sex and age. Boys showed a significant APC of 2.4% (95% CI: 0.4% to 4.4%), whereas incidence rates in girls were stable (APC: -0.7%, 95% CI: -3.5% to 2.2%). The increase in HD incidence was primarily due to the annual increase of 2.6% in 10-14 year old children (95% CI: 0.0% to 4.8%). In this age group, a significant APC was observed among boys (55 cases, APC: 4.4%, 95% CI: 1.4% to 7.4%) but not among girls (43 cases, APC : 0.4, 95% CI: -2.7% to 3.7%) (*not shown in Table*).

There were no significant trends in the incidence of NHL over time (Table 2).

CNS tumors showed an APC of 2.3% (95% CI: 1.6% to 3.1%) (Table 2), involving small increases in incidence rates until 1991, followed by a marked increase in the last two time periods (Figure 1). The rate of increase was similar for boys (APC: 2.4%, 95% CI: 1.5% to 3.5%) and girls (APC: 2.1%, 95% CI: 1.0% to 3.2%). However, substantial differences in the magnitude of APC occurred by age: the largest variation was observed for 10-14 year old children (APC: 3.4%, 95% CI: 2.0% to 4.9%), with smaller rates of increase in 1-4 year olds (APC: 2.5%, 95% CI: 1.2% to 3.9%) and in 5-9 year old children (APC: 1.5%, 95% CI: 0.3% to 2.6%). Astrocytoma accounted for 36.7% of CNS tumors and 8.2% of all childhood cancers. Its incidence increased by 3.8% per year (95% CI: 2.5% to 5.0%); this was similar in both sexes, but was strongest in 10-14 year olds (APC: 7.0%, 95% CI: 4.5% to 9.6%). The time trend pattern was similar to that observed for CNS tumors overall (*not shown in Figure*).

A significant increase of 2.3% per year (95% CI: 1.0% to 3.5%) was observed for sympathetic nervous tumors (neuroblastoma) (7.6% of all cases), with

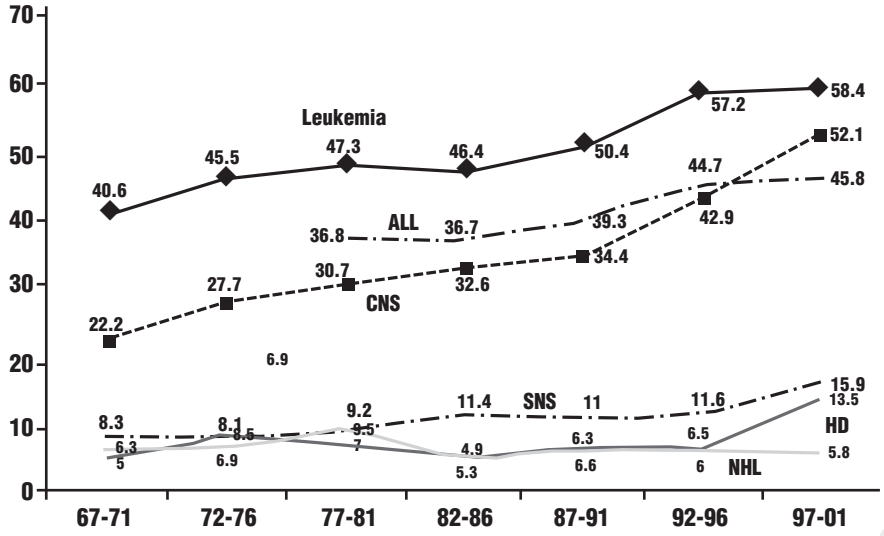

Figure 1. Sex and age-standardized incidence rates by period of diagnosis for selected diagnostic group in the Childhood Cancer Registry of Piedmont, 1967-2001.

similar increases in boys (APC: 2.3%, 95% CI: 0.7% to 4.0%) and girls (APC: 2.2%, 95% CI: 0.3% to 4.1%). The increase was strongest in children younger than one year old (APC 4.8%, 95% CI: 2.5% to 7.2%), while it was weaker and not statistically significant in older children.

The incidence of soft tissue sarcoma showed an annual increase of 1.4% (95% CI: 0.0% to 2.9%). The increase was strongest in the 10-14 year age-group (APC 2.7%, 95% CI: 0.0% to 5.4%).

The rates of renal and bone tumors remained stable over time (Table 2).

Discussion

During the 35-year period from 1967 to 2001, we observed a significant increase in incidence rates for childhood cancer in Piedmont. The increase was statistically significant for all malignancies combined (APC 1.3% per year), leukemia (1.0%), CNS tumors (2.3%), neuroblastoma (2.3%) and soft tissue sarcomas (1.4%). ALL also showed a significant increase for the period 1977-2001. The trends were generally similar in males and females, except for HD which increased significantly in boys (2.4% per year) but not in girls. Differences in time trends by age group were observed for some tumor types, such as for neuroblastoma in infants (4.8% increase per year), for leukemia in children 1-4 years old (1.2%) and for CNS tumors, HD lymphoma (in boys) and soft tissue sarcomas in children in the 10-14 year old age-group (3.4%, 4.4% and 2.7%, respectively).

When considering such time trend data an important issue is whether the observed increases are real, or whether they are due to changes either in data collection and registration methods, or in quality of data or in diagnostic procedures. The quality of data collected by the Childhood Cancer Registry of Piedmont (CCRP) has been uniformly high and CCRP data have been included in all major international studies on childhood cancer incidence.[17,34-37] Cases have always been searched for actively by trained personnel in the relevant hospitals, both pediatric and general. This search has been supplemented by the use of other available databases, such as the Hospital Admission and Discharge Files (HADF), records of reimbursements for cancer treatments carried out abroad, the Piedmont Cancer Registry files and the database of the Italian Association of Pediatric Hematology and Oncology (AIEOP). The availability of these sources has changed over time, but these changes are unlikely to explain the increase in rates since we have no evidence of cases treated in hospitals not previously targeted in the active search. Rather, the availability of filed information is used in order to facilitate the active search. In a sensitivity analysis we re-analyzed time trends for all neoplasms, leukemia (all types), ALL and CNS tumors excluding those cases collected in recent periods from filed information only; the magnitude of the time trends decreased slightly, but the direction and the statistical significance were not affected. The quality of data of the CCRP is high according to the usual indicators adopted by cancer registries: the percentage of cases included on the basis of death certification only was 1.8% for the overall time period, with no such cases being identified after 1982; 90.8% of all cases were microscopically confirmed, with an increasing proportion from 78.5% in 1967-71 to 96.1% in the most recent five-year period. Only CNS tumors (all types) showed a relatively low proportion (76.8%) of microscopically

confirmed cases; however, astrocytoma, medulloblastoma and ependymoma had a high proportion of confirmation (respectively, 97.1%, 97.8% and 98.8%). The variations in the frequency of microscopic verification are unlikely to explain the observed trends, as the categories showing the strongest time trends also showed high overall percentages of microscopic verification (leukemia: 96.6%, ALL: 99.2%, HD: 97.0%, astrocytoma: 97.1%).

It is also unlikely that the observed time trends in incidence are due to variations in the completeness and accuracy of population data, since these were always provided by official sources and based on censuses and municipal data. Addresses of all cases at diagnosis are checked in order to ensure that the cases are assigned to the correct population category.

In order to avoid a possible effect of improved diagnostic techniques we limited the analysis of time trends to the main ICCC tumor groups, so that possible changes in tumor classification within the main tumor groups could not bias the results. Regarding specific tumor types, we also restricted the analysis to periods when diagnostic techniques were not changing. Furthermore we evaluated tumor types showing an increasing trend separately. Specifically regarding leukemia we have no evidence that diagnostic changes were likely to have produced an artefactual trend. The diagnostic changes affected subtype classifications, but not the diagnosis of leukemia as a general category. When evaluating the trend by subtype we limited the analysis to periods after 1977, in order to avoid bias resulting from the improved classification of unspecified leukemia. Regarding CNS tumors, diagnosis has improved since the introduction of computed tomography in the 1980s and magnetic resonance imaging in the 1990s. To our knowledge, no studies are available that would permit an assessment of the impact of these techniques on incidence figures. Regarding our data, it should be noted however that the incidence rates of CNS tumors show a smooth increase over time and not the type of *step function* that would be expected as a result of sudden changes in diagnostic practice. Moreover the incidence rates doubled over the study period and if the trend were due to improved diagnosis only, hundreds of cases would have previously gone undiagnosed which appears very unlikely. On the other hand, for neuroblastoma, we estimate that most of the trend can be attributed to diagnostic changes (*see below*).

The findings of the current study are consistent with the increase in leukemia incidence over time that have been observed previously by ourselves[14] and by other authors.[1-13,15-17] The increases were most marked during the 1980s, and there was little increase in the 1990s. The trend was mainly due to an increase in ALL in the 1-4 year old age-group, i.e. the age category that shows a well-established peak in incidence. In order to minimize the effects of diagnostic improvements on the time trends, the analyses for ALL and AnLL were limited to 1977-2001. We also considered the possibility of misclassification between ALL and NHL, but there is no suggestion that this contributed to the observed trends, as the rates of NHL were stable over time.

In recent years, an increase in leukemia was also observed in Great Britain[10-11] and Sweden[15] but not in the Nordic Countries[13] and in France.[18] In the USA, Ries *et al.*[8] observed an increasing trend until 1987 and stable rates thereafter. McNally *et al.*[10] also observed a specific increase in ALL incidence in 1-4 year olds and concluded that the increase was very likely to be due to the precursor B-cell subtype (common-ALL). They argued that the evidence of space-time clustering and seasonal variation in ALL supported the hypothesis that common-ALL is etiologically linked to delayed exposure to common infections.[38] In contrast, acute myeloid leukemia (AML) has generally displayed stable incidence rates with little evidence of seasonal variation or space-time clustering.[10] In the current study, the APC for AnLL was actually greater than that for ALL, but the numbers were relatively small and the increase was not statistically significant.

There was limited evidence for an increase in Hodgkin's disease or non-Hodgkin's lymphoma, as both showed non-significant changes (1.4% per year and 0.8% per year respectively). The significant trend in boys aged 10-14 years old should be kept under observation in future analyses of incidence rates. Limited information has been reported in the literature on trends for HD in children: a statistically significant reduction was observed in the USA[8] and in Australia,[2] while rates increased in the UK[10] and in Sweden.[15] The Swedish study concluded that the observed increases were real and were unlikely to be due to changes in diagnostic procedures, because a pathological review of cases during 1975-1994 in western Sweden had reported good agreement with the initial diagnosis.[15]

A constantly increasing trend was observed for CNS tumors (Figure 1), a pattern that has been observed in the USA,[7,8] central Italy,[12] Germany,[20] Sweden,[15,22] north-west England,[25] and Hungary.[27] It has been suggested that improvements in diagnostic methods could explain these increases.[39] However, our data show a constant gradual change rather than sudden increases in incidence rates. The changes observed by SEER after the introduction of computed tomography and magnetic resonance imaging followed a very different shape with abrupt increases followed by stable or decreasing rates.[40] Furthermore,

the advent and widespread diffusion of computed tomography scanning in the early 1980s and of magnetic resonance imaging tumors at the end of the 1980s cannot explain the further increase of incidence rates observed in the most recent 10-year period. The increase was not observed for medulloblastoma, which showed stable rates during the 35-year period from 1967 to 2001.

Increasing rates of neuroblastoma have particularly been observed in countries in which screening programs have been implemented.[20,26] No active screening has been conducted in Piedmont, but an increased incidence was also observed, although this was limited to children in the first year of life. The survival of patients with neuroblastoma diagnosed in the first year of life also increased in recent periods.[31] These findings are likely to reflect increased diagnosis of neuroblastoma with good prognosis. In particular, the increase may be linked to antenatal and perinatal ultrasound imaging, which were introduced in Italy in the mid 1980s, i.e. the period when the incidence rates of neuroblastoma started to increase.

No statistically significant trend was observed for renal tumors or for malignant bone tumors. Most published studies have reported stable rates for Wilms' tumors.[2,4,7,8,15,25] Regarding bone tumors, stable rates over time were observed by Bunin,[7] McWhirter,[2] McNally[25] and Dreifald.[15] The SEER data showed an increase for osteosarcoma and a decrease for Ewing's sarcoma.[8]

The incidence of soft tissue sarcomas showed an increasing trend of marginal statistical significance. The interpretation of this trend is unclear as the increase occurred at the end of the 1980s and rates were stable both before and after that time. Relatively stable rates of soft tissue sarcomas were found in some areas of the USA,[7] Australia,[2] UK[25] and Sweden,[15] while an increasing trend was observed in other areas of the USA[8] and UK.[4]

In conclusion our data suggest increases in incidence for leukemia, CNS and neuroblastoma in Piedmont in the period between 1967 and 2001. The observed trends are unlikely to be explained by random variation or reporting biases, and are generally consistent with findings from other countries.

PD: drafting the article and data analysis and interpretation; GP: conception and design, interpretation of data, revising the article; LZ: data analysis and interpretation; MM: data analysis and interpretation; NP: revising the article for important intellectual content; FM: conception and design, interpretation of data, revising the article; CM: conception and design, interpretation of data, revising the article. The authors declare that they have no potential conflict of interest.

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