

## REGULAR ARTICLE

# Incidence and survival analyses in children with solid tumours diagnosed in Sweden between 1983 and 2007

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## ABSTRACT

**Aim:** Solid tumours constitute 40% of childhood malignancies. The Swedish Childhood Cancer Registry is population based and includes all children with cancer reported from the six paediatric oncology centres in Sweden. The aim was to investigate incidence and survival.

**Methods:** We used the new WHO ICCC-3 for reclassification of the patients. Incidence and survival analyses were performed in the study population.

**Results:** Two thousand four hundred and eighty-seven children (<15 years) were diagnosed with solid tumours in Sweden between 1983 and 2007. The distribution of diagnoses was similar to that reported in other studies. The annual incidence was 65.3 per million children. The survival rates at 10 years of follow-up have improved significantly when comparing the two time periods, 1983–1995 and 1995–2007 (76 vs. 82%;  $p < 0.01$ ).

**Conclusions:** The mean annual incidence of solid tumours in children was 65.3/million and has been stable during the study period. Survival rates for solid tumours at 5, 10 and 20 years follow-up were 80, 79 and 76%, respectively.

## INTRODUCTION

Malignant solid tumours constitute about 40% of all cancer diagnoses in children <15 years of age and comprise a wide variety of entities with different incidence rates and histological and clinical characteristics (1–3). The incidence and survival rates of childhood solid tumours based on the National Cancer Registry in Sweden have been high

compared with those reported from other industrialized countries based on data from official cancer registries (4–7). However, these results have been questioned because of a high proportion of unspecified tumours (7–9).

The Swedish Childhood Cancer Registry was initiated in the 1980s, aiming at establishing a complete and more detailed registry than the Swedish National Cancer Registry. Diagnostic criteria, treatment protocols and continuous follow-up data of the patients have been recorded in a population-based setting from the six paediatric oncology centres in Sweden. A study covering incidence and survival data for children with CNS tumours based on the Swedish *Childhood* Cancer Registry was recently published (10), and the aim of the present study was to supplement these data with the corresponding data for other solid tumours. The material has been reclassified according to the latest guidelines from the International Agency for the Research of Cancer (IARC) published in 2005 (11).

## Abbreviations

APC, Annual percentage change; IARC, International Agency for the Research of Cancer; ICCC, International Classification of Childhood Cancer; ICD, International Classification of Diseases for Oncology; NCI, National Cancer Institute; NHL, Non-Hodgkin lymphoma; NOPHO, Nordic Society of Paediatric Haematology/Oncology; OS, Overall survival; SEER, Surveillance Epidemiology and End Results (NCI); SIOP, International Society of Paediatric Oncology; SNOMED, Systematized Nomenclature of Medicine; WHO, World Health Organization.

## PATIENTS AND METHODS

### Classification

The classification of cancer in children is based on morphological findings and not, as in adults, on the organ where the primary tumour is localized. The first generally accepted classification of childhood cancer was published in 1987 and was based on the International Classification of Diseases for Oncology (ICD) codes in the WHO classification, later revised several times (12,13). The diagnoses were divided into 12 main groups, in which solid tumours constituted 10 groups, namely group II and groups IV–XII, each group further subdivided into several subgroups. Some of these subgroups were further subdivided in the latest proposal (Table S1). We have used a combination of ICD/S-NOMED codes, pathology reports at diagnosis and clinical information for the classification.

### Patients

In paediatric oncology in Sweden, children diagnosed before 18 years of age are generally treated in one of the six paediatric oncology centres. The present material only includes all children <15 years of age with a malignant solid tumour diagnosed in Sweden between 1983 and 2007. Reasons for this is to make it comparable with other similar studies (3,14,15) and that it is more difficult to assure that the population above 15 years is strictly population based in the Swedish Childhood Cancer Registry. The diagnosis was confirmed by imaging and histology in the absolute majority of cases. Informed consent to register data was obtained from patients or parents.

### Treatment

Since the formation of the Swedish Childhood Solid Tumour Working Group (VSTB) in 1983, there has been consensus among the regional centres that the different tumours should be uniformly treated in all Swedish children and that the treatment should be delivered at a paediatric oncology unit in those centres. The adherence to these principles has been almost absolute nationwide since then.

Because the numbers of patients are relatively low, most tumours have been treated according to international protocols. A large proportion of the patients have thus been included in clinical trials organized by the International Society of Paediatric Oncology (SIOP), the German Paediatric Oncology Group (GPOH), the Scandinavian Sarcoma Group (SSG) or the Nordic Society of Paediatric Haematology and Oncology (NOPHO). Radiotherapy has been given at each centre, while surgery has been performed by specialized paediatric surgeons at four of the six centres.

### Lymphomas

Hodgkin's disease has generally been treated according to international standards, i.e. MOPP-ABVD-based regimens, with or without radiotherapy, and later according to the different GPOH protocols. Non-Hodgkin lymphomas (NHL) have earlier been treated according to a BFM-based NOPHO protocol and later according to consecutive

GPOH protocols. Anaplastic large cell lymphomas (ALCL) have been included in the ALCL 99 trial since it started.

### Neuroblastomas

The prognosis among patients with neuroblastoma differs depending on age, clinical stage and other risk factors based on molecular biology. They therefore require a wide range of treatment intensities, from surgery only (or 'wait and watch') to high-intensity chemotherapy, surgery, radiotherapy and high-dose chemotherapy followed by stem cell rescue. Those patients have consequently been treated according to several different international protocols, mainly as part of the European Neuroblastoma Study Group trials.

### Renal tumours

Patients with a nephroblastoma (Wilms' tumour), mesoblastic nephroma or a clear-cell sarcoma have been included in the consecutive SIOP renal tumour trials, while renal carcinomas have been managed according to adult principles. Rhabdoid tumours and other renal sarcomas have mainly been treated according to current soft tissue sarcoma protocols until very recently.

### Liver tumours

Patients with hepatoblastoma (and a few with hepatic cancer) have been included in the different SIOP studies (SIOP-PEL) according to their clinical characteristics.

### Bone tumours

The patients with osteosarcomas or Ewing sarcomas have been included in the different SSG studies (some in cooperation with the Italian Sarcoma Group) until the last several years when osteosarcomas have been enrolled in the collaborative European-North American EURAMOS 1 trial and the patients with Ewing sarcoma in the Euro-E.W.I.N.G 99 trial, respectively. Other, rare bone sarcomas have mainly been treated according to adult principles.

### Soft tissue sarcomas

Rhabdomyosarcomas and other soft tissue sarcomas have almost exclusively been treated according to the GPOH principles and included in its consecutive CWS studies, including Ewing family tumours of soft tissue origin (Ewing, Askin and pPNET of soft tissue). Some of the latter cases, however, have been treated according to the current bone tumour protocol.

### Germ cell tumours

The malignant germ cell tumours (GCT, not including mature and immature teratomas) have been treated with surgery and, if required, with platinum-based chemotherapy regimens as well. Cisplatin was used in the early period but was later exchanged for carboplatin according to the UK CCLG protocols, except for adolescent patients who have often been treated according to current adult protocols.

The malignant GCTs originating within the CNS have been treated with surgery, radiotherapy and chemotherapy

according to treatment protocols for non-CNS GCTs during the early period and according to the SIOP, CNS and GCT protocol more recently.

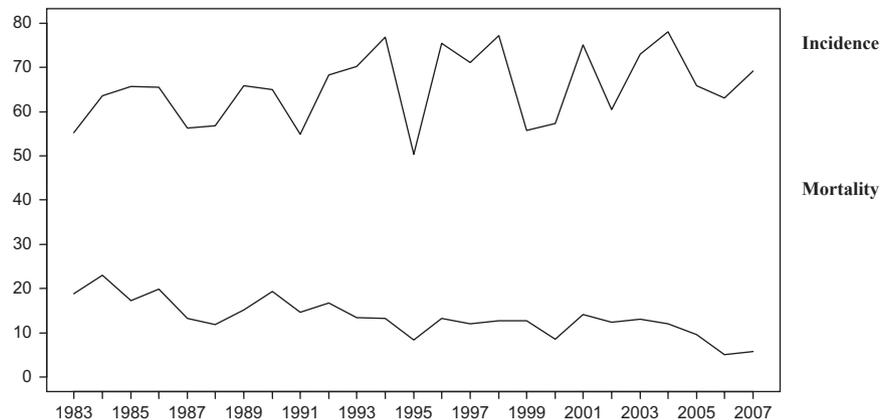
*Miscellaneous*

In Sweden, treatment for retinoblastoma has long been centralized to the St Erik Eye Hospital in Stockholm. Until the last several years, the treatment has been surgery and/or radiotherapy. However, adjuvant chemotherapy and transpupillary thermotherapy (TTT) have become routine in case of bilateral tumours. Those patients have been given multi-agent chemotherapy in connection with the thermotherapy.

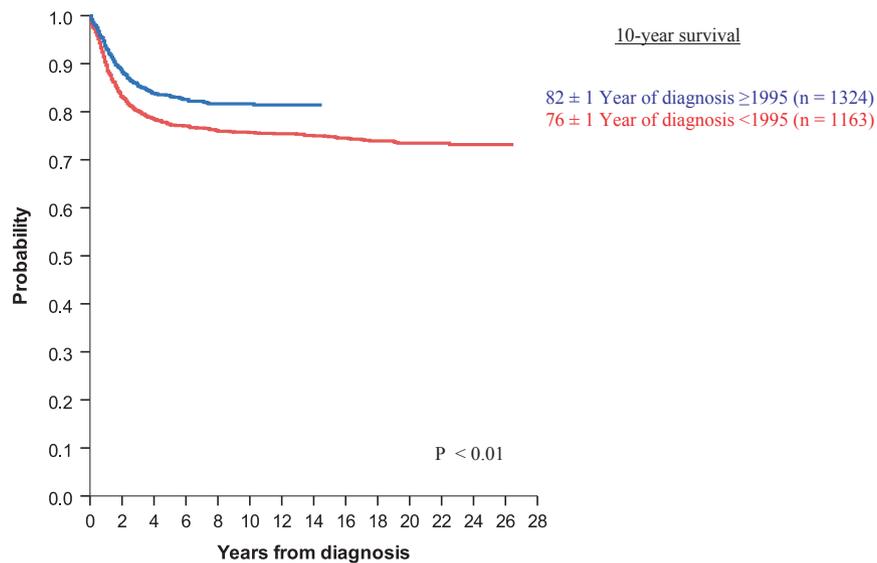
Carcinomas are very rare in childhood. Most of the patients have had surgery only, except for those with thyroid carcinomas (mainly adolescents) who often have been given radio-iodine treatment as well. Patients with melanoma are rarely seen by paediatric oncologists in Sweden. These patients are mostly managed by specialized dermatologists.

**Statistical methods**

SPSS software was used for the statistical analyses (16). We used age-standardized incidence adjusted to the world standard population according to the IARC-1998 (1). Time trend in the incidence data was investigated by the use of US National Cancer Institute (17) Joinpoint regression software, by which the annual percentage change was estimated. The probability of overall survival (OS) was estimated using the Kaplan–Meier method, and the log rank test was used for significance test between groups with a significance level of 0.05 (16). Events were all reported deaths. The deaths were also checked against the Swedish Personal Registry, which is updated monthly. Incidence and mortality rates are presented per million children. Mean follow-up time for living patients was 19.8 years for children diagnosed before 1995 and 7.8 years for children diagnosed 1995 or later. Sixteen patients were lost at follow-up (at mean 16.4 years). The database was frozen 1 July 2009.



**Figure 1** Age-standardized annual incidence and mortality rates per million over time in Swedish children with solid tumours diagnosed between 1983 and 2007.



**Figure 2** Actuarial survival curves in Swedish children with solid tumours diagnosed between 1983 and 2007 according to diagnostic periods.

## RESULTS

Between 1 January 1983 and 31 December 2007, 2487 children below 15 years of age were diagnosed with a malignant solid tumour in Sweden. The classification according to the ICCC-3 recommendation and incidence for different subdiagnoses are shown in Table S1. The lymphomas constituted 21.9%, neuroblastoma 14.7%, soft tissue tumours 14.5%, neuroblastoma 14.3%, germ cells tumours 10.9%, bone tumours 9.4% and other specified tumours 5.3%. The overall annual incidence in this age group was 65.3/million children (Fig. 1). Joinpoint regression analyses for the whole material showed no significant Joinpoint over the time period. The average annual per cent change was 0.6 (95% CI: -0.1 to 1.3).

The diagnostic subgroups and sex-age distributions are shown in Table S2. The overall M/F ratio was 1.16. Male predominance was found for lymphomas, neuroblastoma, hepatic tumours and soft tissue tumours; female predominance was found for retinoblastoma, neuroblastoma, germ cells tumours and other carcinomas.

The mean/median age at diagnosis was 5.9/5.0 for the whole patient group. Children with neuroblastoma were the dominating group among infants, while lymphomas and bone tumours were most frequent in teenagers.

The 5-, 10- and 20-year survival estimates for the whole group were  $80 \pm 1$ ,  $79 \pm 1$  and  $76 \pm 1\%$ , respectively (Table S3). The 10-year survival rate for all children has improved significantly when comparing the time period before 1995 to that after 1995 ( $76 \pm 1$  vs.  $82 \pm 1\%$ ;  $p < 0.01$ ) (Table S3, Fig. 2). This was because of a significantly improved prognosis for children with neuroblastoma, malignant gonadal GCT, Burkitt lymphoma, hepatoblastoma and rhabdomyosarcoma (Table S4, Fig. 3a,b). There was no significant difference in survival at 10 years between boys and girls ( $78 \pm 1$  vs.  $79 \pm 1\%$ ;  $p = 0.4$ ). Infants had a superior prognosis compared to children  $>1$  year of age at diagnosis ( $83 \pm 2\%$  vs.  $77 \pm 1\%$ ;  $p < 0.05$ ) (Table S3). This was explained by a very good prognosis among infants with neuroblastoma, retinoblastoma, neuroblastoma and GCT.

Of the 2487 patients, 477 died within 60 months of diagnosis. The survival rate for the 1641 patients who were alive at 5 years' follow-up was  $98 \pm 1\%$  after another 5 years, i.e. 10 years after diagnosis and they had a  $94 \pm 1\%$  estimate of long-term survival 20 years after diagnosis (55 patients have so far died 60 months or more after diagnosis). The five most common diagnoses among the 532 patients who died were neuroblastoma (24.1% of the deaths), soft tissue sarcomas (18.2%), lymphomas (15.4%), bone tumours (15.2%) and renal tumours (10.9%).

### Diagnostic groups

#### *Lymphomas (n = 545)*

This WHO group is the most frequent diagnosis, constituting 21.9% of the solid tumours, and consists of patients with Hodgkin lymphomas (36%), non-Hodgkin lymphomas (52%), Burkitt lymphoma (10%) and other lymphoreticular neoplasms (2%). The incidence was 13.1 with a pronounced male predominance. (M/F = 2.21) (Tables S1 and S2).

Patients with Hodgkin's disease were further subdivided into nodular sclerosis ( $n = 114$ ), mixed cellularity ( $n = 31$ ), lymphocytic predominance ( $n = 27$ ) and unspecified Hodgkin lymphomas ( $n = 24$ ). The survival rate at 10 years was  $96 \pm 1\%$  and has not improved over time. (Table S3, Figure 3a).

The classification of patients with NHL is complex and has changed over time. The present stratification follows the new classification with four subgroups (Table S1). The frequencies of precursor T- and B-cell lymphomas and mature B-cell lymphomas were equal and constituted 73% of the NHL. The ALCL ( $n = 31$ ) are included in group IIB3 among mature T-cell and NK-cell tumours. The NHL was unspecified in 44/284 cases (15%). The prognosis for the group is  $80 \pm 2\%$  at 10 years and has not improved significantly over time (Tables S3 and S4).

The Burkitt lymphomas have a strong male predominance (M/F = 6.7) (Table S2) with a very good prognosis (OS  $96 \pm 1\%$  at 10 years), which has increased significantly over time ( $p = 0.02$ , Tables S3 and S4).

Group IId comprised 11 cases of malignant histiocytosis. Benign histiocytosis is not included in this study according to recommendations in the new classification.

#### *Neuroblastomas (n = 355)*

Neuroblastoma is the most frequent tumour among infants in this material, and the incidence decreases with increasing age. The total incidence was 10.3 and was stable over time. Age at diagnosis is the most important prognostic factor in this group of patients with an OS of  $81 \pm 3\%$  for children  $<18$  months compared to  $44 \pm 4\%$  for children  $\geq 18$  months of age at diagnosis ( $p < 0.01$ ). The prognosis has improved significantly over time for the whole group (Table S4), which is fully explained by an improvement for children  $\geq 18$  months of age at diagnosis ( $39 \pm 5\%$  vs.  $48 \pm 6\%$ ;  $p < 0.01$ ), while the prognosis for children  $<18$  months has been stable (OS  $81 \pm 4\%$  vs.  $79 \pm 5\%$ ;  $p = 0.8$ ).

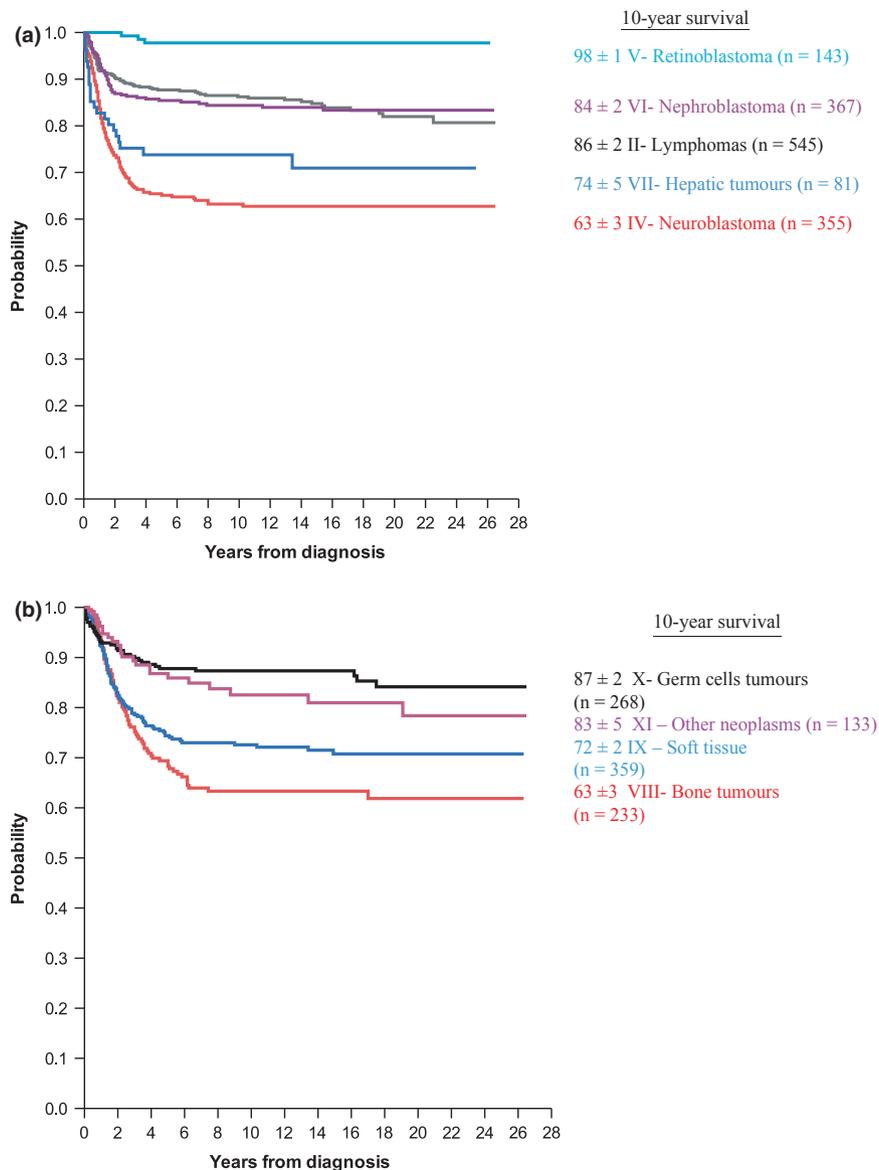
#### *Retinoblastoma (n = 143)*

Almost all children in this group were diagnosed before 5 years of age and there was a female preponderance (M/F = 0.73) (Table S2). Bilateral disease was present in 30% of cases with known localization ( $n = 31/105$ ) and was slightly more common among girls. The prognosis has been good throughout the time period (Tables S3 and S4).

#### *Nephroblastoma (n = 367)*

This is the third most common diagnosis among solid tumours. There is a slight predominance for girls (M/F = 0.90) (Table S2). The age-sex distribution shows an age peak for boys and girls at 1 year of age but for girls, there is a second peak at 3 years.

The prognosis for these children has been good throughout the study period with a stable survival rate of 85% (Tables S3 and S4). The Wilms tumours constitute 91% of the cases in this group and have an incidence of 9.6 (Table S1).



**Figure 3** (a) Actuarial survival curves by diagnostic main groups II, IV–VII in Swedish children with solid tumours diagnosed between 1983 and 2007. (b) Actuarial survival curves by diagnostic main groups VIII–XI in Swedish children with solid tumours diagnosed between 1983 and 2007.

#### Hepatic tumours (n = 81)

These tumours are uncommon and constitute only 3.3%, almost all were classified as hepatoblastomas. There was a male dominance (M/F = 1.46), and 93% of the children were below 5 years of age at diagnosis (Table S2). The prognosis for hepatoblastoma has improved significantly over time (68 ± 8% vs. 88 ± 5%; p = 0.04) (Table S4). Nine children had a hepatic carcinoma and four of these were alive at follow-up.

#### Malignant bone tumours (n = 233)

This group consists of two main groups; osteosarcomas and Ewing tumours. The M/F ratio is close to 1.0 and the incidence increases with age (Table S2). Sixty percentage of the children are ≥10 years at diagnosis. The prognosis is still

serious and has not improved significantly over time (Table S4). Bone tumours and neuroblastomas have the worst prognosis among all solid tumours in this study.

#### Soft tissue sarcomas (n = 359)

The soft tissue sarcoma group constituted 14.5% of the solid tumours and was dominated by rhabdomyosarcomas (57%), fibrosarcomas (19%) and other specified soft tissue sarcomas (23%) (Table S1). There was no case of Kaposi sarcoma reported. The M/F ratio was 1.37 for the whole group (Table S2).

The incidence of rhabdomyosarcomas was 5.5, and 58% of the children were <5 years of age at diagnosis (mostly embryonal type, while alveolar tumours were more common in older children). The prognosis was worse for infants

and children  $\geq 10$  years of age ( $n = 61$ ), compared to children 1–<10 years of age ( $n = 144$ ) ( $53 \pm 4\%$  vs.  $75 \pm 4\%$ ;  $p < 0.01$ ). The prognosis was better for boys compared to girls ( $71 \pm 4\%$  vs.  $64 \pm 4\%$ ;  $p = 0.05$ ), and the prognosis for the whole group has improved significantly over time ( $61 \pm 5\%$  vs.  $76 \pm 4\%$ ;  $p = 0.04$ ) (Table S4). Embryonal tumours had superior OS compared to alveolar tumours ( $81 \pm 6\%$  vs.  $66 \pm 6\%$ ;  $p = 0.05$ ).

The fibrosarcomas had a male predominance and were most frequent in infants and in children over 10 years of age (Table S2). The prognosis exceeds 80% and has been unchanged during the study period (Table S4). Other specified soft tissue sarcomas comprise a very heterogeneous group of tumours with few children in each group but constitute the second most common diagnostic subcategory within this group. The 10-year survival exceeds 80% for the later time period (Table S4).

#### *Germ cells tumours (n = 268)*

The malignant gonadal (ovarian or testicular) germ cells' tumours constituted 54%, the intracranial 17% and the extracranial/extragonadal 25% of the germ cells' tumours in this material. A majority of the patients with gonadal and intracranial germ cells tumours were more than 10 years of age, while most of the patients with extracranial/extragonadal tumours were <5 years of age (Table S2). Teratomas were the most frequent diagnosis among gonadal and extragonadal/extracranial germ cells tumours and constituted 54% of all germ cells tumours (Table S1). Yolk sac tumours were diagnosed in 31/268 cases (12%).

There was a female predominance in the whole group explained by higher frequencies of girls in the gonadal and extracranial/extragonadal groups. The 10-year OS after 1995 exceeds 90% for the gonadal and extracranial/extragonadal tumours vs.  $69 \pm 6\%$  for the intracranial tumours. The prognosis has improved significantly over time (Table S4).

#### *XI Other malignant epithelial neoplasms and malignant melanomas (n = 133)*

This diagnostic group consists of children with different forms of carcinomas and malignant melanomas. The group comprised 5.3% of the solid tumours (Table S1). At diagnosis, 77% of the children were 10 years of age or older and <10% were below 5 years. Thyroid carcinomas and malignant melanomas were the most frequent diagnoses. The survival estimate was  $88 \pm 4\%$  during the last diagnostic time period, and no improvement was seen over time (Table S4).

#### *XII Other and unspecified malignant neoplasms (n = 3)*

Two of these patients had pleuropulmonary blastomas, while the third patient was classified as malignant tumour UNS. One patient is alive.

## DISCUSSION

Data on incidence and survival in childhood cancer have been published from pooled European Cancer Registries

(4–7). The conclusions from most of these studies have been that the Nordic countries have high incidence and survival rates compared to other European countries. One problem concerning data from the Swedish National Cancer Registry has been that a significant number of diseases were classified as unspecified cancer (4). This has raised the question of whether the relatively high survival rates among patients with unspecified tumours in the northern countries may indicate that these registries include patients not included in other regions (8,9). The proportion of unspecified tumours in the present study is below 1%.

Since the publication of the extended classification of childhood cancer in 2005 (7), the National Registry of Childhood Tumours in Britain has published population-based data over all childhood cancer in Britain between 1991 and 2000 stratified according to the new classification (3). Results from the USA are annually reported from the Surveillance Epidemiology and End Results (NCI) (SEER) databases (14).

## Incidence

The incidence in the present study (65.3 per million children) is high compared to earlier publications covering the 1980s and 1990s. One study based on the Swedish National Cancer Registry included children diagnosed with all cancer between 1960 and 1998 found a general annual increase in incidence of 1% (18). This study covered a long time period starting in the 1960s with low incidence figures during the first decades, which may be the main reason for the increase found during the whole time period. The present survey covers the time interval from 1983 to 2007 during which no significant increase in incidence occurred.

The first complete publication based on ICC-3 included all children in Britain diagnosed with cancer between 1991 and 2000 (3). The overall incidence rate for solid tumours was 60.2 per million child, which is slightly below the present study.

The incidence rates for the present study compared with the British study were higher for neuroblastomas (10.5 vs. 8.3), NHL (7.0 vs. 5.6) and GCT (6.9 vs. 4.5). Malignant melanomas were more frequent in Britain (1.4 vs. 0.8).

The incidence reported from the USA in December 2009 was 69.5 per million for solid tumours, which is slightly higher than our data (14). The major difference occurred in group XI (6.1 vs. 3.0) and especially for the subgroup thyroid carcinomas and malignant melanomas. Other diagnoses with higher incidence in the USA were group IId-miscellaneous lymphoreticular neoplasms (1.1 vs. 0.2), group IX d and e, other specified or unspecified soft tissue sarcomas (4.2 vs. 2.8) and bone tumours (6.8 vs. 5.4). The incidence was lower in the USA compared to our data for neuroblastoma (7.4 vs. 10.5) and GCT (5.8 vs. 6.9). The marginal differences in these data may reflect small variations in the true incidence of some diagnoses or could possibly be explained by failure to report all patients.

Thus, the most up to date and relevant data from these population-based registries show an annual incidence of solid tumours between 60 and 70 per million children.

No trend in the incidence rate has been shown in a study from the USA covering between 1992 and 2004 (15). The incidence trends in Britain are reported in detail for children diagnosed over the 35-year study period between 1966 and 2000 (3). It was concluded that the incidence had increased by 1% annually over the study period, but the major increase occurred during the first 20 years with a tendency to level off during the last 15 years.

### Survival

The results of this 20-year registration of Swedish children confirm that this is a large and heterogeneous group of patients with different prognoses. Although the OS is close to 80% at 10 years, there are still groups where the chance of cure is below 65%. It would have been interesting to know the causes of death during follow-up. Unfortunately, we cannot account for this in this population because it was not registered in the earlier days. However, in the future, we will be able to do this. Neuroblastomas constituted 14.3% of all cases but are responsible for 24.1% of the deaths. Corresponding figures for bone tumours are 9.4% and 15.2%, respectively.

Updated and detailed survival data from Britain for children diagnosed with solid tumours from 1991 to 2000 classified according to the ICCC-3 system (3) and updated SEER data from the USA including 5-year survival data on children diagnosed from 1999 to 2005 (14) present survival data that are close to the results in the present study.

In two earlier studies based on National Cancer Registries from 20 European countries covering the years between 1983 and 1994, it was concluded that the Nordic countries had the best OS results among children with cancer (4,5). However, in a recent publication from the same database with inclusion of new cases diagnosed from 1995 to 2002, it was concluded that the gap between the Nordic countries and other West-European countries had been reduced and that especially Eastern European countries with poor survival in earlier reports had improved their results notably. The 5-year survival rate for all cancer was 81% and had improved in some countries but remained stable in the Nordic countries (19). One reason might be that the Nordic countries had achieved good results earlier than other countries but have reached a plateau in the survival rate, which seems difficult to increase further. As pointed out by the EURO CARE Working Group, enrolment in clinical trials, development of international collaboration, access to effective protocols and development of health infrastructures/allocation of resources may all have contributed to this improved survival in Eastern Europe (19).

An associated editorial comment by the same Working Group addressing comparative cancer information in Europe (20) stresses the need for high-quality population-based survival studies for clinicians to use as a standard against which their own outcomes can be compared, administrators and policy makers to set priorities for the provision of cancer care and to inform cancer survivors and the public.

The present study confirms results from other recent publications that the annual incidence of childhood solid

tumours is stable at 60–70/million children and that the 10-year survival rate is close to 80%.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Table S1** Classification of children with solid tumours in Sweden 1983–2007. Number of children, WHO-classification and incidence per million children.

**Table S2** Classification of children with solid tumours in Sweden 1983–2007. Number, sex- and age- distributions.

**Table S3** Classification of children with solid tumours in Sweden 1983–2007. Overall Survival ( $\pm$ SE) at 5- 10- and 20 years' follow up.

**Table S4** Classification of children with solid tumours in Sweden 1983–2007. Ten- year Overall Survival ( $\pm$ SE) for children diagnosed <1995 vs.  $\geq$ 1995.

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