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Trends in Neuroblastoma in Great Britain: Incidence and Mortality, 1971–1990

C.A. Stiller

Incidence and mortality rates for neuroblastoma in Britain from 1971 onwards were examined using data from the population-based National Registry of Childhood Tumours. Incidence throughout 1971–1990 was within the range previously reported from Europe, North America and Oceania. The age-standardised rate rose, however, by 26% between 1971–1975 and 1986–1990, and there were increases of 36% both among infants aged under one year and also among children aged 1–9. There was a pattern of increasing risk with more recent years of birth up to 1985. It is implausible that improved diagnosis could explain the increase in rates since 1971, though it may account for a marked decrease in recorded incidence at the age of 10–14. Age-standardised mortality fell by 27% between 1971–1975 and 1981–1985, but rose again during 1986–1990. This was the result of a halt in the improvement in survival rates for neuroblastoma combined with a substantial and as yet unexplained increase in incidence.
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INTRODUCTION

NEUROBLASTOMA HAS a poor prognosis compared with most of the more common childhood cancers and the outlook for older children with advanced disease at diagnosis is particularly poor. Survival rates have improved substantially during the past 20 years, but survival from late stage neuroblastoma is even now only achieved in a minority of cases, and at the cost of very intensive treatment which is debilitating whilst in progress and carries a substantial risk of a range of late effects.

An alternative strategy for reducing mortality from neuroblastoma is population screening, in the expectation that most cases could be diagnosed at an earlier age and stage, allowing a high cure rate with less intensive treatment. Screening is technically feasible, since the great majority of children with neuroblastoma have increased levels of catecholamine metabolites in their urine, which can be detected in samples by chromatographic methods.

As with any cancer, some clues to the degree of success of screening for neuroblastoma may be obtained by observing changes in the distribution of cases by age and stage and in their survival rates, but the ultimate test is whether screening has any effect on mortality [1]. This is particularly important in the case of neuroblastoma for two reasons. The first is that the most malignant forms may not have a sufficiently long presymptomatic period to be reliably detected by screening [2]. The second is the well known phenomenon of spontaneous regression in neuroblastoma, which has recently been reported in a case detected by screening at age 6 months [3]. Although the screen-

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ing procedure itself is completely safe, there is a risk of morbidity and mortality resulting from the treatment of tumours detected by screening which would otherwise have resolved without becoming symptomatic. The problems of interpretation of data from studies of neuroblastoma screening so far published have been reviewed elsewhere [4, 5].

In Japan experimental screening for neuroblastoma started in the 1970s and in 1985 national screening began. Impressively high survival rates have been reported among the cases detected by screening [6] but there have been no studies of mortality in screened and non-screened populations. Population-based trials of screening are now in progress or planned in Canada, the United States, Great Britain and various European countries. The purpose of the present study is to document mortality and incidence rates for neuroblastoma in Britain during the past 20 years so as to provide necessary background information for evaluating the outcome of any large scale trial of screening in this country. In the light of reported increases in neuroblastoma incidence in Scandinavia during an earlier period [7, 8], trends in incidence were also investigated.

MATERIALS AND METHODS

The analyses are based on data from the National Registry of Childhood Tumours (NRCT) maintained by the Childhood Cancer Research Group (CCRG). The registry includes all cases of cancer arising in children aged under 15 years and notified through the National Cancer Registration Schemes, specialist regional children's cancer registries, the United Kingdom Children's Cancer Study Group (UKCCSG) and death certificates. Diagnoses and other clinical information are verified from medical records about 1 year after death for children who have died and about 5 years after diagnosis for those who have survived. Notifications from the UKCCSG are generally made within a few months of diagnosis and include an abstract of any pathology report. In addition, the UKCCSG supplies check lists of children included in the studies of the European Neuroblastoma Study Group. Receipt of cancer registrations is complete nationally to the end of 1987, and from many regional registries to the end of 1990. All UKCCSG notifications have been received to the end of 1990. Unpublished analyses of NRCT data indicate that in recent years around 90% of all children with neuroblastoma have been under the care of UKCCSG members. Thus, although a few cancer registrations may be missing for children diagnosed in 1988 onwards who have not been notified by any other means, it seems reasonable to assume that ascertainment of cases is virtually complete to the end of 1990. All death certificates for persons dying in Britain before the age of 20 with a neoplasm as the underlying cause have been received up to the end of 1990. Survivors diagnosed before 1987 have been traced and flagged in the National Health Service Central Registers (NHSCR) so that the CCRG is notified of any further deaths including those coded to non-neoplastic causes. Children registered with the UKCCSG are followed up annually. Thus virtually all deaths among children with neuroblastoma up to the end of 1990 have been notified to the NRCT.

The analyses of incidence which follow relate to children diagnosed with neuroblastoma during 1971–1990. The analyses of mortality rates relate to deaths occurring among children who had neuroblastoma and who died during the same period.

RESULTS

Incidence

Table 1 shows the registration rates for neuroblastoma ascertained from all the sources described above during 1971–1990. The age-specific rates and a crude rate for the entire age range 0–14 are followed by the age-standardised rate (ASR), calculated using the World Standard Population, and a cumulative rate which corresponds to the total risk during the first 15 years of life. These latter rates allow comparisons to be made with results from the international study of childhood cancer incidence coordinated by the International Agency for Research on Cancer [9].

The incidence was highest, around 30 per million, during the first year of life. More than half of all cases were diagnosed before the third birthday. The cumulative incidence over the first 15 years of life was about 110 per million.

The ASR increased by 26% for all ages combined between 1971–1975 and 1986–1990, while the cumulative rate increased by 23%. Incidence rose by 36% both among infants aged under 1 year and among children aged 1–9 between the same two periods, but in the 10–14 age group, which has always had a low incidence rate, it fell by 70%.

Table 2 shows the cumulative incidence of neuroblastoma per million live births at successive intervals after birth among children born during 1971–1989. Mortality from other causes has been ignored and a zero net effect of migration has been assumed. There is a pattern of increasing risk with more recent years of birth until 1985 up to the ages for which data are available. Even among the most recent cohort, however, it seems very unlikely that the cumulative incidence to age 15 will exceed the levels frequently found in Western populations.

Mortality

Table 3 shows the mortality rates based on all deaths of children with neuroblastoma during 1971–1990. Children who had neuroblastoma but whose death was certified as due to some other type of neoplasm or to a non-neoplastic cause are included in Table 3; children who were certified as having died of neuroblastoma but who in fact never had the disease are excluded. The first type of misclassification appears to have been roughly three times as common as the second but the net effect is small; mortality rates calculated on the basis of death certificate diagnoses alone appear to underestimate the true death rate by about 5%.

Age-standardised mortality declined by 27% between 1971–1975 and 1981–1985, with a particularly marked decrease occurring at age 0. There was relatively little change in the rates for children aged 1–9. The mortality rate at age 10–14 was much lower throughout, but nevertheless declined substantially between the two quinquennia. Between 1981–1985 and 1986–1990, however, although there was a further decrease in mortality at age 0, the age-standardised mortality for all ages combined rose by 18%, to the same level as during 1976–1980.

Table 4 shows the cumulative mortality rates based on deaths of children with neuroblastoma who were born during 1971–1989. The same assumptions have been made regarding competing causes of death and migration as for the analysis of incidence rates by year of birth described above. Mortality in the first year of life fell by over 40% between 1971–1975 and 1976–1980 births, though the cumulative rates for the first 10 years of life differed hardly at all between these two birth cohorts. The death rates in the first year of life again fell substantially for infants born during 1981–1989 but the reduction in mortality at age 1 year and above has been more modest.

Table 1. Numbers of registered cases of neuroblastoma from all sources of ascertainment and annual incidence per million population in Great Britain, 1971–1990

Years of diagnosis	Age at diagnosis (years) 0	1	2	3	4	1–4	5–9	10–14	0–14	ASR	Cumulative
1971–1975											
No.	100	58	69	51	37	215	79	43	437	—	—
Rate	26.0	14.5	16.6	12.0	8.6	12.9	3.5	2.0	6.8	7.7	105
1976–1980											
No.	87	62	53	42	21	178	52	22	339	—	—
Rate	26.4	19.0	16.2	12.3	5.8	13.1	2.6	1.0	5.7	7.2	98
1981–1985											
No.	122	69	53	45	39	206	40	8	376	—	—
Rate	35.1	19.9	15.4	13.3	11.8	15.1	2.4	0.4	7.0	8.3	109
1986–1990											
No.	131	99	79	46	32	256	68	10	475	—	—
Rate	35.4	27.0	21.9	12.9	9.1	17.8	3.9	0.6	9.1	9.7	129

ASR = age standardised rate

Table 2. Cumulative incidence of children with neuroblastoma per million live births in Britain

Birth years	Age 6 months	1 year	2 years	3 years	4 years	5 years	10 years	15 years
1971–1975	16.6	26.0	40.2	56.2	67.5	74.4	85.7	87.5
1976–1980	15.1	27.3	47.7	63.1	75.9	86.0	102.9	—
1981–1985	23.3	34.7	56.0	74.5	87.1	99.0	—	—
1986–1989	17.1	32.5	60.7*	79.0*	88.6*	—	—	—

The rates represent the cumulative risk to cohorts of children born in given years until immediately before a given age and are based on children born during 1971–1989 and diagnosed during 1971–1990. *Rates estimated from cohorts for whom follow-up is not yet complete.

Table 3. Numbers of deaths of children with neuroblastoma and annual mortality per million population in Great Britain 1971–1990

Years of death	Age at death (years) 0	1	2	3	4	1–4	5–9	10–14	0–14	ASR	Cumulative
1971–1975											
No.	53	40	59	44	33	176	88	42	359	—	—
Rate	13.8	10.0	14.2	10.3	7.6	10.5	3.9	2.0	5.6	6.2	85
1976–1980											
No.	23	37	33	25	38	133	73	29	258	—	—
Rate	7.0	11.4	10.1	7.3	10.6	9.8	3.6	1.3	4.3	5.1	71
1981–1985											
No.	22	29	32	34	33	128	52	6	208	—	—
Rate	6.3	8.4	9.3	10.0	9.9	9.4	3.1	0.3	3.9	4.5	61
1986–1990											
No.	21	27	46	41	25	139	83	15	258	—	—
Rate	5.7	7.4	12.8	11.5	7.1	9.7	4.8	0.9	5.0	5.3	73

ASR = age standardised rate.

Table 4. Cumulative mortality of children with neuroblastoma per million live births in Britain

Birth years	Age 6 months	1 year	2 years	3 years	4 years	5 years	10 years	15 years
1971–1975	7.9	12.6	22.1	33.9	42.3	52.6	67.5	70.2
1976–1980	3.3	7.4	19.9	28.5	38.2	47.7	67.9	—
1981–1985	3.7	5.4	11.7	21.9	33.6	41.8	—	—
1986–1989	4.0	5.7	14.2*	27.1*	31.2*	—	—	—

The rates represent the cumulative risk to cohorts of children born in given years until immediately before a given age and are based on children born during 1971–1989 and dying during 1971–1990. *Rates estimated from cohorts for whom follow-up is not yet complete.

DISCUSSION

The data presented here suggest that the cumulative incidence of neuroblastoma during childhood in Britain increased by 23% between 1971–1975 and 1986–1990. When the data are analysed by period of birth, there is evidence of increasing incidence among cohorts of children born in successive quinquennia during 1971–1985. The incidence rates have nevertheless remained within the range previously reported from registries in Europe, North America and Oceania [9].

Few data are available on trends in neuroblastoma incidence in other Western countries. In Denmark there was a significant increase in the recorded incidence of neuroblastoma among children aged less than 5, and especially less than 1 year, throughout 1943–1980 [8]. The increase was most marked between 1971–75 and 1976–80, and was tentatively attributed to improvements in diagnosis and to changes in the social composition of the population and in the level of exposure to unidentified environmental carcinogens. In the Manchester Children's Tumour Registry, the ASR rose by 10% from 6.8 per million during 1954–1970 to 7.5 per million during 1971–1983 [10]. The increase in Manchester, in contrast to Denmark, took place largely at the age of 1–4, and the incidence among infants aged less than 1 year was very similar in the two calendar periods. Any increase in the Manchester region is unlikely to have been artefactual since ascertainment was estimated to be at least 95% complete even in the early years of the registry, and the histological diagnoses are reviewed from time to time [10].

It is implausible that improved diagnosis could explain the increased incidence of neuroblastoma in Britain during the past two decades, especially since most of the increase took place in the most recent quinquennium. The use of raised levels of excretion of catecholamines in the differential diagnosis of neuroblastoma was well established by the start of the study period [11] and so it seems unlikely that many cases of neuroblastoma would have been missed. Until recently, however, some cases of other small-celled tumours, such as primitive (peripheral) neuroectodermal tumour, would have been misdiagnosed on histological grounds as neuroblastoma [12]. This probably explains the decrease in recorded incidence at the age of 10–14, especially since 35/65 (54%) of cases in this age group during 1971–1980 were in the thoracic or pelvic regions, which are the most common sites for neuroectodermal tumour outside the central nervous system [13], and only 6/65 (9%) were in the adrenal gland, the most common primary site for neuroblastoma.

The evidence on socio-economic status and neuroblastoma incidence is hard to interpret. In Denmark [8] and the United States [14], neuroblastoma has been found to be more common among less affluent sections of the population. During a period of improving living standards, this would suggest that the incidence should have fallen rather than risen.

Increases during the study period in the proportion of children in Britain who are members of ethnic minorities are also unlikely to account for increases in neuroblastoma incidence of the magnitude observed. Children of Asian or West Indian ethnic origin in Britain appear to have a small, non-significant excess risk of neuroblastoma compared with Caucasians [15] while in the United States, black children have a lower incidence than whites [9, 14].

International comparisons of neuroblastoma mortality are hard to make, as mortality data are usually presented according to the International Classification of Diseases which groups neoplasms by site rather than histology. A substantial decrease in the mortality rate for neuroblastoma in Japan has recently been reported [16]. The annual mortality at ages 1–4 declined from 11 per million during 1979–1982 to 9 per million during 1983–1987; during the final 3 years, 1985–1987, the rate was 7 per million. These rates show a steeper fall than that which took place for the same age group during 1971–1985 in Britain, and are consistent with improved treatment results.

Survival rates for neuroblastoma in Britain increased substantially during 1971–1985, with a significant trend in all age groups [17]. Overall, 5-year actuarial survival improved from 15% for children diagnosed in 1971–1973 to 43% in 1983–1985, with the largest increases taking place during 1977–1982. There has been only a relatively modest decline in neuroblastoma mortality during the past two decades because the dramatic improvements in prognosis were largely offset by increasing incidence. The NRCT does not have data on tumour stage for all children, and possible variations over time in the scope of diagnostic investigations would make analyses of trend-specific incidence rates unreliable. The absence of further improvements in survival between 1983 and 1988 suggests, however, that the increased incidence is not solely the result of an increasing tendency to diagnose early stage tumours and that there has been a true increase in the poor prognosis group of neuroblastoma. Unpublished data from the NRCT for 1986–1988 give an actuarial 3-year survival rate of 44%, only slightly higher than the 5-year survival for children diagnosed during the preceding 3-year period. The increased mortality during the most recent quinquennium is thus the consequence of a halt in the improvement in survival rates combined with a substantial and as yet unexplained increase in incidence.

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Hyaluronan and Hyaluronectin in the Extracellular Matrix of Human Brain Tumour Stroma

Bertrand Delpech, Catherine Maingonnat, Nicole Girard, Claude Chauzy, Roger Maunoury, Annie Olivier, Jean Tayot and Pierre Creissard

Hyaluronan (HA) and the hyaluronan-binding glycoprotein hyaluronectin (HN) were measured in 23 gliomas and 8 meningiomas and their location was revisited in 35 tumours. A clear-cut difference was found in the HN/HA ratio values of glioblastomas (below 0.5) and that of astrocytomas (above 0.5 $P < 0.001$). Besides their location in the intercellular part of gliomas, HA and HN displayed a perivascular location in 1/3 astrocytomas, 17/24 glioblastomas, and 3/7 meningiomas, suggesting they could be produced also by the vascular stroma of tumours and that they would characterise the neoangiogenesis. All cultivated glioma cells tested produced HA *in vitro*, whereas only 1/11 cell lines produced HN, at a low level. The results obtained suggest that glioma HA and HN are produced by both cancer cells and vascular stroma cells, which contribute to the edification of the extracellular matrix. In meningiomas only the stroma would be responsible for HA and HN production.
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INTRODUCTION

THE TUMOUR stroma is developed from normal tissues which grow along with and support cancer cells. The tumour stroma comprises new blood vessels, desmoplasia whose extracellular matrix is a major part, and inflammatory cells. The stroma is particularly important in tumour development. The nutritive blood supply and signalling components (hormones, growth factors) are brought to or emitted by cancer cells through the extracellular matrix. Among the numerous extracellular matrix components, hyaluronan (hyaluronic acid, HA[1]) is the object of an increasing interest in relation to its role in cancer cell development and invasion. HA is a highly polymerised saccha-