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The epidemiology of infant cancers

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Summary Cancers in infants represent less than 0.05% of all malignant neoplasms, but form a particulary interesting group for study. The ratio of solid tumours to leukaemias is 2:1 in children aged 1–14 but 5:1 in infants less than 1 year. The rate for neuroblastoma which is the most common malignancy in infants is four times higher in children aged under 1 year than in 1–14 year olds. Other embryonal tumours, e.g. Wilms', heptablastoma and retinoblastoma also show higher rates in infants. The ratios of incidence in males to females differed in a number of instances in the two age groups, e.g. in leukaemias and liver tumours the male to female ratio is greater than one in 1–14 year old children but less than one in infants. These observations suggest that many infant tumours may be aetiologically distinct. Their early onset and predominantly embryonal nature suggest a pre-natal origin and genetic factors may be important.

In England and Wales in 1985 there were 200,818 newly-registered malignant neoplasms. Of these, 982 (0.5%) were diagnosed in children aged under 15 years, and among the childhood cancers 92, that is 0.05% of all malignant neoplasms, were in infants aged less than 1 year. In spite of their rarity, infants diagnosed with malignant disease at less than 12 months of age comprise a particularly interesting group for study. In older children with cancer, although genetic factors and prenatal exposures may be important, exposure to post-natal environmental factors may also be involved. In young infants, however, the development of malignant disease may be assumed to be entirely prenatal in origin. In such children, therefore, there is a short, known time period between conception and birth when all the important steps in carcinogenesis must have taken place.

There is some evidence from studies of case series that many malignant neoplasms presenting in infancy differ in their biological characterisitics from their counterparts presenting in older children. For example, in a national study of retinoblastoma reported by Sanders *et al.* (1989), over 60% of bilateral (genetic) cases presented under 1 year of age. Among a series of 24 patients aged 1 year or younger who were diagnosed as having Wilms' tumour, only 12 on review were considered to be typical Wilms' tumours, and two of these were bilateral. The remainder were morphologically distinct variants of Wilms' tumour, normally rare among general series of childhood renal tumours. These included rhabdoid tumour (six cases, three bilateral), sarcomatous Wilms' tumour (two cases), epithelial neophroblastoma (two cases) and cystic nephroma (two cases) (Ugarte *et al.*, 1981).

In a review of 78 patients younger than 1 year of age registered in the Intergroup Rhabdomyosarcoma Study (IRS) there was an excess of undifferentiated sarcoma and botyroid tumours compared with the IRS series as a whole, and primary sites in the bladder, prostate and vagina were more than twice as common in this age group than in the whole series (Ragab *et al.*, 1986).

Stage IVS neuroblastoma is a distinct subtype which is widely disseminated at diagnosis, with foci in liver, skin or bone marrow, but having small primary tumours as originally described by Evans *et al.* (1971). In spite of widespread disease in a normally lethal tumour, this subtype has a good prognosis, and will often spontaneously regress without treatment. Stage IVS neuroblastoma typically presents in young infants (Evans *et al.*, 1980).

Leukaemia in children under 1 year of age has a considerably worse prognosis than that in older children, and infants typically present with extensive disease and morphological characteristics associated with poor risk. Cytogenetically, translocations involving apparently non-random breakpoints at 4q21 and 11q23, and breakpoints corresponding to known fragile sites were observed in a series of infant leukaemias (Stark *et al.*, 1989).

These distinct characteristics observed in infant malignancies suggest that aetiological factors separate from those in older children apply to young infants with cancer. Studies of the descriptive epidemiology of disease can provide clues with respect to possible aetiological factors, and lead to hypotheses which can then be tested in analytical epidemiological studies.

Methods

In order to explore the pattern of neoplasms seen in infants, we have analysed cases included in the Manchester Children's Tumour Registry during the 35-year period 1954–1988 inclusive. The Manchester Children's Tumour Registry is population based, and gathers detailed clinical and histopathological data on all cases of malignant disease occurring in children who were diagnosed before their 15th birthday, and who were resident within the North Western Regional Health Authority area of England (Manchester Regional Hospital Board area before 1974) at the time of their diagnosis. Benign intracranial tumours and certain other benign tumours, for example benign endocrine tumours, mesoblastic nephroma and teratomas are also included. Histopathological material on each solid tumour is circulated to an international panel of pathologists to establish the diagnosis. The Manchester Children's Tumour Registry is described in greater detail by Birch (1988).

Cases were grouped by diagnosis according to the classification scheme described by Birch and Marsden (1987). Incidence rates per million child-years were calculated, using the sum of the mid-year population estimates for the years 1954–1988 for the North West Regional Health Authority (Manchester Regional Hospital Board before 1974), for children aged 0–14 as denominators.

Results

Table I compares the incidence for main diagnostic groups in infants aged less than 1 year with that in children aged 1–14 years. The pattern of cancers seen in infants differs somewhat from that seen in the older children. In the older children, leukaemias form the most common group, and the ratio of solid tumours to leukaemias in children aged 1–14 is 2:1. In infants leukaemia represents a relatively less important

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Table I Incidence per 10^6 child years malignant disease in children aged 0–14 years, Manchester Children's Tumour Registry 1954–1988

	Age < 1 year			
	M	*F*	*M & F*	*Ratio M:F*
Leukaemia	18.25	21.09	19.63	0.87
Lymphoma	13.90	8.25	11.15	1.68
CNS tumours	22.59	14.67	18.24	1.54
Neuroblastoma	23.46	21.09	22.30	1.11
Retinoblastoma	18.25	15.58	16.95	1.17
Renal tumours	16.51	9.17	12.94	1.80
Hepatic tumours	3.48	5.50	4.46	0.63
Bone tumours	0.87	–	0.45	–
Soft tissue sarcoma	10.43	7.33	8.92	1.42
Germ cell tumours	4.34	0.92	2.68	4.72
Carcinoma and other epithelial	–	2.75	1.34	–
Other	2.61	1.83	2.23	1.43
Total	134.69	108.18	121.29	1.25
	Age 1–14 years			
	M	*F*	*M & F*	*Ratio M:F*
Leukaemia	37.38	30.48	34.02	1.23[c]
Lymphoma	15.10	8.01	11.65	1.89[c]
CNS tumours	26.90	23.19	25.09	1.16[a]
Neuroblastoma	5.74	4.93	5.34	1.16
Retinoblastoma	2.25	2.04	2.14	1.10
Renal tumours	5.37	5.58	5.47	0.96
Hepatic tumours	0.62	0.07	0.35	8.86[b]
Bone tumours	4.68	6.11	5.38	0.77
Soft tissue sarcoma	5.80	4.40	5.12	1.32
Germ cell tumours	2.31	3.48	2.88	0.66
Carcinoma and other epithelial	2.43	2.56	2.50	0.95
Other	1.44	1.12	1.28	1.29
Total	110.02	91.97	101.22	1.20[c]

M = male, F = female. [a]$P<0.05$; [b]$P<0.01$; [c]$P<0.001$.

group, and in children aged under 1 the ratio of solid tumours to leukaemias is 5:1. An identical ratio of solid tumours to leukaemias was also found in the series reported by Bader and Miller (1979).

Lymphomas are equally common in both age groups, but central nervous system tumours are somewhat less frequent in infancy than in older children. One of the most striking differences is the incidence of neuroblastoma. Neuroblastoma is the most common cancer found in infants, and the rate is more than four times higher in infants than in older children. Again Bader and Miller similarly found neuroblastoma to be the most frequent malignancy in their population-based study of infant cancers in the United States.

Other embryonal tumours, including retinoblastoma, Wilms' tumour and hepatoblastoma are also relatively more frequent in infants, whereas bone tumours are very rare during infancy, and are more common in older children.

When the male to female incidence ratio in infants is compared with that in older children some interesting differences emerge. In both age groups the ratio was greater than one in the majority of tumour types. Among 1–14 year olds the higher incidence in males was statistically different for leukaemias, lymphomas, CNS tumours, hepatic tumours and all diagnoses combined. Among infants aged less than 1 year, although the ratios were similar in many diagnostic groups due to small numbers, the differences in incidence between males and females did not reach statistical significance e.g. lymphomas and CNS tumours. However, among leukaemias and liver tumours whereas the male to female ratio is greater than one in the 1–14 year old children it is less than one among infants. The reverse is true of renal tumours and germ cell tumours where in infants there is a higher incidence in males. These reversals of male to female incidence ratios in infants compared with older children may indicate aetiologically distinct sub-groups.

Table II gives a more detailed breakdown of tumour types occurring during the first year of life, including certain benign tumours. All the main types of brain tumours seen in childhood are found during the first few months of life, but whereas five out of nine cases of medulloblastoma were diagnosed under 6 months of age, eight out of nine astrocytomas were diagnosed over 6 months of age. Among renal tumours, true Wilms' tumour was not found during the first 3 months of life, but two cases of mesoblastic nephroma were diagnosed soon after birth. No mesoblastic nephromas have been observed after 6 months of age. Rhabdoid sarcoma of the kidney is a rare cancer typically found in infants, and there were two examples in the present series.

Soft tissue sarcomas were distributed throughout the first 12 months of life, with rhabdomyosarcoma being the most common morphological type seen. Although malignant germ cell tumours do occur in infancy, these are uncommon, whereas benign germ cell tumours, particularly congenital benign sacrococcygeal teratomas, are more common, and a germ cell tumour diagnosed in infancy, particularly below the age of 6 months, will almost certainly be benign.

Population-based data by immunophenotype in acute lymphoblastic leukaemia (ALL) is available in the Manchester Children's Tumour Registry from 1979, and Table III shows the incidence of ALL by age and immunophenotype. Among this 10-year series there were 26 T-cell, five B-cell, 160 Common, 40 Null and 13 of unspecified cell type cases of ALL. It can be seen that while T-cell and B-cell ALL were not found

Table II Distribution of specified tumours by age during the first year of life Manchester Children's Tumour Registry 1954–1988

	Age (months)					
	<1	*1–2*	*3–5*	*6–8*	*9–11*	*Total*
Brain tumours						
Ependymoma	0	0	1	2	2	5
Astrocytoma	0	1	0	1	7	9
Medulloblastoma	0	0	5	1	3	9
Choroid plexus papilloma	0	1	0	1	2	4
Pineal tumours	0	0	1	1	0	2
Meningioma	1	0	0	0	1	2
Unspecified	0	0	2	1	2	5
Total	1	2	9	7	17	36
Renal tumours						
Wilms' tumour	0	0	7	8	12	27
Clear cell sarcoma (BMRT)	0	0	0	1	0	1
Rhabdoid sarcoma	0	0	2	0	0	2
Mesoblastic nephroma	2	0	3	0	0	5
Total	2	0	12	9	12	35
Soft tissue sarcomas						
Fibrous histiocytoma	1	0	0	0	0	1
Fibrosarcoma	0	0	2	0	0	2
Haemangiopericytoma	1	1	1	0	0	3
Schwannoma	1	0	0	0	0	1
Neuroepithelioma	0	1	0	0	0	1
Rhabdomyosarcoma	0	2	2	3	3	10
Embryonal sarcoma	0	0	1	0	1	2
Soft tissue sarcoma NOS	1	0	0	1	0	2
Total	4	4	6	4	4	22
Germ cell tumours						
Malignant	1	1	1	0	2	5
Benign	46	3	2	3	2	56
Total	47	4	3	3	4	61

Table III Manchester Children's Tumour Registry. Incidence ALL per 10^6 child-years by age and immunophenotye, 1979–1988

	Age (Years)				
	0	*1–4*	*5–9*	*10–14*	*0–14*
T-cell	0	3.4	3.1	3.7	3.2
B-cell	0	1.0	0.4	0.7	0.6
Common	5.6	41.6	18.2	8.4	19.7
Null	13.0	2.0	0.8	0.3	1.7
Unspecified	0	4.4	0	1.4	1.6

Table IV International incidence (per 10^6 child years) of infant cancers

	All cancers		Central nervous System tumours		Neuroblastoma		Retinoblastoma		Germ cell tumours	
	No.	*Rate*	*No.*	*Rate*	*No.*	*Rate*	*No.*	*Rate*	*No.*	*Rate*
New York Whites	239	174.35	21	15.32	67	48.88	19	*13.86*	17	13.86
Blacks	334	*109.28*	(5)	(16.07)	(3)	(9.64)	(3)	(9.64)	(3)	(9.64)
Brazil, Fortaleza	185	126.52	17	*11.63*	20	*13.68*	(8)	(5.47)	11	*5.28*
England and Wales	844	131.20	122	18.96	158	24.56	107	16.63	34	16.59
Sweden	291	219.35	41	30.90	67	50.50	35	*26.38*	22	16.59
Federal Republic Germany	312	172.61	31	17.15	89	49.24	34	18.81	(8)	(4.43)
Hungary	219	137.84	25	15.74	55	34.62	(9)	(5.66)	(8)	(5.04)
Israel Jews	136	199.69	11	16.15	41	*60.20*	(7)	(10.28)	(6)	(8.80)
non-Jews	35	161.69	(5)	(23.10)	(5)	(23.10)	(3)	(13.86)	(1)	(4.62)
Japan, Osaka	362	*251.81*	53	*36.87*	39	27.13	29	20.17	27	*18.79*
Australia, New South Wales	196	165.64	19	21.03	50	36.81	16	17.71	12	13.28

Where number of cases is less than ten figures are shown in brackets and these have not been taken into account in comparisons of rates.

in infants under 1 year of age, Common ALL occurred throughout childhood, but predominated in the 1–4 year age group. Null-cell ALL occurred almost exclusively in infancy.

Discussion

From these analyses it is clear that embryonal-type tumours together with germ cell tumours predominate in young infants, and it is likely that a two-hit mechanism, as demonstrated for retinoblastoma and Wilms' tumour, will also apply to other infant cancers (Cavenee *et al.*, 1989). Infant cancers might not only provide an informative group in which to look for loss of constitutional heterozygosity in candidate tumour suppressor genes, but in view of their very early onset it might also prove fruitful to seek germline mutations in tumour suppressor genes in these children. Germline mutations in the tumour suppressor gene p53 have recently been described in association with the Li-Fraumeni syndrome, which includes cancers in young children (Malkin *et al.*, 1990; Srivastava *et al.*, 1990).

International variations in incidence and studies of migrant populations can suggest clues to aetiology and the relative importance of genetic and environmental factors. A recent study of childhood cancer incidence co-ordinated by the International Agency for Research on Cancer (IARC) tabulated age-specific rates for cancers in children derived from more than 70 registries throughout the world (Parkin *et al.*, 1988).

Table IV shows data extracted from the monograph for children aged under 1 year from selective population-based registries distributed around the world, and for groups of tumours where marked variations in incidence were observed. For all cancers in infants the highest rate was found among Japanese children and the lowest in New York Black children, with more than a two-fold difference overall.

For central nervous system tumours the lowest rates were observed in Brazil and the highest in Japan, with more than a three-fold difference. In neuroblastoma again the lowest rates were observed in Brazil, but the highest rate was found among Israeli Jewish children, with more than a four-fold difference in the rates. In retinoblastoma the highest incidence was found in Sweden, where the rate was double that among New York White children. Finally, for germ cell tumours the lowest rate recorded by those registries considered in this comparison was England and Wales, and the highest in Japan, where the rate was over three-fold higher.

Because of the rarity of infant cancers, even for large registries such as New York, Osaka and England and Wales, the numbers for individual types are very small, and while ascertainment is probably good in the population-based registries in developed countries, this is probably less reliable in developing countries. Nevertheless in spite of these limitations the above comparisons probably do reflect considerable underlying variations in rates of infant cancers between different populations. There is therefore scope for comparing possible aetiological factors in these different populations. In order to exploit this unique group of tumours with respect to elucidation of aetiology, an international collaborative effort is required. The IARC are at present co-ordinating case-control studies of childhood leukaemia, and it is to be hoped that childhood solid tumours can also be studied on an international basis. If this can be acheived, separate analyses of infant cancers may be particularly rewarding.

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