Epidemiology of Childhood Tumours

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Classification

Traditionally, descriptive data on cancers occurring in people of all ages combined have been presented with the diagnoses categorised according to the International Classification of Diseases (ICD), in which cancers other than leukaemias, lymphomas, Kaposi sarcoma, cutaneous melanoma and mesothelioma are classified purely on the basis of primary site. The malignant solid tumours of children are histologically very diverse and a substantial proportion consists of characteristic entities that are rarely seen in adults. Therefore, it is appropriate to group childhood cancers in a way which more fully takes morphology into account, and standard classifications have been devised with the categories defined according to the codes for topography and morphology in the International Classification of Diseases for Oncology (ICD-O) [1–3]. The current scheme is the International Classification of Childhood Cancer, Third Edition (ICCC-3), based on the third edition of ICD-O [3]. ICCC-3 contains 12 main diagnostic groups:

I. Leukaemias, myeloproliferative diseases, and myelodysplastic diseases
II. Lymphomas and reticuloendothelial neoplasms
III. CNS and miscellaneous intracranial and intraspinal neoplasms
IV. Neuroblastoma and other peripheral nervous cell tumours
V. Retinoblastoma
VI. Renal tumours
VII. Hepatic tumours
VIII. Malignant bone tumours
IX. Soft tissue and other extraosseous sarcomas
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads
XI. Other malignant epithelial neoplasms and malignant melanomas
XII. Other and unspecified malignant neoplasms

All of the groups except retinoblastoma are split into subgroups, and the most heterogeneous subgroups are in turn split into divisions. Most groups contain only malignant neoplasms, but groups III and X also include non-malignant intracranial and intraspinal tumours since they are usually recorded by cancer registries.

Successive classifications have been designed to have as much continuity as possible with their predecessors, while recognising advances in understanding of tumour pathology and biology. Although the nomenclature of many groups and subgroups has changed since the previous version of the classification, their contents are largely the same.

Incidence

The annual incidence of cancer in children under 15 years of age is usually between 100 and 160 per million. There is a risk of 1 in 650 to 1 in 400 that a child will be affected during the first 15 years following birth. Table 2.1 shows annual incidence rates per million children in the UK for 1998–2007 based on data from the population-based National Registry of Childhood Tumours. The total incidence, just under 150 per million, and the relative frequencies of the different groups and subgroups were typical of those in industrialised countries. In the table, the ICCC-3 subgroups for Burkitt lymphoma and other non-Hodgkin lymphoma (NHL) have been combined because they are usually considered together clinically, and data for some other subgroups and divisions are not shown separately because of small numbers.

Leukaemia formed the most frequent diagnostic group, about one third of the total incidence. The lymphoid subgroup, which in childhood consists almost entirely of precursor cell

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Table 2.1 Registration rates for cancers diagnosed at age 0–14 years in the UK, 1998–2007

		Annual rates per million children for age group (years)				Age standardised rates per million (World standard population)		
ICCC-3 categories	Total registrations	0	1–4	5–9	10–14	Boys	Girls	Children
I-XII. All Cancers	15,729	209.5	198.2	112.5	119.9	158.3	138.6	148.7
I. Leukaemias	4971	45.5	81.6	36.8	26.7	52.4	44.2	48.4
(a) Lymphoid leukaemias	3884	19.7	69.2	30.1	18.4	41.6	34.3	38.0
(b) Acute myeloid leukaemias	742	17.5	8.3	4.7	5.6	7.4	6.8	7.1
(c) Chronic myeloproliferative diseases	114	1.3	0.5	0.7	1.7	1.0	1.0	1.0
(d) Myelodysplastic syndrome and other myeloproliferative	188	5.7	2.9	1.0	0.8	2.1	1.6	1.9
(e) Other and unspecified	43	1.3	0.6	0.3	0.2	0.3	0.5	0.4
II. Lymphomas etc	1621	1.6	8.1	13.5	23.2	18.2	9.0	13.7
(a) Hodgkin lymphoma	733	–	1.6	4.4	13.7	7.3	4.5	5.9
(b, c) Non-Hodgkin lymphomas	862	1.0	6.2	8.9	9.3	10.5	4.4	7.6
(d, e) Other and unspecified	26	0.6	0.3	0.2	0.2	0.4	0.1	0.2
III. CNS, intracranial, intraspinal	3992	37.4	42.5	36.5	31.4	38.8	35.0	36.9
(a) Ependymomas and choroid plexus tumours	399	9.1	6.3	2.4	1.9	4.6	3.3	4.0
1. Ependymomas	292	2.6	4.8	2.0	1.7	3.3	2.4	2.8
2. Choroid plexus tumours	107	6.6	1.5	0.3	0.2	1.3	0.9	1.1
(b) Astrocytomas	1700	9.4	17.7	18.0	13.9	15.1	16.1	15.6
(c) Intracranial and intraspinal embryonal tumours	743	9.3	9.4	6.9	4.3	8.5	5.6	7.1
1. Medulloblastomas	546	3.3	6.4	5.9	3.4	6.5	3.6	5.1
2. Primitive neuroectodermal tumour	129	3.4	1.8	0.8	0.7	1.2	1.3	1.3
3. Atypical teratoid/rhabdoid tumour	65	2.6	1.2	0.1	0.2	0.8	0.6	0.7
(d) Other gliomas	400	1.1	4.1	4.5	2.9	3.8	3.5	3.7
(e) Other specified	543	3.3	3.5	4.6	6.6	4.9	4.6	4.7
1. Pituitary adenoma and carcinoma	52	–	0.1	0.2	1.1	0.4	0.5	0.4
2. Craniopharyngioma	189	0.3	1.0	2.3	2.0	1.7	1.5	1.6
3. Pineal parenchymal tumours	53	0.9	0.7	0.3	0.4	0.5	0.5	0.5
4. Neuronal, neuronal-glial	204	2.1	1.5	1.6	2.3	1.9	1.7	1.8
5. Meningiomas	45	–	0.3	0.3	0.7	0.3	0.4	0.4
(f) Unspecified	207	5.1	1.5	1.7	1.8	2.0	1.9	1.9
IV. Neuroblastoma etc	946	44.2	17.7	3.0	0.8	10.3	9.9	10.1
(a) Neuroblastoma and ganglioneuroblastoma	930	44.2	17.6	2.9	0.6	10.1	9.8	10.0
(b) Other peripheral nervous cell	16	–	0.2	0.1	0.2	0.2	0.1	0.1
V. Retinoblastoma	417	24.8	7.9	0.5	0.1	4.3	4.8	4.6
VI. Renal tumours	862	16.3	19.3	4.3	1.3	8.3	9.8	9.0
(a) Nephroblastoma and other non-epithelial	844	16.3	19.3	4.3	0.9	8.2	9.6	8.9
1. Nephroblastoma (Wilms tumour)	771	12.3	18.1	4.1	0.8	7.2	9.0	8.1
2. Rhabdoid	31	3.0	0.3	0.0	–	0.3	0.3	0.3
3. Sarcomas	34	0.9	0.9	0.1	0.0	0.5	0.2	0.4
4. Peripheral neuroectodermal tumour	8	0.1	0.0	0.0	0.1	0.1	0.1	0.1
(b) Renal carcinoma	16	–	0.0	0.0	0.4	0.1	0.1	0.1
(c) Unspecified	2	–	–	0.1	–	0.0	0.0	0.0
VII. Hepatic tumours	182	8.4	3.1	0.4	0.6	2.0	1.8	1.9
(a) Hepatoblastoma	146	7.8	2.9	0.2	0.1	1.7	1.4	1.6
(b) Hepatic carcinoma	32	0.1	0.2	0.2	0.5	0.3	0.3	0.3
(c) Unspecified	4	0.4	–	–	0.0	0.0	0.0	0.0

Table 2.1 (continued)

		Annual rates per million children for age group (years)				Age standardised rates per million (World standard population)		
ICCC-3 categories	Total registrations	0	1–4	5–9	10–14	Boys	Girls	Children
VIII. Malignant bone tumours	620	0.3	1.1	4.8	10.8	5.2	4.9	5.0
(a) Osteosarcoma	322	–	0.3	2.2	6.0	2.6	2.5	2.6
(c) Ewing sarcoma family	262	0.1	0.7	2.2	4.2	2.2	2.1	2.2
(b, d, e) Other and unspecified	36	0.1	0.1	0.3	0.5	0.3	0.3	0.3
IX. Soft tissue and extraosseous sarcomas	993	12.0	10.4	7.4	9.0	10.1	8.1	9.2
(a) Rhabdomyosarcoma	499	5.3	7.4	4.5	2.4	5.5	4.1	4.8
(b) Fibrosarcoma etc	72	1.9	0.3	0.2	1.1	0.7	0.6	0.6
(c) Kaposi sarcoma	4	–	0.0	0.0	0.1	0.0	0.0	0.0
(d) Other specified	356	3.4	2.1	2.3	4.9	3.3	2.9	3.1
1, 2. Ewing sarcoma family	147	0.9	1.1	1.1	1.8	1.1	1.5	1.3
3. Extrarenal rhabdoid tumour	20	1.4	0.2	0.1	0.1	0.3	0.2	0.2
4. Fibrohistiocyytic tumours	46	0.4	0.1	0.4	0.7	0.5	0.3	0.4
5. Synovial sarcoma	71	–	0.3	0.4	1.3	0.7	0.4	0.6
(e) Unspecified	62	1.4	0.6	0.4	0.6	0.6	0.5	0.6
X. Germ cell, trophoblastic and gonadal	518	16.4	3.7	2.1	5.8	4.3	5.3	4.8
(a) Intracranial and intraspinal germ cell	176	1.7	0.6	1.1	2.7	1.9	1.0	1.5
(b) Other malignant extragonadal	144	11.7	1.6	0.2	0.3	1.0	2.1	1.5
(c) Malignant gonadal germ cell	189	3.0	1.5	0.6	2.7	1.4	2.0	1.7
(d, e) Other and unspecified gonadal	9	–	–	0.1	0.1	0.0	0.1	0.1
XI. Other malignant epithelial and melanoma	517	1.4	1.9	2.9	9.1	3.6	5.0	4.3
(a) Adrenocortical carcinoma	28	0.6	0.6	0.1	0.1	0.2	0.4	0.3
(b) Thyroid carcinoma	118	–	0.4	0.7	2.1	0.7	1.3	1.0
(c) Nasopharyngeal carcinoma	28	–	–	0.0	0.7	0.3	0.1	0.2
(d) Malignant melanoma	129	0.9	0.5	0.7	2.2	0.8	1.3	1.1
(e) Skin carcinoma	108	–	0.2	0.7	2.0	0.8	0.9	0.9
(f) Other and unspecified carcinomas	106	–	0.1	0.7	2.0	0.7	1.0	0.8
XII. Other and unspecified	90	1.3	0.9	0.3	1.1	0.8	0.8	0.8
(a) Other specified	20	0.6	0.3	0.0	0.2	0.2	0.2	0.2
(b) Unspecified	70	0.7	0.6	0.3	1.0	0.6	0.6	0.6

Source: National Registry of Childhood Tumours

acute lymphoblastic leukaemia (ALL), accounted for 78 % of leukaemias and one quarter of all childhood cancers; nearly all the remaining leukaemias were acute myeloid (AML). The most numerous solid neoplasms were CNS and other intracranial and intraspinal tumours, accounting for one quarter of total cancer incidence. The next most frequent diagnostic groups were, in descending order of incidence, lymphomas, soft tissue sarcomas, neuroblastoma and other peripheral nervous cell tumours and renal tumours, each accounting for 5.5–10 % of the total. The remaining groups together accounted for 15 %. Overall, incidence in the first 5 years of life was about 1.7 times that at 5–14 years of age. Boys were affected 1.1 times as often as girls. There were, however, pronounced differences in age distribution and sex ratio between different types of childhood cancer. The principal embryonal tumours, namely those of the CNS (including medulloblastoma and other primitive neuroectodermal tumours), neuroblastoma, retinoblastoma, nephroblastoma (Wilms tumour) and hepatoblastoma, all had their highest incidence in early childhood, and about 40 % of the cumulative incidence of retinoblastoma and hepatoblastoma were observed in the first year of life. Contrastingly, incidence of some diagnostic categories increased with age, and more than two thirds of the cumulative childhood incidence of Hodgkin lymphoma and osteosarcoma occurred at age 10–14 years. Incidence was higher among boys than girls in most diagnostic categories and NHL had a male:female ratio of more than 2:1, but for a few cancers, notably germ cell tumours of certain sites, thyroid carcinoma and malignant melanoma, there was a marked excess of girls.

Table 2.2 shows the distribution by morphology of childhood cancers in selected anatomical sites, based on the same data as Table 2.1. The proportions of lymphomas in some sites are probably underestimates, as some cases coded to less specific or multiple sites may in fact have arisen in one of the sites listed. While most cancers of most sites in adults are carcinomas, the pattern in childhood is strikingly different. Tumours of the head and neck included substantial numbers of lymphomas and sarcomas. Lymphomas predominated among cancers of the gastro-intestinal tract. Most cancers of the liver, kidney and eye were characteristic childhood embryonal tumours. Cancers of the ovary were nearly all germ cell tumours. The majority of testicular cancers were germ cell tumours, but there were also substantial numbers of paratesticular rhabdomyosarcomas. Rhabdomyosarcoma was the most common type of childhood cancer in other genito-urinary sites of both sexes.

Table 2.2 Histological types of cancers of selected primary sites diagnosed at age 0–14 years in the UK, 1998–2007

Primary site (ICD-O-3)	Type	Number of registrations
Major salivary glands (C07-08)	Total	52
	Lymphoma	8 (15 %)
	Rhabdomyosarcoma	4 (8 %)
	Carcinoma	40 (77 %)
Other mouth (C00-06)	Total	34
	Lymphoma	2 (6 %)
	Rhabdomyosarcoma	9 (26 %)
	Other sarcoma	5 (15 %)
	Germ-cell tumour	1 (3 %)
	Carcinoma	14 (41 %)
	Unspecified	3 (9 %)
Tonsil (C09)	Total	45
	Lymphoma	45 (100 %)
Nasopharynx (C11)	Total	72
	Lymphoma	13 (18 %)
	Rhabdomyosarcoma	30 (42 %)
	Other sarcoma	1 (1 %)
	Carcinoma	28 (39 %)
Other upper aerodigestive (C10,12-14,30-32)	Total	71
	Lymphoma	15 (21 %)
	Neuroblastoma	1 (1 %)
	Esthesioneuroblastoma	8 (11 %)
	Rhabdomyosarcoma	33 (46 %)
	Other sarcoma	5 (7 %)
	Germ cell	2 (3 %)
	Carcinoma	3 (4 %)
	Unspecified	4 (6 %)
Stomach (C16)	Total	6
	Lymphoma	2 (33 %)
	Germ cell	3 (50 %)
	Carcinoma	1 (17 %)
Small intestine (C17)	Total	44
	Lymphoma	39 (89 %)
	Carcinoma	4 (9 %)
	GIST	1 (2 %)
Colon, rectum (C18-19)	Total	51
	Lymphoma	30 (59 %)
	Carcinoma	19 (37 %)
	Unspecified	2 (4 %)
Liver (C22)	Total	224
	Lymphoma	10 (4 %)
	Hepatoblastoma	146 (65 %)
	Carcinoma	32 (14 %)
	Sarcoma	30 (13 %)
	Germ cell	2 (1 %)
	Unspecified	4 (2 %)
Pancreas (C25)	Total	5
	Lymphoma	2 (40 %)
	Sarcoma	1 (20 %)
	Pancreatoblastoma	2 (40 %)
Lung (C34)	Total	36
	Lymphoma	6 (17 %)
	Sarcoma	6 (17 %)
	Carcinoid/bronchial adenoma	6 (17 %)
	Other carcinoma	5 (14 %)
	Pleuropulmonary blastoma	11 (31 %)
	Mesothelioma	1 (3 %)
	Unspecified	1 (3 %)
Ovary (C56)	Total	135
	Lymphoma	4 (3 %)
	Neuroblastoma	1 (1 %)
	Sarcoma	2 (1 %)
	Germ cell	120 (89 %)
	Carcinoma	4 (3 %)
	Sertoli-Leydig	2 (1 %)
	Mesothelioma	1 (1 %)
	Unspecified	1 (1 %)
Other female reproductive (C52-55,57)	Total	27
	Rhabdomyosarcoma	13 (48 %)
	Other sarcoma	1 (4 %)
	Germ cell	11 (41 %)
	Carcinoma	2 (7 %)
Prostate (C61)	Total	8
	Rhabdomyosarcoma	8 (100 %)
Male genital (C62-63)	Total	124
	Lymphoma	1 (1 %)
	Rhabdomyosarcoma	51 (41 %)
	Germ cell	70 (56 %)
	Sertoli cell	1 (1 %)
	Unspecified	1 (1 %)

Table 2.2 (continued)

Primary site (ICD-O-3)	Type	Number of registrations
Kidney (C64)	Total	895
	Lymphoma	12 (1 %)
	Neuroblastoma	17 (2 %)
	Nephroblastoma (Wilms)	767 (86 %)
	Rhabdoid	31 (3 %)
	Clear cell sarcoma	34 (4 %)
	pPNET	8 (1 %)
	Other sarcoma	7 (1 %)
	Germ cell	1 (<0.5 %)
	Carcinoma	16 (2 %)
	Unspecified	2 (<0.5 %)
Bladder (C67)	Total	43
	Lymphoma	1 (2 %)
	Rhabdomyosarcoma	32 (74 %)
	Other sarcoma	6 (14 %)
	Carcinoma	3 (7 %)
	Paraganglioma	1 (2 %)
Orbit (C69.6)	Total	65
	Chloroma	3 (5 %)
	Lymphoma	5 (8 %)
	Rhabdomyosarcoma	56 (86 %)
	Other sarcoma	1 (2 %)
Other eye (C69.0-69.5,69.7-69.9)	Total	432
	Lymphoma	1 (<0.5 %)
	Medulloepithelioma	1 (<0.5 %)
	Retinoblastoma	417 (97 %)
	Melanoma	8 (2 %)
	Sarcoma	4 (1 %)
	Unspecified	1 (<0.5 %)
Thyroid (C73)	Total	124
	Lymphoma	3 (2 %)
	Differentiated carcinoma	91 (73 %)
	Medullary carcinoma	27 (22 %)
	Unspecified	3 (2 %)

Source: National Registry of Childhood Tumours

In addition to the diseases included in ICCC-3, children can also develop many types of non-malignant neoplasm. They are not generally notified to cancer registries, hence estimates of their incidence are difficult to obtain. A few categories, however, have been routinely ascertained by some specialist population-based registries, or have been the subject of special studies. The incidence of Langerhans cell histiocytosis (LCH) has recently been reported as around 6 per million in Germany [4] and Switzerland [5] and 4 per million in the UK and Ireland [6]. Mesoblastic nephroma accounted for 3 % of all renal tumours in North-west England [7], 4 % in Germany [4] and 6 % in the West Midlands of England [8], indicating an annual incidence of about 0.4 per million. In North-west England 61 % of all extracranial germ cell tumours were non-malignant [9]; they represented 48 % of germ cell tumours in the testes, 60 % in the ovaries and 69 % in other sites. In the West Midlands of England, all 49 extracranial germ cell tumours diagnosed in the first 3 months of life were benign teratomas, though four did recur as malignant tumours [10]; benign teratomas represented 29 % of all registered neoplasms in this age group, making them more numerous than neuroblastomas. Adrenocortical adenoma accounted for 29 % of adrenocortical tumours in North-west England [11], implying an annual incidence of about 0.1 per million. It is not always possible to distinguish morphologically between benign and malignant adrenocortical tumours, however, and they should perhaps be regarded as lying on a continuum of clinical behaviour [12]. Carcinoid tumours of the appendix had an annual incidence of 1.1 per million children in the West Midlands of England [13].

There are pronounced variations in the occurrence of different types of childhood cancer between ethnic groups and world regions. ALL is less common among less affluent populations, including not only those of developing countries but also African-Americans in the USA. The deficit is largely due to the attenuation or even the absence of the early childhood peak that has been characteristic of western industrialised countries since the mid-twentieth century. Lymphomas, on the other hand, tend to be more frequent in less developed countries, the most extreme example being the very high incidence of Burkitt lymphoma in a broad band across equatorial Africa and also in Papua New Guinea.

Increases in the incidence of various childhood cancers have been recorded in many countries during past decades [14–17]. Mostly the changes have been quite small, often no more than 1 % per year [14]. There have, however, been a few examples of much larger increases. Where population screening for neuroblastoma in infancy was offered either as a service or in the context of a scientific study, there was a dramatic increase in incidence resulting from detection of additional cases that would otherwise never have presented clinically [18–20]. The very large increase in childhood Kaposi sarcoma in some sub-Saharan African countries is linked to the AIDS epidemic, through immunosuppression consequent on HIV infection allowing HHV-8 viral load to increase uncontrollably [21]. The equally spectacular rise in thyroid cancer among children in regions most severely contaminated with radioactive fallout from Chernobyl was certainly due in part to radiation exposure, though intensive screening also contributed [22]. Incidence has fallen to lower levels among children who were born after the Chernobyl accident [23].

Increases in the incidence of CNS tumours, especially low-grade gliomas, are consistent with improved detection following the introduction of computed tomography (CT) and magnetic resonance imaging [17, 24]. It is difficult to apportion the relative contributions of improved detection

and diagnosis, improved registration and genuine increases in risk to the rather small increases in incidence of most other childhood cancers [16, 17].

Aetiology

Despite intensive research over several decades, very little is known about the causes of most childhood cancers. Some of the most well established risk factors are genetic in nature. An increasingly long list of hereditary syndromes, mostly associated with identified single gene defects, carry a raised risk of specific childhood cancers [25–27]. Germline mutations or deletions of RB1 give rise to heritable retinoblastoma. Children with neurofibromatosis 1 have an increased risk of gliomas, soft-tissue sarcomas and juvenile myelomonocytic leukaemia. Germline mutations of TP53 carry a raised risk of various cancers including soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, brain tumours and leukaemia, as well as pre-menopausal breast cancer; Li-Fraumeni syndrome is the resulting aggregation of specific combinations of these cancers within a family. An especially wide range of genetic disorders, both heritable and sporadic, is associated with Wilms tumour, including Beckwith-Wiedemann, Denys-Drash, WAGR, and Simpson-Golabi-Behmel syndromes [28]. Constitutional chromosomal abnormalities are implicated in about 1 % of all childhood cancers [29]. The most important is Down syndrome, which carries a greatly raised risk of leukaemia and almost certainly an increased risk of germ cell tumours, though the total excess of cancer is reduced by an apparent protective effect against several other types of solid tumours [30]. Risks associated with other, usually isolated, congenital abnormalities will be discussed towards the end of this section.

In 1991 it was estimated that genetic conditions were responsible for about 3 % of all childhood cancer [31]. That figure will now be higher, not least because the 1991 estimate did not include Li-Fraumeni syndrome, but the proportion attributable to known genetic disorders is probably still under 5 % in most populations. The main exception must be North African populations with high frequencies of the recessive DNA repair disorder xeroderma pigmentosum (XP), which carries a 1000 fold increased risk of skin cancer among children and adolescents [32]. In a series of 900 childhood cancers other than leukaemia from the National Cancer Institute in Tunisia, 8 % were skin carcinomas associated with XP [33].

The largest study of parental age as a risk factor for childhood cancer found positive linear trends in risk with maternal age for several diagnostic groups but there was little evidence of any effect of paternal age after adjustment for maternal age [34]. It was not possible to determine the mechanisms whereby cancer risk increased with mother's age, but it seemed likely to involve germline mutations.

An enormous number of exogenous or environmental exposures have been investigated as possible risk factors for childhood cancer [35, 36]. The only ones to which more than a handful of cases can be attributed worldwide are ionising radiation and certain infectious agents.

The relationship between *in utero* radiation exposure from obstetric x-rays and subsequent cancer in the child was established almost half a century ago [37]. At that time as many as 1 in 20 cases of childhood cancer may have been attributable to obstetric irradiation but the proportion nowadays must be much lower since ultrasound has largely supplanted x-rays. The use of x-rays to treat certain benign conditions produced an increased risk of cancer but this practice is also obsolete and therefore responsible for virtually no new cases of childhood cancer. A large national study of cancer following CT scans before the age of 22 years found that a cumulative dose of 50 mGy might almost triple the risk of leukaemia and cumulative dose of 60 mGy might triple the risk of a CNS tumour [38]. Radiotherapy treatment for childhood cancer is itself carcinogenic but the numbers of subsequent malignancies occurring within childhood are relatively small. Large numbers of thyroid carcinomas occurred among children in the areas of Ukraine, Belarus and Russia most heavily exposed to radioactive iodine as a result of the Chernobyl nuclear power station explosion in 1986 but there is little evidence of increased risk in less severely contaminated regions [39]. It has been estimated that around 15 % of childhood leukaemia in Britain may be attributable to natural background ionising radiation [40].

Ultraviolet (UV) radiation from the sun causes malignant melanoma and skin carcinomas, mainly in adults. The excess of skin cancers in children with XP results from UV exposure of a highly susceptible group. The possibility of carcinogenic effects of electromagnetic fields arising from electric power cables has caused public concern for more than two decades. A moderately raised risk of leukaemia has consistently been found for the highest exposure levels experienced by fewer than 1 in 20 children in industrialised countries but the reasons for this are unclear [41–45]. There is little evidence for an association between magnetic field exposure and childhood brain tumours [44, 46, 47].

Several specific infections are known to increase the risk of cancer. Among children worldwide, the types of cancer with the largest numbers of cases attributable to infectious agents are Burkitt lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma (all associated with Epstein-Barr virus, with malaria as a cofactor for Burkitt lymphoma in the region of highest incidence), hepatocellular carcinoma (hepatitis B) and Kaposi sarcoma (HHV-8) [48]. The introduction of universal vaccination against hepatitis B has been followed by reductions of around 70 % in the occurrence of childhood hepatocellular carcinoma in Taiwan and South Korea [49, 50].

Many epidemiological studies support the suggestion that infection is involved in the aetiology of some childhood leukaemias [51]. Most of these studies are relevant to either or both of two hypotheses. Kinlen's hypothesis that leukaemia is a rare response to a specific, but unidentified infection is supported by the finding of increased incidence in many situations of population mixing which could have led to impaired herd immunity [52]. Greaves's hypothesis that common ALL can arise as an abnormal response to infectious challenge, especially in children with weaker immunity, is supported by studies showing a protective effect of breast feeding and early daycare attendance [53–55].

Some medical treatments are undoubtedly carcinogenic. The excess risk from radiotherapy has already been mentioned. Some chemotherapeutic drugs used to treat cancer produce an increased risk of subsequent cancers but relatively few of these occur in childhood. Children who receive a solid organ transplant are especially vulnerable to neoplasms, of which post-transplant lymphoproliferative disorder and skin carcinomas are the most frequent [56]. Daughters of women who took diethylstilboestrol (DES) in pregnancy had an increased risk of clear cell carcinoma of the vagina or cervix [57] but most of these tumours occurred in early adulthood and DES ceased to be used more than 30 years ago. Many studies have found associations between exposure to other medical treatments *in utero* or postnatally and various childhood cancers but there has been little consistency between reports.

With the increasing use of assisted reproductive technology (ART), there has been a succession of anecdotal reports of cancer in children born following ART. Combined data from studies up to 2005 of children born after ART failed to reveal any significant increase in the risk of cancer [58, 59], but the expected numbers of cancers were relatively small and follow-up was short for children born after some types of ART. A more recent study in Sweden found a significantly increased odds ratio of 1.34 for cancer (excluding LCH) in children born after in vitro fertilization, but there were fewer than 50 cases of cancer of all types combined [60]. In the same study there were 6 cases of LCH compared with 1.0 expected [60]. No other study has reported an association of LCH with ART.

A wide range of other exogenous exposures to the child, to the mother antenatally or to the father preconceptionally, have been suggested as contributing to the aetiology of childhood cancer. Mostly the evidence comes from a small number of studies or is inconsistent between studies [61, 62].

Malformations and other physical characteristics associated with certain childhood cancers could be markers for underlying genetic or environmental causes. In large population-based studies, 3–4 % of children with malignant solid tumours also had a congenital anomaly, in many cases not as part of any recognised syndrome [63, 64]. The overall relative risk is about 3 for all anomalies [65] , and about 1.5 for non-chromosomal anomalies [64]. Such occurrences could result from an unknown genetic defect or, as seems more likely, for example, in the association of hernia with Ewing sarcoma, have a common environmental cause [66].

High birth weight has been associated with raised risk of several types of childhood cancer, notably leukaemia [67, 68], CNS tumours [69], and neuroblastoma [70], perhaps resulting from increased growth rate *in utero*. By contrast, infants with very low birth weight have a greatly increased risk of hepatoblastoma which may be attributable to exposures in neonatal intensive care units but there is as yet no conclusive evidence [71]. Children who are twins have consistently been found to have a risk of cancer around 80 % of that in singleton children [72, 73]. The reasons for this are unknown but possible explanations include lower birth weight, earlier restriction of growth in twin pregnancies, and higher *in utero* death rates of embryos in which tumorogenesis is initiated shortly after conception [73]. Patients with osteosarcoma are significantly taller than the general population, indicating a role of accelerated long bone growth around puberty [74].

Survival

Table 2.3 shows actuarial 5-year survival rates for children in Great Britain with cancer diagnosed during 2003–2007 [75]. More than three quarters of children survived for 5 years, and the survival rate comfortably exceeded 80 % for several important diagnostic groups. Five-year survival rates above 75 % are seen in many other industrialised countries [76, 77]. Survival tends to be lower in less affluent countries of Eastern Europe [77], and lower still in developing countries [78]. The prognosis for many childhood cancers has improved dramatically over past decades. In Great Britain, 5-year survival of children diagnosed in 1971–1975 was 39 %, compared with 77 % for those diagnosed a quarter century later [75]. This means that the risk of death within 5 years from diagnosis was reduced by 63 %. Figures 2.1, 2.2 and 2.3 show that survival for all major diagnostic groups increased in Britain between 1983 and 1987 and 2003–2007, though the timing of the largest increases varied between diagnostic groups. Broadly similar trends have been observed in other industrialised countries [79–83].

The results quoted here are derived from cancer registry data and estimate survival rates at the population level. Survival data can also be found in countless publications from clinical trials and single or multi-institutional case series. Very often the results appear better than those from population based data, but they could well be unrepresentative of all cases in the population because of selective exclusion of those with a poor prognosis or not offered

Table 2.3 Five year survival of children in Great Britain with cancer diagnosed during 2003–2007

	Five-year survival (%)
All cancers	79
Leukaemia	86
ALL	90
AML	68
Lymphomas	89
Hodgkin	94
Non-Hodgkin (incl. Burkitt)	85
CNS tumours	71
Ependymoma	70
Astrocytoma	81
Embryonal	53
Other glioma	43
Craniopharyngioma	95
Neuroblastoma	63
Retinoblastoma	99
Renal tumours	84
Nephroblastoma (Wilms tumour)	90
Hepatic tumours	71
Hepatoblastoma	78
Bone tumours	64
Osteosarcoma	63
Ewing sarcoma family	63
Soft tissue sarcoma	68
Rhabdomyosarcoma	65
Germ cell and gonadal	92
CNS germ cell	89
Other extragonadal germ cell	87
Gonadal germ cell	99
Thyroid carcinoma	100
Malignant melanoma	91

Source: National Registry of Childhood Tumours [75]

most effective treatment. Increases in survival have, nevertheless, occurred concurrently with the development of paediatric oncology clinical trials groups and increased referral to specialist treatment centres in many countries. Several studies have found that survival was higher for children who were treated at large or specialist centres or entered in clinical trials [84, 85]. A recent national study in Britain found that for a wide range of childhood cancers changes in population-based survival between the eras of successive clinical trials paralleled those reported by the relevant trials [86].

Improved survival has resulted in increasing numbers of long-term survivors of childhood cancer. The cumulative risk of a second primary malignancy is about 3.6 % within 25 years of diagnosis [87] and about 5 % by the age of 40 years [88]. Many other aspects of the health of long-term survivors and their offspring are the subject of several large epidemiological studies [89–98].

Mortality

Population mortality rates from childhood cancer in western countries have fallen dramatically since the mid twentieth century, in line with the moderate increase in incidence and very marked improvements in outcome. Table 2.4 shows estimated age standardised mortality rates for childhood cancer by world region in 2008 [99]. In wealthy industrialised countries, mortality was typically around 20–30 per million. It was considerably higher in Eastern Europe, reflecting the lower survival rates still obtained in that region. Results for other world regions are harder to interpret because of incompleteness and inaccuracy in the data for many countries [100].

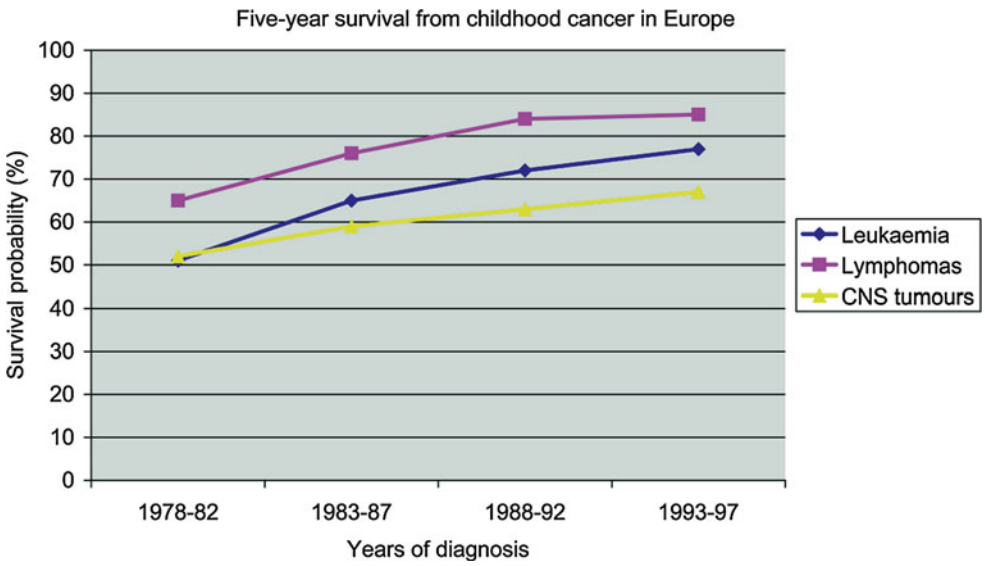

Fig. 2.1 Five year survival of children in Great Britain with leukaemias, lymphomas and CNS tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

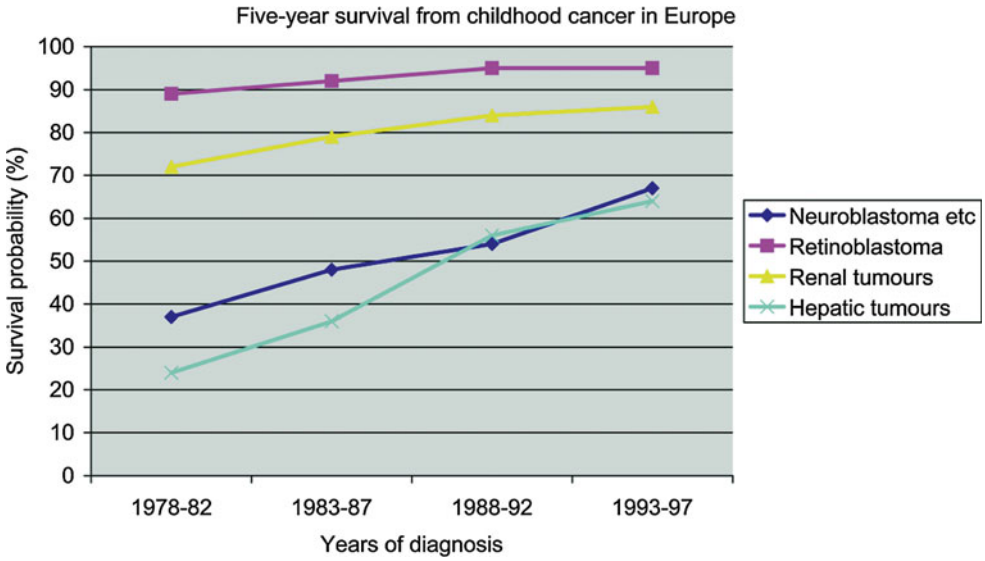

Fig. 2.2 Five year survival of children in Great Britain with neuroblastoma and other peripheral nervous cell tumours, retinoblastoma, renal tumours and hepatic tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

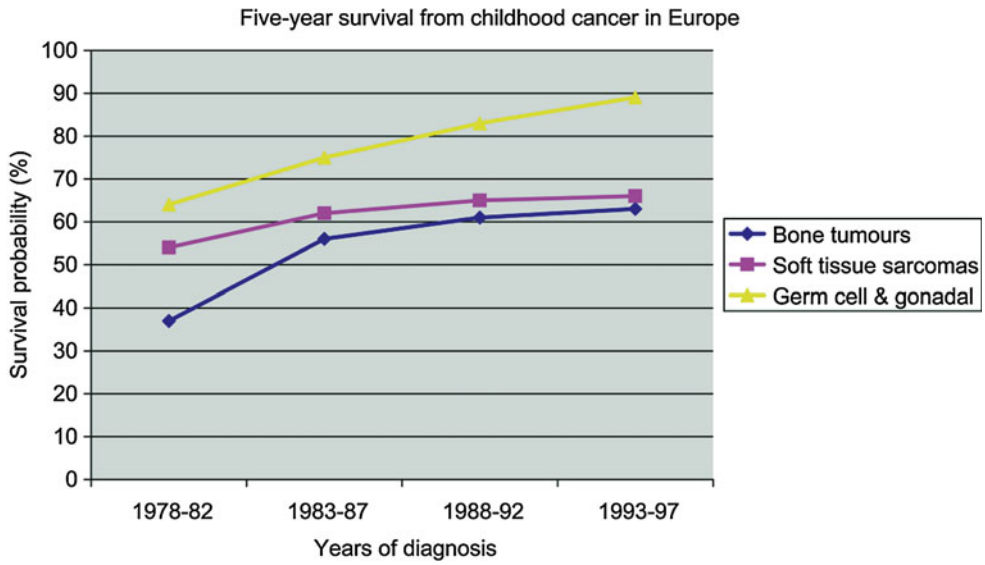

Fig. 2.3 Five year survival of children in Great Britain with bone tumours, soft tissue sarcomas and germ cell and gonadal tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

Overall, and for cancers other than those of the brain and nervous system, mortality rates tended to be highest in developing countries, reflecting their generally lower survival rates. Mortality from cancers of the brain and nervous system showed a different pattern with low rates in developing countries outside the Americas and Western Asia; since survival is lower in these countries, the lower mortality must be a result of under-recording and lower incidence.

Table 2.4 Estimated age-standardised mortality rates per million for cancer at age 0–14 years, 2008, by world region

	Total	Leukaemia	Lymphoma	Brain/nervous system	Renal
Northern Africa	78	19	17	9	9
Sub-Saharan Africa	68	8	21	2	8
USA/Canada	24	7	1	7	1
Central America	63	32	5	9	1
South America	46	19	3	9	2
Western Asia	77	29	16	10	5
India	37	13	4	5	1
Other South and Central Asia	59	20	9	6	3
China	46	25	2	10	1
Japan	19	7	1	5	<1
South-Eastern Asia	70	34	6	8	3
Nordic Countries	28	10	1	9	1
British Isles	27	7	1	9	1
Former USSR in Europe	41	12	2	12	2
Other Eastern Europe	36	12	3	12	1
Western Europe	21	6	1	9	1
Southern Europe	30	10	1	9	1
Australia/New Zealand	25	8	<1	10	1

Source: GLOBOCAN 2008 [99]

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