

### Introduction

The term 'childhood cancer', that is, cancer diagnosed before the age of 15, includes a wide range of illnesses that are generally unlike adult cancers. Many types of cancer that occur in children are hardly ever seen in adults; conversely, the cancers most frequently seen in adults in developed countries – carcinomas of the lung, female breast, prostate and large bowel – are all extremely rare among children. For adults, cancer incidence data can be classified largely in terms of the site of the disease; for children the cell type (histology) also needs to be taken into account. Childhood cancer rates are usually presented as rates per million rather than per 100,000 as for adults, because cancer is much less common in children than in adults.

In industrialised countries, about a third of all childhood cancers are leukaemias, a quarter are brain and spinal tumours, and about a tenth are lymphomas. **Figure One** shows the average annual numbers of new cases of childhood cancer in Britain (1989-98) in each of the 12 main groups of the International Classification of Childhood Cancer<sup>1</sup> (ICCC), based essentially on the primary site of the disease. The **Appendix** gives registration rates in more detail, using a simplified version of the histology-based ICCC subgroups.<sup>2</sup>

### Incidence

Around 1,500 new cases of childhood cancer are diagnosed each year in the UK, about 20% more in boys than in girls (**Table One**).<sup>2,3</sup>

The risk for an individual child in Britain of being diagnosed with cancer before the age of 15 is about 1 in 500. This is made up of risks of about 1 in 1600 for leukaemia, 1 in 2200 for a brain or spinal tumour and 1 in 1100 for all other cancers combined. Different types of childhood cancer have widely varying distributions of age at diagnosis, illustrated by age-specific incidence curves in **Figure Two** (overleaf).<sup>2</sup>

### Leukaemias

The proportions of the leukaemia subtypes seen in children are completely different from those seen in adults. By far the most common type in childhood is acute lymphoblastic leukaemia (ALL). In Britain this makes up about four-fifths of childhood leukaemias and thus a quarter of all childhood cancers. The age-specific incidence curve for ALL in Britain has a clear peak between the ages of one and six, with the highest rates at ages two and three. This is typical for an affluent Western population; the peak is less marked in less developed countries. ALL is about 30% more frequent in boys than in girls. Acute non-lymphocytic leukaemia, consisting in children almost entirely of acute myeloid leukaemia (AML), accounts for only about 15% of childhood leukaemias, and chronic myeloid leukaemia for less than 4%. AML is about 20% more frequent in boys than in girls.

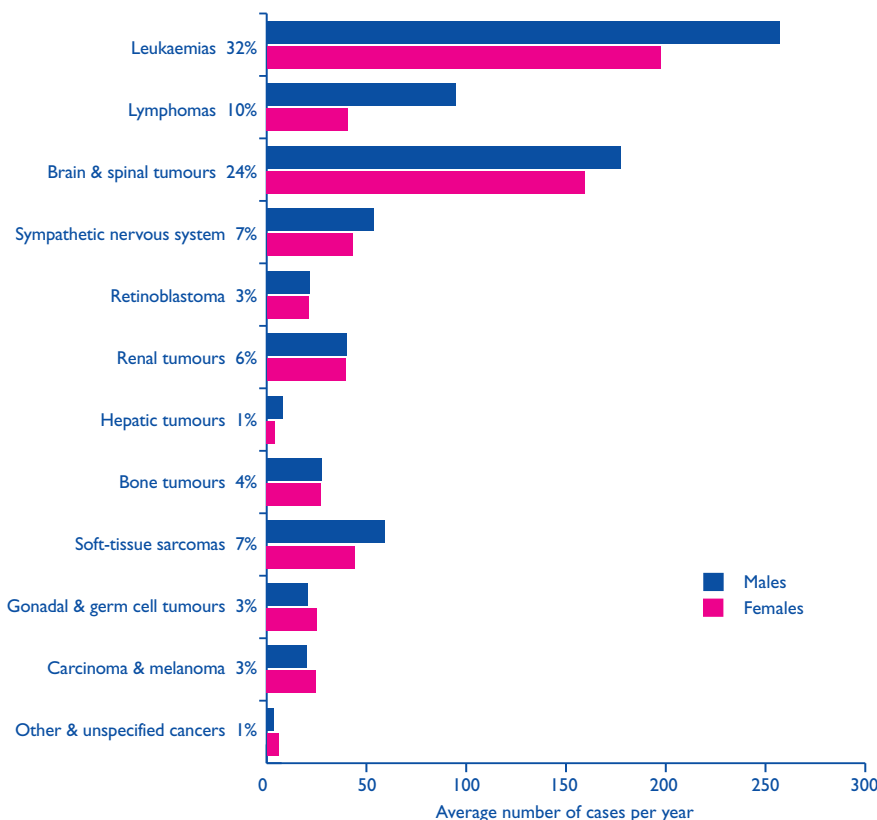
### Lymphomas

Lymphomas are more than twice as common in boys as in girls, and very rarely occur before the age of about two. There are two main groups: Hodgkin's disease and non-Hodgkin lymphomas (NHL). The incidence of Hodgkin's disease increases steadily with age. The incidence of NHL hardly changes between the ages of three and fourteen.

### Brain and spinal tumours

About three quarters of this large and varied group can be classified as either astrocytoma (two fifths of the group), primitive neuroectodermal tumour (PNET) (a fifth) or ependymoma (a tenth). The most common type of PNET is medulloblastoma, which belongs to the group of embryonal tumours

**Figure One:** Annual average number of cases by diagnostic group and sex, ages 0-14 Great Britain 1989-98



**Table One:** Annual average numbers of cases of childhood cancer registered in the UK, 1994-98 (averages are rounded to nearest whole number)

	Males	Females	Total
England & Wales	731	601	1,331
Scotland	69	56	125
Northern Ireland	32	25	58
UK	832	682	1,514

(see below). Astrocytoma is equally frequent in boys and girls, whereas PNET is 60% more common in boys than in girls.

### Embryonal tumours

This broad group of childhood tumours crosses over the standard classification, because embryonal tumours occur in many different parts of the body. They include medulloblastoma in the brain, neuroblastoma in the sympathetic nervous system, retinoblastoma in the eye, Wilms' tumour (nephroblastoma) in the kidney, hepatoblastoma in the liver and embryonal rhabdomyosarcoma in soft tissue. They are characterised by the proliferation of tissue that is normally seen only in the developing embryo. They are generally very rare after childhood, and occur most commonly in the first few years of life. Several types of embryonal tumour have a peak of incidence in the first year of life. Some types are occasionally found to be present at birth.

### Bone tumours

The two main types of bone tumour that occur in childhood – osteosarcoma and Ewing's sarcoma of bone – are very rare in children under five years, increase in incidence with age and peak in adolescence, probably because this is the peak time of bone growth. Unlike most childhood cancers, osteosarcoma, the larger category of bone tumours, is slightly more common in girls than in boys between the ages of seven and thirteen, perhaps reflecting the earlier age of puberty in girls.

### Soft tissue sarcomas

More than half of soft tissue sarcomas in childhood are classified as rhabdomyosarcomas, which derive from primitive striated muscle cells. Most childhood rhabdomyosarcomas are of the embryonal type, with the highest incidence in the first few years of life. Among the 'other specified' category (see **Appendix**), about half the tumours are of the Ewing's sarcoma family and the remainder are a wide variety of rarer types.

### Germ cell and gonadal tumours

Although male and female gonadal germ cell tumours are grouped together in the standard classification, their constituent subtypes are different and they have entirely different age distributions.

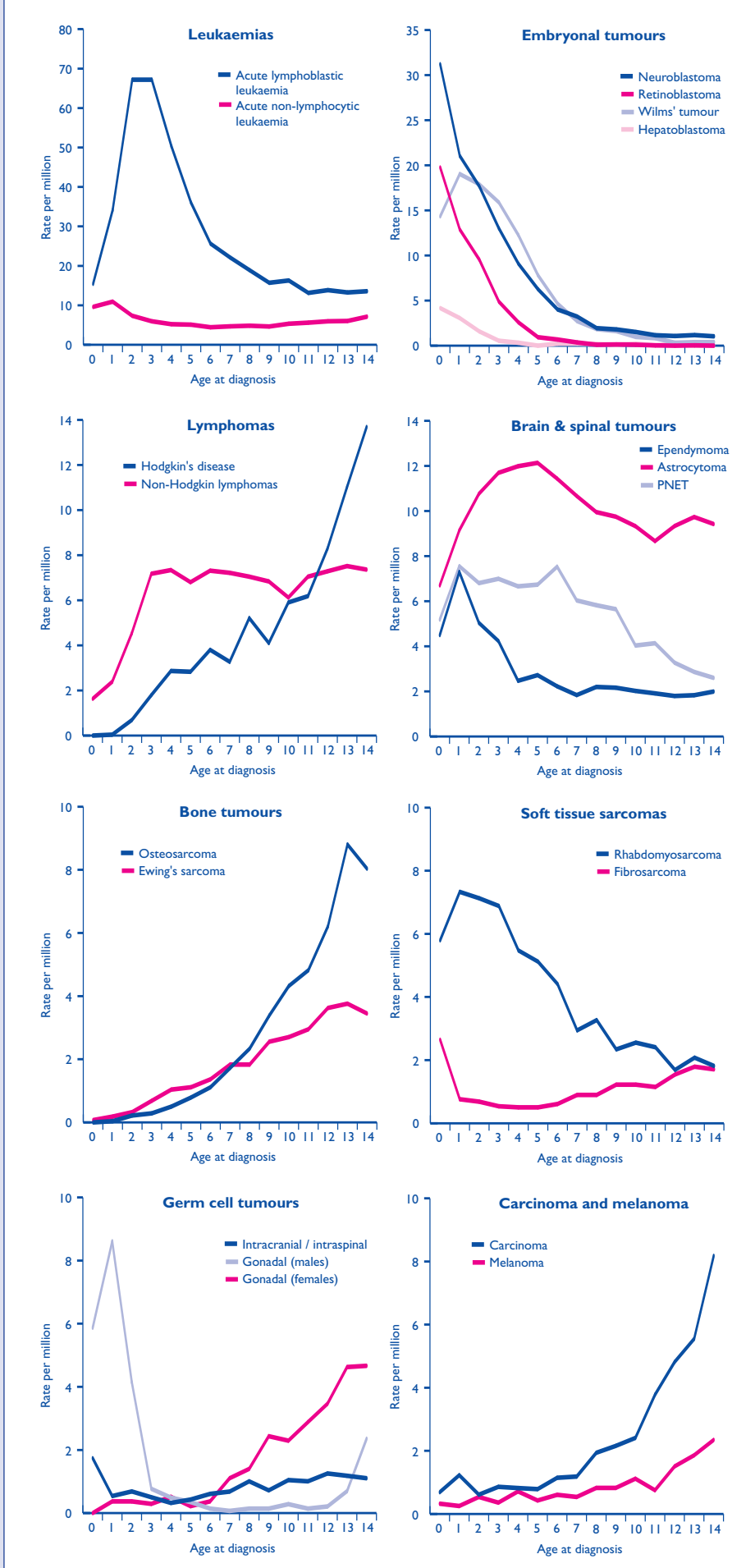
### Carcinoma and melanoma

Most of these cancers are very rare in early childhood, increase in incidence steadily with age, and are much more common in adults. Unusually for childhood cancers, melanoma and several types of carcinoma are more common in girls than in boys.

### Geographical variation in incidence

There was little variation in age standardised rates between the English Government Office Regions, Wales and Scotland in the period 1971-97.<sup>2</sup>

**Figure Two:** Age-specific incidence rates per million, selected childhood cancers, Great Britain 1962-97



There seems to have been some variation in incidence rates between large cancer registries in various European countries within the period 1993-97 (Figure Three), although this may be partly explained by chance. In eastern Europe, the incidence of ALL was somewhat lower than in the west and the peak in early childhood was less marked. Recent results from the Czech Republic indicate that the incidence of ALL among children aged 1-4 years in eastern Europe has been increasing with improved socio-economic conditions, resulting in a more marked early childhood peak.<sup>5</sup> The high rate for cancers other than leukaemias and brain and spinal tumours in Belarus is accounted for by a sharp increase in thyroid cancer following the explosion at Chernobyl in 1986.

**Survival**

The great majority of five-year survivors of childhood cancer may be regarded as cured, with only a 10% risk of death from recurrent tumour or a treatment-related cause during the ensuing ten years.<sup>6,7,8</sup> About 75% of all childhood cancer patients in Britain currently survive for at least five years after diagnosis (Figure Four).<sup>2</sup> Patients with retinoblastoma, gonadal germ cell tumours and Hodgkin's disease do particularly well, with five-year survival rates of about 95%. Only one of the common diagnostic groups, primitive neuroectodermal tumours, had a recent five-year survival rate of less than 50%.

Survival in western Europe is similar to that in the USA<sup>9</sup> but survival in eastern Europe tends to be lower.<sup>10</sup>

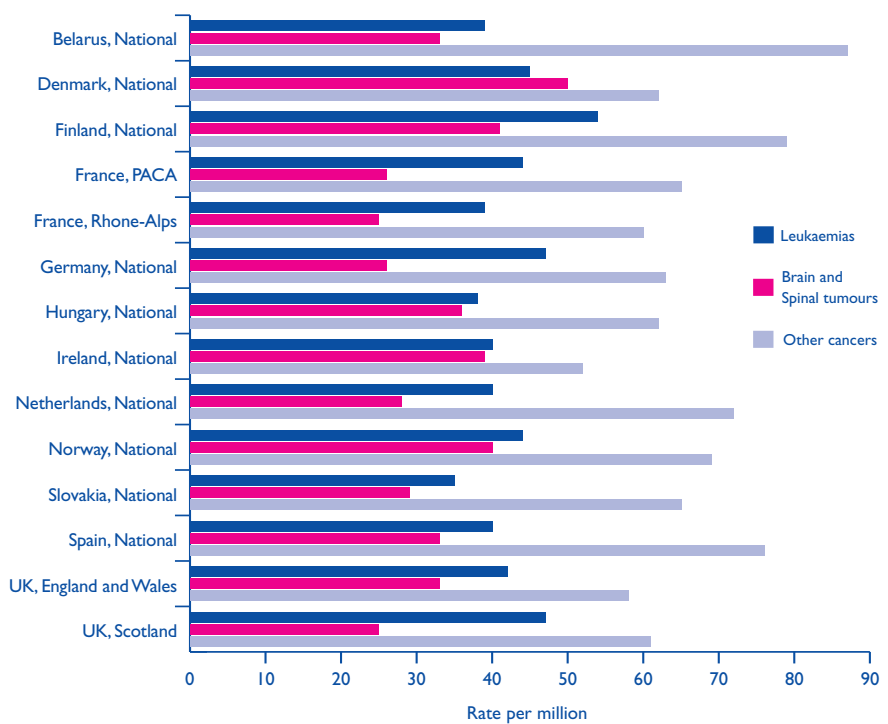
**Mortality**

About 300 deaths per year from cancer in children aged under 15 were recorded on death certificates in the UK in the three-year period 2000-02. There were about 33% more deaths in boys than in girls (Table Two).<sup>11-13</sup>

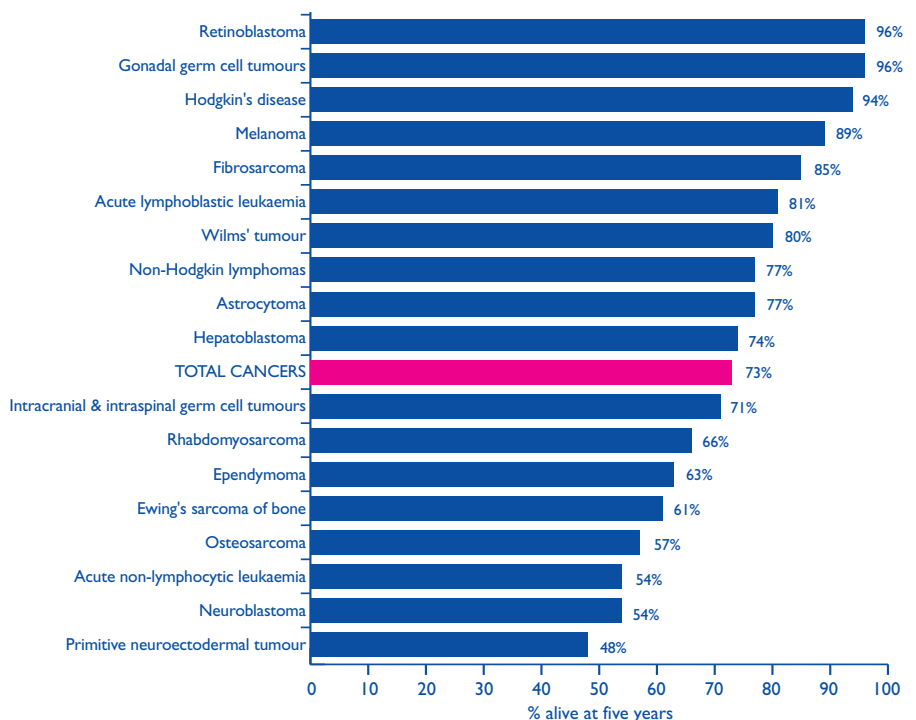
Although cancer in children is relatively rare and survival rates are now good, death in childhood after infancy from other causes in the UK is now so rare that cancer is still an important cause of death in older children (Table Three).<sup>11</sup> Nearly a quarter of all deaths in the age group 5 to 14 in England and Wales in 2000-02 were recorded as being caused by cancer. In this age group cancer was the most common cause of death in girls, and the second most common (after accidents) in boys. In the age group 1-4 years, cancer caused nearly 15% of deaths.

In childhood cancer patients in Britain, the diagnostic group with the largest number of deaths under the age of 15 during the period 1997-2001 was leukaemias (32%), followed by brain and spinal tumours (30%) (Figure Five overleaf).<sup>2</sup> In nearly all the main diagnostic groups, deaths were more common in boys than in girls. There were about 80 deaths per

**Figure Three:** European age standardised incidence rates for cancers diagnosed at ages 0-14, large European cancer registries, incidence periods within 1993-97



**Figure Four:** Percentage of patients still alive five years after diagnosis, childhood cancers, Great Britain, 1992-96



**Table Two:** Annual average number of deaths from cancer before age 15, UK 2000-2002 (averages are rounded to nearest whole number)

	Males	Females	Total
England & Wales	148	119	267
Scotland	16	9	25
Northern Ireland	8	2	9
UK	172	129	301

year under the age of 15 in ALL patients, and about 35 in neuroblastoma patients (see Appendix).

### Trends

#### Trends in incidence and mortality

Since 1962 there have been gradual changes in childhood cancer registration and death rates in Britain (Figure Six).<sup>2</sup> Registration rates increased by 0.8% per year on average between 1962 and 1998, a total increase of 35%. As a result of improvements in survival (see below), death rates fell by 2.6% per year on average between 1962 and 2001, a reduction of more than half.

Improvements in the efficiency of systems for the diagnosis and registration of cancer may have contributed to the increase in registration rates. In the past some children may have been recorded as dying of non-cancer causes that were in fact related to an underlying undiagnosed cancer. It has also probably become easier to track and record the diagnosis of new patients as treatment has become more centralised. The amount of real change, if any, in the underlying incidence rates is not clear.

There were differences in registration trends between diagnostic groups. For example, from 1963 to 1997 the average annual increase in the age standardised registration rate was 0.6% per year for leukaemias and lymphomas, 1.0% for brain and spinal tumours, and 1.4% for bone and soft tissue sarcomas combined (Figure Seven).<sup>2</sup>

#### Trends in survival

The considerable reduction in childhood cancer mortality in Britain since the 1960s in spite of stable or increasing incidence rates reflects dramatic improvements in survival. Only about 25% of children with cancer diagnosed in Britain during the decade 1962-1971 survived for more than five years. Nearly 75% of those diagnosed during 1992-96 survived for more than five years (Figure Eight overleaf).<sup>2</sup>

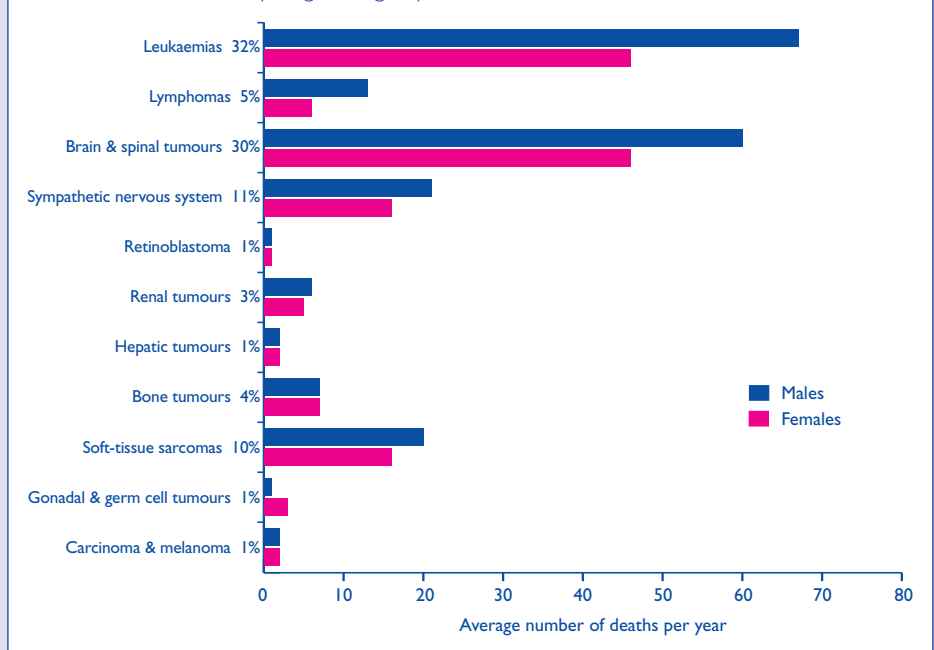
The initial large improvements followed the introduction of combination chemotherapy in the late 1960s and early 1970s. Since then, clinical trials have contributed to the testing and rapid adoption of refinements in diagnosis and treatment, and the gradual centralisation of specialised care has ensured that the great majority of patients in Britain receive the best treatment currently available.

The most impressive improvement is in the most frequent type of childhood cancer, ALL: the proportion of patients in Britain who were still alive five years after diagnosis has increased from 12% of those diagnosed during the decade 1962-71 to more than 80% of those

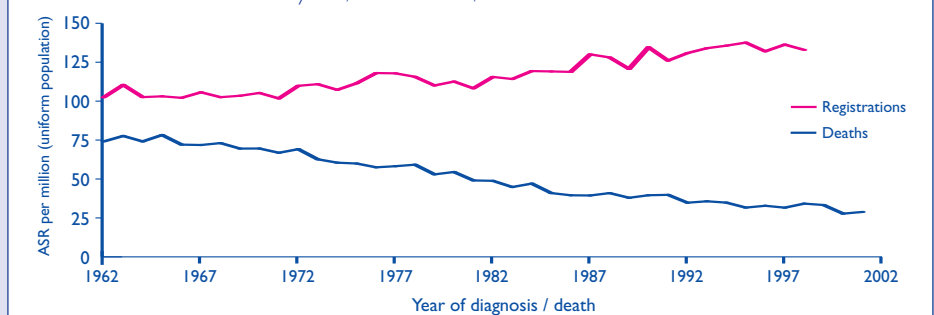
**Table Three:** Main causes of child mortality, ages 1-14, by sex and age group, England and Wales, 2000-2002

Cause of death	Males		Females	
	% of total 1-4 years	% of total 5-14 years	% of total 1-4 years	% of total 5-14 years
Infections	11	3	7	5
Cancers	14	23	13	24
Nervous system and sense organs	14	15	12	14
Circulatory system	4	5	7	6
Respiratory system	9	5	8	8
Congenital anomalies	14	7	15	9
Accidents	17	30	16	19
Other	17	12	20	16
<b>Total number of deaths</b>	<b>968</b>	<b>1,444</b>	<b>752</b>	<b>1,049</b>

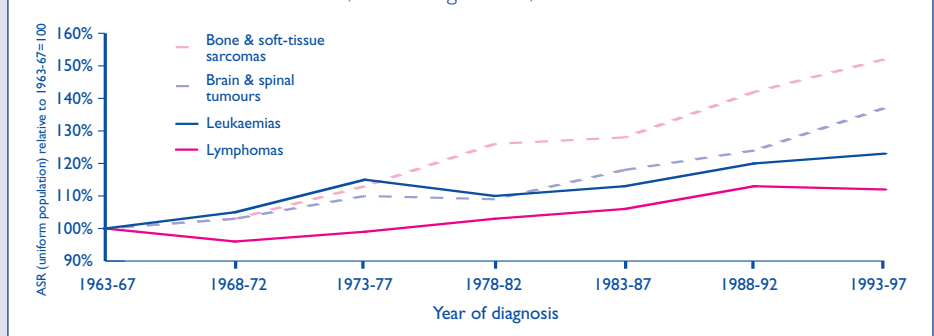
**Figure Five:** Annual average number of deaths in children aged under 15 previously diagnosed with cancer; by diagnostic group and sex, Great Britain 1997-2001



**Figure Six:** Trends in age standardised (uniform population<sup>a</sup>) cancer registration and death rates, children and 0-14 years, Great Britain, 1962-1998/2001



**Figure Seven:** Registration rates for successive calendar periods, expressed as proportions of the rate for 1963-67, children aged 0-14, Great Britain 1963-97



<sup>a</sup> The uniform population assumes a constant birth rate and no net migration or deaths. Therefore equal weight is given to each year of age.

diagnosed in 1992-96. There have been striking improvements in almost all the other common diagnostic groups too; for example from 21% to over 75% in non-Hodgkin lymphomas, from 17% to more than 50% in neuroblastoma, and from 35% to more than 80% in Wilms' tumour (Figure Nine).<sup>2</sup>

In the Nordic countries subsequent mortality among five year survivors of childhood cancer diagnosed in the 1980s was over a third less than for those diagnosed in the 1960s and 1970s and the impressive gains in survival were not offset by any increase in treatment related mortality.<sup>7</sup>

*Trends in prevalence*

The improvement in survival rates, combined with stable or increasing incidence, has resulted in there being a large increase in the number of people who have been affected by childhood cancer and are still alive (Figure Ten).<sup>2</sup> At the end of 1961 there were probably fewer than 2,500 people of all ages living in Britain who at some time in the past had been diagnosed with childhood cancer. At the end of the year 2000 there were more than 26,000.

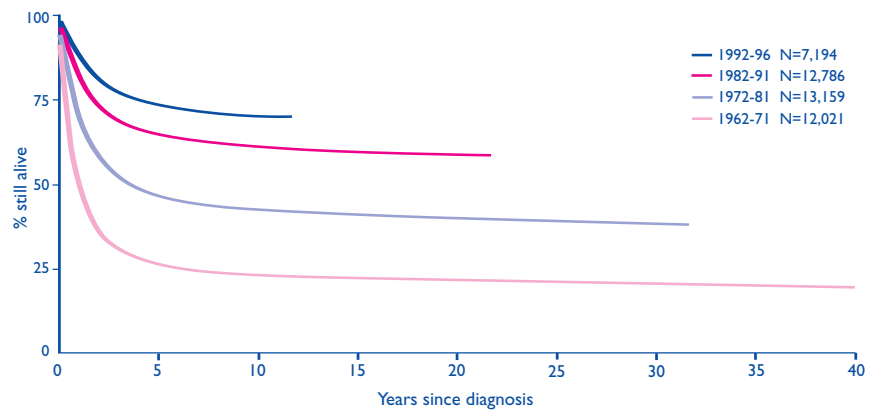
**Risk factors**

Very little is known about the causes of most childhood cancers. For many diagnostic groups, the occurrence of the highest incidence at an early age and the cell type of origin strongly suggest that causative factors operate before birth and possibly even before conception. Chromosome translocations involved in many childhood leukaemias have been shown to originate before birth on the basis of studies of identical twins who both have the same type of leukaemia and by detection in neonatal blood spots.<sup>14, 15</sup>

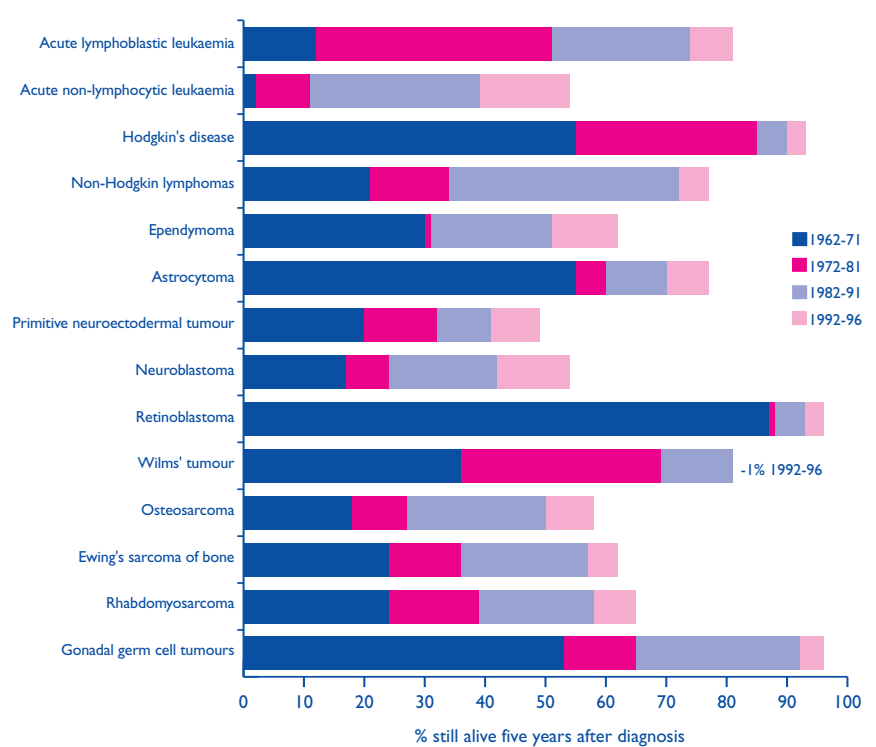
Putative risk factors can be somewhat arbitrarily divided into environmental and genetic. Some birth characteristics could be markers for environmental or genetic risk, while some predisposing genetic abnormalities may have environmental origins and gene-environment interactions could well be important in the induction of malignant disease. Aetiological studies have often been concerned with exposures occurring during the mother's pregnancy, although pre-conception and postnatal factors have also been investigated.

Numerous domestic and other environmental exposures have been linked with childhood cancers. Interpretation is limited by the wide range of cancers studied, variation in the timing of exposure ranging from before conception to during the child's lifetime, the small number of exposed subjects in many studies and lack of information on specific substances. There is only limited consistency between the numerous studies of most

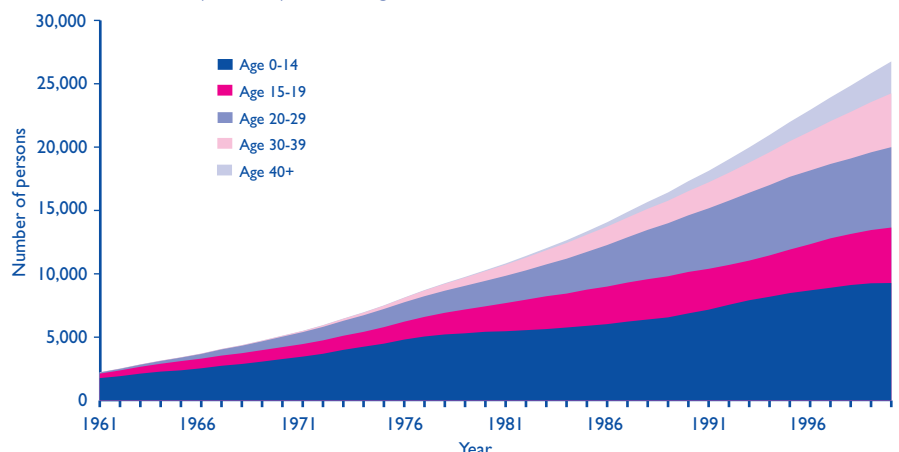
**Figure Eight:** Survival of childhood cancer patients diagnosed in successive periods, Great Britain, 1962-96



**Figure Nine:** Five year survival rates for childhood cancers, showing cumulative improvements for patients diagnosed in successive periods, Great Britain, 1962-96



**Figure Ten:** Number of people in the specified age group alive at the end of each calendar year who had previously had a diagnosis of childhood cancer, Great Britain, 1961-2000



suspected risk factors for childhood cancer. Many studies, particularly those involving rather few cases, have been inconclusive. It is impossible to say for any specific study whether this is because there was no excess risk attributable to the factor in question or because the study was too small to detect it. This problem has led to an increased emphasis on large national or international studies such as the UK Childhood Cancer Study (UKCCS)<sup>16</sup> and the SEARCH collaborative study of childhood brain tumours<sup>17</sup>, and also to the analysis of pooled data from several pre-existing studies.

#### *Ionising radiation*

The increased risk of childhood cancer associated with antenatal obstetric irradiation was discovered over 40 years ago.<sup>18</sup> Since then, obstetric x-ray examination in pregnancy has been largely superseded by ultrasound examination. There is no evidence that ultrasound causes childhood cancer:

Environmental ionising radiation could be a cause of childhood cancer, especially leukaemia, although there is little evidence of any increase in leukaemia incidence attributable to fallout from the Chernobyl nuclear power plant accident in 1986,<sup>19</sup> and no evidence of a general increase in the incidence of childhood leukaemia around nuclear power stations.<sup>20,21</sup> The possibility that paternal preconception exposure to ionising radiation could lead to excesses of leukaemia in the vicinity of certain nuclear installations in Britain was supported by a small case-control study in the area around the Sellafield nuclear reprocessing plant.<sup>22</sup>

A review of the evidence from two large, overlapping studies of UK radiation workers employed at Sellafield and elsewhere, however, concluded that there was unlikely to be any simple causal relationship.<sup>23,24,25</sup>

It has been suggested that inhalation of radon, a natural radioactive gas that is present everywhere but in varying concentrations, may result in irradiation of the bone marrow and thereby increase the risk of leukaemia, but the UKCCS and earlier studies have shown that it accounts for few, if any, cases of childhood leukaemia.<sup>26,27</sup> Similarly, the UKCCS found no evidence to link higher levels of natural background gamma radiation with childhood cancer.<sup>28</sup>

#### *Non-ionising radiation*

There has been much public concern about the possible health effects of electromagnetic fields arising from electrical sources such as power lines and domestic wiring. Analyses of pooled data from case-control studies have shown no evidence for raised risk of childhood leukaemia with exposure to power frequency (50-60Hz) fields at the levels experienced by over 95% of children in

western countries.<sup>29,30</sup> A doubling of risk has been found at the very highest exposure levels but the reasons for this are unknown and it remains possible that it is partly due to bias or confounding factors. Excessive exposure to the ultraviolet component of sunlight increases the risk of skin cancer, predominantly in adults, and this might explain the relatively high incidence of childhood melanoma in Australia and New Zealand.<sup>31</sup> There is no conclusive evidence that other non-ionising radiation can cause cancer.

#### *Infections*

Exposure to infection, especially by viruses, certainly plays a part in the aetiology of some childhood cancers. Worldwide, the most important examples numerically are Burkitt's lymphoma, Hodgkin's disease and nasopharyngeal carcinoma (all associated with Epstein-Barr virus), liver carcinoma (hepatitis B) and Kaposi's sarcoma (HIV and HHV8)<sup>32</sup> but together these associations account for a very small proportion of childhood cancer in western countries. The early childhood peak of leukaemia incidence in affluent western populations and the persistently lower incidence in socio-economically disadvantaged groups and less developed countries generally has suggested that ALL could be associated with an infectious agent linked to public hygiene conditions.<sup>33</sup> Two hypotheses suggest that abnormal response to infection has a key role in the development of leukaemia. Under the 'delayed infection' hypothesis, ALL can result from lack of exposure to infection and consequent failure of immune system modulation during infancy.<sup>34</sup> This model is supported by epidemiological studies showing that children with ALL tend to have had relatively few infections in the first months of life, fewer immunisations in infancy and a shorter period of breastfeeding, and are more likely to be first born or only children.<sup>35</sup> Under the 'impaired herd immunity' hypothesis, leukaemia is a rare response to a common infection in particularly susceptible children. This is supported by a series of studies in which high levels of population mixing, often but not always as a result of migration, were accompanied by increased incidence of leukaemia.<sup>36</sup>

#### *Drugs and medication*

There have been reports of the possible carcinogenic effects of many different drugs taken by mothers during pregnancy. The only one firmly established as a transplacental carcinogen is diethylstilboestrol (DES), a hormone which in some countries used to be given to pregnant women with threatened abortion. Exposure to DES *in utero* caused clear cell adenocarcinoma of the vagina or cervix mostly in young women, though a few cases were observed in girls aged under 15<sup>37</sup>; however, as its use was discontinued about 30 years ago, and there is no direct evidence for a transgenerational effect, it is unlikely that

further childhood cancers attributable to DES will be seen.

Much controversy and public concern was generated by a study that found that intramuscular vitamin K given to infants to prevent vitamin K deficiency bleeding was associated with a doubling of the risk of childhood cancer.<sup>38</sup> A pooled analysis of six case-control studies, including the one which gave rise to the controversy, found little evidence for raised risk of leukaemia or other cancer among children recorded as having received intramuscular vitamin K, though interpretation was rendered difficult by the poor quality of much of the vitamin K data.<sup>39</sup>

#### *Parental occupation*

Many associations have been reported between parental occupation and childhood cancer. When 48 studies were reviewed, there was rather little consistency between them, though a few biologically plausible associations found in more than one study would merit further investigation.<sup>40</sup> The UKCCS was typical of more recent studies in finding no strong evidence to link parental occupational exposures with an increased risk of childhood cancer.<sup>41</sup>

#### *Smoking*

The offspring of mothers who smoke during pregnancy have an increased risk of adverse effects, including low birth weight and perinatal mortality, but the evidence on parental smoking and cancer in children has been somewhat inconclusive. In a meta-analysis of more than 30 studies there was a 10% increase in risk of all neoplasms with maternal smoking during pregnancy but no evidence for an increased risk of any specific cancer.<sup>42</sup> In the UKCCS there was no significant evidence that parental smoking is a risk factor for any of the main types of childhood cancer.<sup>43</sup>

#### *Parental age*

The risk of ALL increases with increasing age of either parent, despite the tendency for risk to be lower with higher birth order.<sup>35</sup> This is true even after exclusion of children with Down syndrome, which is more common among the offspring of older mothers and carries an increased risk of childhood leukaemia (see **Genetic factors** section below).

*Second malignancies* – see **Follow up** section

#### **Genetic factors in the occurrence of childhood cancer**

*Evidence for the genetic origin of some childhood cancers*

A small proportion of childhood cancer cases (less than 5%) have an obvious family history. The most important example of a childhood cancer for which there are familial aggregations of cases is retinoblastoma; about 40% of the cases of this tumour are heritable. Such

aggregations also occur, though to a much smaller extent, for Wilms' tumour. The pattern of inheritance for the heritable form of retinoblastoma is relatively simple and is well understood; that for Wilms' tumour is more complicated. In addition, certain childhood cancers are associated with rare inherited conditions such as neurofibromatosis, tuberous sclerosis, Fanconi's anaemia, ataxia telangiectasia, and xeroderma pigmentosum, though the actual number of cases of childhood cancer in which these conditions occur is small. In these and other rare conditions more than one child, and also other family members, may have an associated cancer. Familial aggregations, involving both child and adult cases, also occur in the 'Li-Fraumeni syndrome' which is associated with mutations in the *TP53* gene. There are also associations with various chromosome abnormalities; the most important of these is Down syndrome which occurs in a small percentage of cases of childhood leukaemia: the risk of acute leukaemia among children with Down syndrome is between 10 and 30 times as high as that for other children.<sup>44</sup> The striking ethnic distribution of Ewing's sarcoma, which is almost absent from black populations both in Africa and the USA, suggests that genetic influences are important in the aetiology of this tumour. It is clear from these and other observations that the causes of some childhood cancers are partly genetic. For a detailed discussion of genetic factors in the epidemiology of childhood cancers.<sup>45</sup>

#### *Retinoblastoma*

There are about 45 cases of retinoblastoma in Great Britain each year, and about 20 of these are of the type that can be inherited. The pattern of inheritance is that of an autosomal dominant condition with a high degree of penetrance, though the disease is actually the result of mutation in the tumour suppressor gene *RBI*. Retinoblastoma may be either bilateral, that is, affecting both eyes, or unilateral. All bilateral cases are heritable; a few unilateral cases are known to be heritable because a related family member also has retinoblastoma. Nearly half the children of a parent with heritable retinoblastoma will themselves be affected. For children of cases not known to be heritable the estimated risk is very low, around 1%. Likewise if there is no previous family history the risks for siblings of unilateral and bilateral cases are respectively about 1% and 2%.<sup>46</sup> Using modern molecular genetics and pre-natal screening more definite advice about the risk can often be obtained.

#### *Risk to siblings*

When a child is diagnosed with cancer it is likely that questions will be raised concerning the risks to the siblings of the affected child. Sometimes a second sibling will be affected by cancer purely as a result of chance; in other cases such an occurrence may reflect an

increased risk in particular families. In the general population the chance of a child developing cancer is about 1 in 500. In the absence of a relevant clinically observed genetic condition in the child, or a family history of such a disease, or a 'cancer syndrome', and excluding twins, the risks for siblings of affected children are about double what would be expected by chance, giving a risk of 1 in 250; this is the risk that such siblings will develop cancer between birth and age 15.<sup>47</sup> It should be emphasised that the risk is less than 1 in 250 for siblings who are already part way through childhood when the affected child is diagnosed, and have therefore passed part of the period when they would be at risk. The risks are considerably higher if the affected child is a member of a family affected by one of the genetic conditions referred to above. The existence of such a condition may actually be recognised as a result of a second sibling being affected. In fact, many familial aggregations of childhood cancer can, sometimes retrospectively, be recognised as forming part of a known genetic condition or syndrome.<sup>48</sup> But, for genetic counselling, risk estimates sometimes have to be made before such knowledge becomes available for a particular family, and in this situation the estimated doubling of the population risk for the siblings of affected cases is appropriate.

#### *Risk to twins*

For a child with cancer who has a twin the situation is different. For dizygotic (non-identical) twins of affected children, although there is little direct evidence, it can be assumed that the risks are the same as they would be for other siblings in the same family. For monozygous (identical) twins there is a high risk for the co-twins of children with leukaemia, especially those diagnosed in the first year of life.<sup>14</sup> In this case the risk for co-twins appears to be usually, if not always, attributable to the transfer of leukaemic cells from one twin to the other during pregnancy. An identical twin of a child with retinoblastoma also has a high risk of developing retinoblastoma, though the actual level of risk will vary a great deal, depending on whether or not there is a family history and whether the tumour is bilateral or unilateral. For other childhood cancers there is insufficient information to make any estimate of risk, but it seems likely that identical co-twins of affected children will have a high risk of developing the same disease.

#### *Risk for offspring of children with cancer in the absence of known genetic disease in the family*

Now that large numbers of children survive their cancer and go on to have children of their own, there is inevitably concern about whether their offspring will have an increased risk of cancer. In general, after the exclusion of hereditary cancer syndromes, there is no evidence of a significantly raised risk of cancer among the offspring of survivors.<sup>49</sup>

### Symptoms and diagnosis

The symptoms of childhood cancer depend upon the site of the tumour. Leukaemias can cause anaemia, frequent infections or abnormal bleeding and bruising. Very rarely a solid 'lump' of leukaemia may be the first sign of the disease. Most other tumours produce symptoms related to their position and will be brought to medical attention either because a lump is felt or because the tumour or tumours are impairing normal functioning of one or more organs.

With the exception of some brain tumours, tissue from the tumour is required to make a definitive diagnosis. (Some brain tumours are in positions that would make taking a biopsy so dangerous that it is considered best to rely on scans to make the diagnosis.) This tissue is essential to confirm the type and subtype of the disease and thus determine the optimal treatment. Often additional blood tests, bone marrow examinations, X-rays and body scans of various types (including CT – computed tomography or MRI – magnetic resonance imaging) are required to determine the extent of the disease.

#### *Screening*

Screening for childhood cancer has been adopted as standard only for families with high risk of retinoblastoma for whom there is proven benefit.<sup>50</sup> Population screening of infants for neuroblastoma began in parts of Japan in 1973 and was offered nationally from 1985, and has been evaluated in trials in North America, Germany and England. It has not been adopted as routine because it was not shown to have any beneficial effect on the mortality from this disease, and has now been discontinued in Japan. This was because many neuroblastomas, especially in very young children, regress spontaneously and the screening programmes detected large numbers of such cases which would otherwise have resolved without treatment; the invariable result of screening was a large increase in incidence but little effect on mortality rates.<sup>51-54</sup>

### Treatment

The treatment of childhood cancer in the UK and Ireland is usually co-ordinated, if not carried out, by one of the 22 United Kingdom Children's Cancer Study Group centres. Much of this treatment is based on the results of previous clinical trials or part of current national or international clinical trials.<sup>55</sup> For several types of cancer, survival has been found to be higher among children treated in clinical trials or treated at specialist centres.<sup>56,57</sup>

Surgery, chemotherapy, radiotherapy and combinations of any or all of these form the mainstay of treatment for most childhood cancers. Stem cell transplantation is becoming more widely used for some conditions, and other new therapies are being tried.

**Follow-up***Long-term clinical follow-up*

There is currently some debate about which survivors of childhood cancer should continue to be followed up indefinitely.<sup>58</sup> Individuals who have had surgery only, or a small amount of chemotherapy with drugs that have no known long-term effects, may need no follow-up. These include, for example, some Wilms' tumour patients treated with surgery alone, who need only to be made aware of the fact that one kidney has been removed and the reason.

Children who have had intensive, prolonged multi-agent chemotherapy or radiotherapy should be followed up by clinicians who have experience in diagnosing and treating problems which occur after such treatment. Many of the individuals who are going to have ongoing problems are obvious by five years from the end of treatment – a time at which many clinicians choose to transfer patients to a long term follow-up clinic. There are also groups of patients who are recognised as being at increased risk of running into specific problems. For example, high doses of anthracyclines can damage cardiac muscle, and either radiotherapy to certain sites or high-dose therapy combined with stem-cell treatment may lead to a reduction in fertility.<sup>59</sup>

*Second malignancies*

All children who have had one cancer are at slightly higher risk of having a second malignant neoplasm. Overall, the risk of developing a second cancer within 25 years is about 4%.<sup>60-62</sup> The risk will be higher if they are from a family with increased risk of

cancer<sup>63</sup> and there is a particularly high risk of developing a second cancer for survivors of the heritable form of retinoblastoma.<sup>64</sup> The risk is also higher for survivors who have had radiotherapy or certain drugs as part of their treatment.<sup>63,65</sup> Among survivors who have had radiotherapy the risk increases with radiation dose.<sup>63</sup>

Survivors of ALL treated after 1983 in the USA showed a cumulative incidence of any second neoplasm of 1.2% at 10 years (a 7.2-fold increase). The risk of second neoplasm increased with radiation dose.<sup>66</sup> The commonest second tumours after ALL are in the central nervous system and the risk is greatest for those treated at younger ages. A study looking especially at the risk after total body irradiation (as used in bone marrow/stem cell transplantation) found rates of new solid cancers 8.3 times higher than expected among those who survived ten or more years.<sup>67</sup>

The evidence for chemotherapeutic agents as risk factors for the development of subsequent neoplasms is less clear-cut.

Epipodophyllotoxins, alkylating agents and antimetabolites have all been implicated. The risk of secondary AML or myelodysplasia in children treated with epipodophyllotoxins is 2-4% at six years<sup>68</sup>; in some studies the risk increased with cumulative dose<sup>69,70</sup>, while in others it was related to schedule and dose intensity.<sup>68,71</sup>

*Epidemiological studies of late effects*

Other, less serious late effects have until recently been less well documented, but large epidemiological studies of long-term survivors

of childhood cancer in the UK and North America will in due course yield a comprehensive picture of the health and quality of life of the rapidly increasing number of adult survivors.<sup>58,72</sup>

**Future**

Although great strides have been made in the treatment of many types of childhood malignancy, in others there is room for more improvement. For example there are currently international clinical trials of new drugs and new ways of giving radiotherapy in childhood brain tumours.

For diseases such as ALL, where the cure rate is as high as 80%, the relatively small proportion of children who do not respond adequately to treatment continue to be a challenge to the clinicians. The more recent trials aim to give those individuals at greater risk of relapse more intensive and prolonged therapy. There are also continued efforts to improve the safe delivery of multi-agent chemotherapy and bone marrow transplantation.

For details on current clinical trials in childhood cancer see [www.ukccsg.org.uk](http://www.ukccsg.org.uk)

The improvements in the treatment of childhood cancer since the 1960s have meant that for children diagnosed with cancer today the chance of cure is high. The challenges for the future are to minimise the long term effects, both physical and psychological, of these cures, while striving for further increases in survival.

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The statistics for childhood cancer incidence, survival and mortality in Britain presented in this chapter were extracted from the National Registry of Childhood Tumours (NRCT). The NRCT holds records of cancers diagnosed under the age of 15 in England, Wales and Scotland since 1962. It is maintained by the Childhood Cancer Research Group, within the Department of Paediatrics of Oxford University. It combines data from the national and regional cancer registries, the Office for National Statistics and the General Register Office for Scotland, with information supplied by clinical trials organisations and, particularly, the paediatric oncologists and data managers of the United Kingdom Children's Cancer Study Group. Without their help it would have been impossible to produce results for incidence and survival at this level of detail.

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**Appendix:** Average annual number of cases, annual registration rates and sex ratios, Great Britain 1989-98; average annual number of deaths, annual death rates and sex ratios, Great Britain 1997-2001.

	Average annual number of cases			Annual registration rate per million for age group*					Sex ratio			Average annual number of deaths					Annual death rate per million for age group*					Sex ratio				
	14-16	0	1-4	0	1-4	5-9	10-14	0-14	M/F	0	1-4	5-9	10-14	0-14	M/F	0	1-4	5-9	10-14	0-14	M/F	0	1-4	5-9	10-14	0-14
<b>Total cancers</b>	1416	1813	181.8	104.5	106.9	131.1	131.1	1.2	284	349	33.7	29.9	32.4	1.3												
<b>Leukaemias</b>	454	360	75.8	33.5	24.1	41.8	1.3	114	80	10.1	10.4	11.3	10.4	1.5												
Acute lymphoblastic leukaemia	368	179	66.1	28.2	16.6	33.8	1.3	81	3.3	6.3	8.5	7.9	7.4	1.5												
Acute non-lymphocytic leukaemia	69	136	7.7	4.3	5.9	6.4	1.2	24	3.3	2.4	1.6	2.5	2.2	1.1												
Chronic myeloid leukaemia	11	1.8	1.4	0.6	1.0	1.0	2.0	8	0.6	1.2	0.2	0.8	0.7	2.5												
Other & unspecified leukaemia	7	2.7	0.6	0.4	0.6	0.7	0.9	2	0.9	0.2	0.1	0.1	0.2	-												
<b>Lymphomas</b>	136	14	7.9	12.2	19.4	12.7	2.3	19	0.6	1.3	2.1	1.9	1.7	2.2												
Hodgkin's disease	53	0.0	1.3	4.0	10.1	5.0	1.9	1	0.0	0.0	0.1	0.2	0.1	-												
Non-Hodgkin lymphomas	79	1.1	6.4	8.0	8.9	7.4	2.6	17	0.3	1.2	1.9	1.7	1.6	2.3												
Other & unspecified lymphomas	3	0.3	0.3	0.3	0.4	0.3	5.8	1	0.3	0.1	0.1	0.0	0.1	-												
<b>Brain &amp; spinal</b>	337	338	34.1	33.5	26.1	31.2	1.1	106	8.6	10.6	11.5	7.7	9.8	1.3												
Ependymoma	35	6.7	5.3	2.2	1.8	3.2	1.3	14	1.5	2.2	1.2	0.7	1.3	2.4												
Astrocytoma	145	11.0	14.7	14.5	12.0	13.5	0.9	30	2.4	1.6	3.1	3.4	2.7	1.1												
Primitive neuroectodermal tumour	67	7.4	7.4	7.5	3.6	6.2	1.6	28	2.1	3.9	2.6	1.7	2.6	1.7												
Other glioma	40	2.1	3.1	4.8	3.5	3.7	0.9	23	0.0	1.5	3.7	1.4	2.1	0.9												
Other specified brain and spinal tumours	33	2.9	2.1	3.1	3.7	3.0	1.2	5	0.0	0.6	0.4	0.3	0.4	0.6												
Unspecified brain and spinal tumours	17	3.7	1.4	1.3	1.5	1.6	1.2	6	2.7	0.7	0.4	0.3	0.6	1.3												
<b>Sympathetic nervous system</b>	97	36.5	17.7	3.9	1.1	8.8	1.2	37	2.4	6.4	4.0	0.8	3.5	1.3												
Neuroblastoma	91	36.1	17.4	3.2	0.6	8.3	1.3	37	2.4	6.4	4.0	0.8	3.5	1.3												
Other sympathetic nervous system tumours	6	0.4	0.4	0.7	0.5	0.5	1.2	0	0.0	0.0	0.1	0.0	0.0	-												
<b>Retinoblastoma</b>	43	23.5	7.9	0.6	0.1	3.9	1.0	2	0.0	0.4	0.1	0.1	0.2	-												
<b>Renal tumours</b>	80	15.7	17.4	3.7	1.1	7.3	1.0	10	0.9	1.7	0.9	0.4	1.0	1.3												
Wilms' tumour	78	15.4	17.4	3.5	0.7	7.1	1.0	10	0.9	1.7	0.9	0.4	0.9	1.2												
Renal carcinoma	2	0.0	0.0	0.1	0.4	0.2	1.1	0	0.0	0.0	0.0	0.1	0.0	-												
Other & unspecified renal tumours	0	0.3	0.0	0.1	0.0	0.0	-	0	0.0	0.0	0.0	0.0	0.0	-												
<b>Hepatic tumours</b>	12	4.8	1.9	0.4	0.4	1.1	1.8	4	0.6	0.6	0.1	0.5	0.4	1.2												
Hepatoblastoma	10	4.8	1.8	0.2	0.2	0.9	2.0	2	0.6	0.4	0.1	0.1	0.2	-												
Hepatic carcinoma	2	0.0	0.1	0.2	0.3	0.2	1.2	2	0.0	0.2	0.0	0.4	0.2	-												
<b>Bone tumours</b>	55	0.7	0.8	3.9	10.9	5.2	1.0	14	0.0	0.1	1.0	2.6	1.2	0.9												
Osteosarcoma	29	0.0	0.2	2.3	6.0	2.8	1.0	9	0.0	0.0	0.7	1.6	0.8	0.9												
Ewing's sarcoma of bone	21	0.1	0.6	1.5	4.1	2.0	1.1	4	0.0	0.1	0.3	0.8	0.4	1.6												
Other & unspecified malignant bone tumours	4	0.5	0.0	0.2	0.8	0.4	0.8	1	0.0	0.0	0.0	0.2	0.1	-												
<b>Soft tissue sarcoma</b>	104	15.7	11.5	7.7	8.8	9.6	1.3	36	5.0	3.1	3.2	3.2	3.3	1.2												
Rhabdomyosarcoma	56	6.6	8.8	4.5	2.5	5.1	1.6	17	0.6	1.6	1.8	1.6	1.6	1.4												
Fibrosarcoma	12	2.3	0.4	0.8	1.8	1.1	1.0	2	0.0	0.1	0.2	0.3	0.2	-												
Other specified soft-tissue sarcomas	29	5.1	2.0	2.0	3.7	2.7	1.1	12	2.7	1.2	0.9	1.1	1.2	0.6												
Unspecified soft-tissue sarcomas	7	1.6	0.4	0.4	0.8	0.6	1.4	4	1.8	0.1	0.3	0.2	0.3	2.6												
<b>Gonadal &amp; germ cell tumours</b>	46	10.8	4.4	1.8	5.2	4.3	0.8	4	1.5	0.5	0.1	0.3	0.4	0.5												
Intracranial/intraspinal germ cell tumours	14	1.6	0.7	0.9	2.1	1.3	1.2	2	0.6	0.2	0.1	0.1	0.2	-												
Other extra-gonadal germ cell tumours	11	5.5	2.0	0.1	0.2	1.0	0.4	2	0.9	0.3	0.0	0.1	0.2	-												
Gonadal germ cell tumours	20	3.6	1.8	0.8	2.6	1.8	1.0	0	0.0	0.0	0.0	0.1	0.0	-												
Other & unspecified gonadal tumours	1	0.1	0.0	0.1	0.3	0.1	-	0	0.0	0.0	0.0	0.1	0.0	-												
<b>Carcinomas &amp; melanoma</b>	45	0.7	1.3	2.6	9.0	4.3	0.8	5	0.6	0.1	0.3	0.8	0.4	0.9												
Adrenocortical carcinoma	2	0.0	0.3	0.1	0.1	0.2	0.3	1	0.0	0.1	0.1	0.1	0.1	-												
Thyroid carcinoma	6	0.0	0.1	0.4	1.4	0.6	0.6	0	0.0	0.0	0.0	0.0	0.0	-												
Nasopharyngeal carcinoma	2	0.0	0.0	0.1	0.6	0.2	3.6	0	0.0	0.0	0.0	0.1	0.0	-												
Malignant melanoma	16	0.7	0.6	1.1	2.8	1.5	0.7	1	0.6	0.1	0.1	0.2	0.1	-												
Skin carcinoma	6	0.0	0.1	0.4	1.3	0.6	1.0	0	0.0	0.0	0.0	0.0	0.0	-												
Other carcinoma	12	0.0	0.2	0.5	2.8	1.2	0.9	2	0.0	0.0	0.1	0.4	0.2	-												
<b>Other &amp; unspecified cancers</b>	9	1.8	1.0	0.6	0.8	0.9	0.6	1	0.3	0.1	0.0	0.3	0.1	-												

\* Rates for age group 0-14 are standardised to a uniform population

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