

Epidemiology of childhood cancer

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What is epidemiology?



Epidemiology is the study of the occurrence and outcome of disease at the population level. This may not sound too exciting, but epidemiology is the tool that provides (or attempts to provide) the answers to the most important and urgent questions that families and doctors ask when a child is diagnosed with cancer:

- Why has my child got this disease?
- Who else gets this disease?
- What is going to be the outcome?

From an epidemiological point of view, the study of childhood cancer presents a real challenge because it is such a rare disease. It can be very difficult to conduct studies of sufficient size to have enough statistical power to answer the questions posed of them in a reliable and robust way. Even missing one or two cases in some instances can bias results, leading the researcher towards an erroneous conclusion. Bias can go in either direction, suggesting a positive association or effect when none exists, or suggesting no relationship between two factors when the truth is that there may well be an association hidden under an unsatisfactory study design. Because the numbers of cases of cancer in children do tend to be small, especially when considering subgroups, such as particular forms of leukaemia or solid tumours, it is very important to be aware of the limitations of all epidemiological studies in this field, and to understand the importance of the 95% confidence interval in indicating uncertainty.

Uncertainty in epidemiology

Uncertainty is unavoidable in epidemiological investigation. Even in calculating something as apparently straightforward as an incidence rate (see Definitions  pp.17–19), which is the ratio of two numbers (the *numerator* being the number of cases observed in a given time period and the *denominator* being the population from which those cases were drawn), there are several potential sources of uncertainty. For example, in the numerator there is the potential for some cases to have been missed altogether and, for some cases, to be counted when, in fact, they are not truly cases of the disease of interest. This can happen for a number of reasons, including clerical coding error and misdiagnosis. So the number of cases identified in a population can be inflated or deflated. The number of cases arising from a given size of population will also vary from time to time and from place to place merely because of chance. The denominator is also uncertain, since in general the census is relied upon to inform about the 'population at risk', but since the census only happens every 10 years, in between censuses an educated guess is made as to what the population is. These uncertainties can have particularly big effects in childhood cancer, where numbers of cases are small and, in some instances, time periods and spatial units of interest are small too.

Much of epidemiological research is about to trying to find associations between past exposures and current disease leading to clues about disease causation. A much used study design for this is the case-control study (see Definitions  pp.17–19), where exposure history is constructed for a group with disease (*cases*) and compared with the exposure history of a group of similar, but disease free individuals (*controls*). The objective is to identify exposures which are associated with having the disease, and the measure of the magnitude of any such association is reported as the odds ratio (OR; see Definitions  pp.17–19). An OR of 1.3, for example, implies a 30% increase in risk of disease in those who had the exposure under study, and an OR of 2 indicates a doubling of risk. Uncertainty is even more of a problem in producing ORs than in producing incidence rate estimates. This is because measuring 'exposure' is always challenging. By definition, in a case-control study, the 'exposure' is in the past and this adds the potential for the introduction of error into the exposure estimate. A further complication is that cases and especially controls included in research studies may not be typical of all potential cases or all potential controls, and this can introduce bias into the study and, again, lead the researcher to the wrong conclusion. Case-control studies of the causes of childhood cancer have included investigation of factors, such as the role of maternal diet, exposures to agrochemicals, X-rays, paternal occupations, etc. In all of these cases, there is uncertainty and error in exposure estimates because of limitations in recording, measurement, or recall.

Confidence intervals

While the assessment of error in exposure estimates is generally not fully addressed in the majority of reports of epidemiological studies, we have a major tool to help us estimate the extent of uncertainty associated with rates or odds ratios – the 95% confidence interval (95% CI). All studies report a point estimate for rates or odds ratios, but not all studies should (nor do) carry the same weight – some studies are better than others, either because of their size (bigger is usually better) or the precision of their exposure assessments. The 95% CI for each estimate tells us the range of likely values that the point estimate could take, given the characteristics of the study. For example, two studies may have investigated the association between *in utero* X-ray exposure and risk of childhood cancer. Both produce the same OR, but one study has a much narrower confidence interval. Therefore, its effect estimate (OR) is more likely to be robust and reliable.

In epidemiology there is a move away from reporting the traditional statistical significance of a finding (e.g. $p = 0.05$) towards reporting the 95% CI of the effect estimate. This is because, for the reasons outlined above, the 95% CI, in addition, gives an indication of the robustness and reliability of the point estimate.

Who gets childhood cancer?

Disease groups

There are about 1400 new cases of childhood cancer in the United Kingdom each year. Around a third of childhood cancers are leukaemias, a quarter are brain tumours and the remainder comprise a number of increasingly rare diseases, including neuroblastoma, bone tumours, sarcomas, and other rare tumours (see Fig. 1.1).

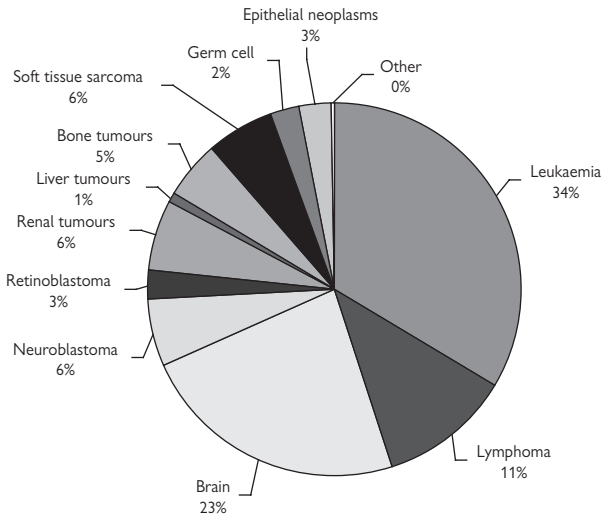


Fig. 1.1 Distribution of types of childhood cancer.

Leukaemias, lymphomas, brain tumours, and soft tissues sarcomas are themselves groups of distinct diseases, the constituents of which are shown in Fig. 1.2.

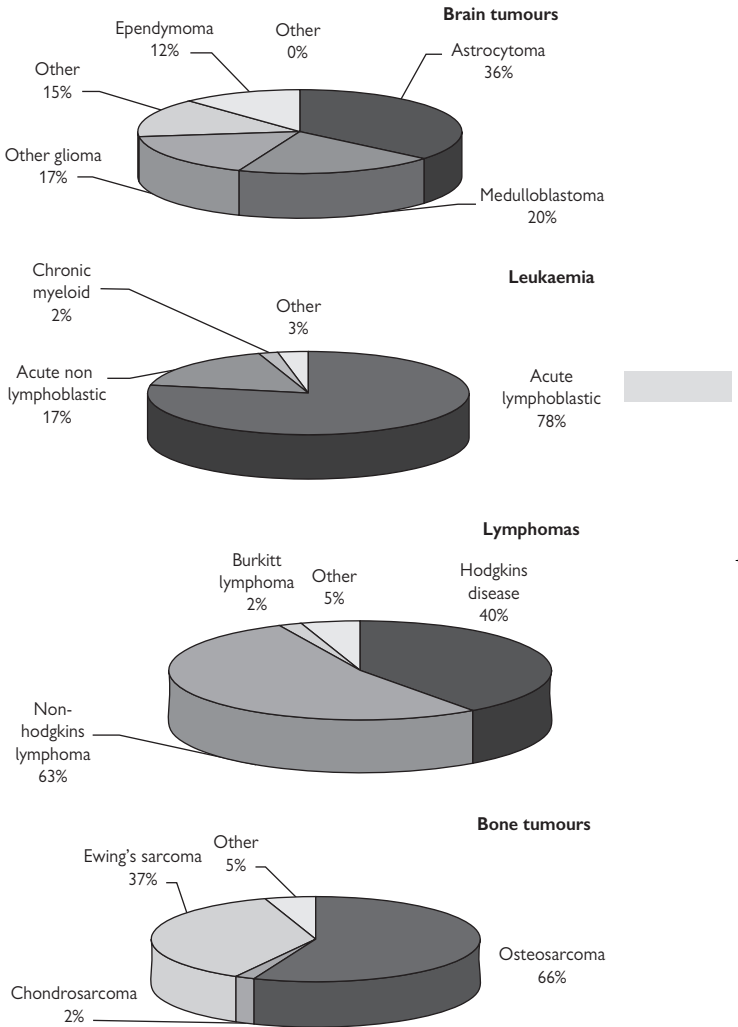


Fig. 1.2 Distribution of types of malignancy within the major subgroups of childhood cancer.

Incidence rates

Overall, childhood cancer is a rare disease and accounts for <1% of all cancer cases. Cancer affects 1 in 600 individuals by the age of 14 years and 1 in 300 by the age of 24. Boys are around 20% more likely to develop cancer than girls (see Fig. 1.3).

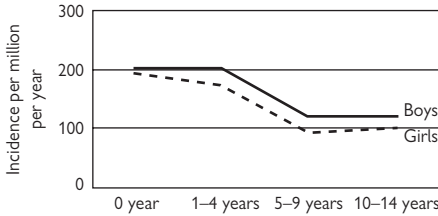


Fig. 1.3 Cancer incidence by age and sex (Europe).

Knowing the overall incidence of childhood cancer and its constituent parts is relevant to the ability to plan and develop the appropriate health and health-related services required to care for these children in both the short- and long-term.

Understanding changes in incidence over time and differences between different populations, e.g. between boys and girls, the affluent and the less affluent, and different populations (e.g. countries, people of different ethnicity) provides essential clues to the aetiology of disease, and in particular the balance between genetic factors vs. environmental and lifestyle factors in the causation of the disease.

The incidence of many childhood cancers, especially leukaemias, melanomas, and brain tumours has been increasing in most Western countries in recent decades (Table 1.1). This implies that environmental factors play a role in the aetiology of these diseases and that changes in environmental exposures result in changing patterns of disease. This does not preclude the potential of gene environment or epigenomic environment interactions to play a role in determining individual risk of cancer in the face of changing environmental risk.

Table 1.1 Temporal trends in childhood cancer rates in Europe 1970–1999

Malignancy	Annual Percentage Increase in Incidence Rate
Leukaemia	1.4%
Lymphoma	1.3%
Hodgkin disease	1.5%
Central nervous system (Eastern Europe)	2.5%
Central nervous system (Western Europe)	0.8%
Neuroblastoma	2.0%
Germ cell tumours	1.8%
Renal tumours	1.1%
Hepatic tumours	1.0%
Bone tumours	0.4%

What happens to children with cancer?

Survival

In the developed world the majority of children diagnosed with cancer will survive for at least 5 years and most of these will probably be cured.

There are big differences in survival for different cancers: death from retinoblastoma for example is uncommon with 5 year survival being in excess of 99% for this disease. Over 85% of children with leukaemia will be cured but for many of the solid tumours survival is lower; e.g. 5-year survival from brain tumours is around 75% and for bone tumours it is 72%. For each disease within the childhood cancer spectrum, there are characteristics of the child and disease at diagnosis, which allows identification of those in lower and higher risk groups, and therapy is tailored not only for each disease, but also for the various risk groups within each disease. Factors such as age, gender, and burden of disease at diagnosis, all influence response to treatment and, hence, whether an individual child is perceived as low or high risk for that particular disease.

Figure 1.4 shows the changes in survival over time for children with a number of different malignant diseases.

The surgical, chemotherapy, radiotherapy, and stem cell transplant regimens used in childhood cancer, and advances in supportive care have been responsible for the tremendous improvements in outcome over recent decades. However, all of these modes of treatment are toxic and cure has come at a cost, one of which is iatrogenic disease, which includes secondary cancer. Children treated with these therapies are at an average risk of a second malignancy at least four times that of the rest of the population. The implications of this are that, while it is important to reduce exposures wherever possible and to protect patients from their consequences, long-term follow-up and education of survivors is a necessary part of care of these patients (Long-term follow-up [pp.294–312](#)).

Survival for specific cancers has not only changed over time, but also varies between countries and, for many (but not all), is consistently poorer in the UK than elsewhere in mainland Europe and North America. The reasons for these differences are complex and may include differences in treatment delay (the interval between onset of symptoms and starting appropriate therapy), as well as differences in therapeutic approach.

Late effects of cancer therapy

The cure of cancer does not come without cost and there are many late effects of cancer therapy (Long-term follow-up [pp.294–312](#)). At least 60–70% of all cancer survivors have a long-term medical condition consequent to their cancer therapy and second malignancy is a major cause of death later than 5 years from diagnosis.

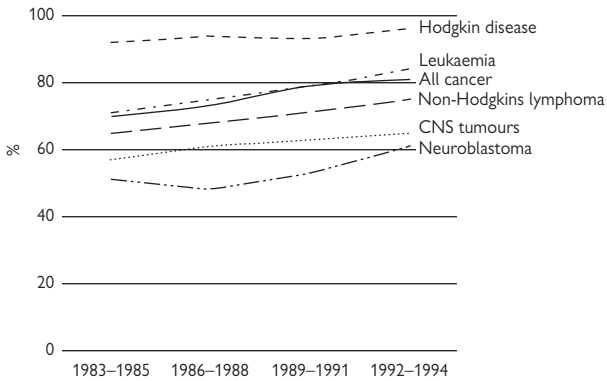


Fig. 1.4 Trends in 5-year survival in childhood cancer (Europe).

Causes of childhood cancer

Childhood cancer is a rare disease, affecting only 1 in 600 children by the age of 14 years. This is in dramatic contrast with adult cancer, the lifetime risk of which is 1 in 2 in men and 1 in 3 in women. Many of the causes of adult cancers are known and most involve long-term exposures over years or decades to exogenous agents, such as the 4000 or so carcinogenic or otherwise noxious constituents of tobacco smoke, high fat and low antioxidant diets, or endogenous agents, such as oestrogen. For children, the obvious observation is that they have not yet lived long enough to have had the opportunity to have been exposed to anything for years let alone decades. The pattern of cancers in children reflects this: carcinomas, which make up the majority of adult cancers, are rare in children, whereas two-thirds of cancers comprise leukaemia and brain tumours.

The causes of the majority of childhood cancers are unknown. With a few rare exceptions (such as bilateral retinoblastoma, which accounts for less than 1% of all childhood tumours, and some rare heritable conditions, such as Li Fraumeni syndrome), childhood cancer is not an inherited disease. Overall, the heritable component of childhood cancer is estimated to be around 2–3% at most. That said, the siblings of children with some malignancies, e.g. infantile acute lymphoblastic leukaemia, are at higher risk of developing malignancies, although the increase in risk is small. For children with some constitutional genetic conditions, e.g. Down syndrome and neurofibromatosis, the risk of cancer is increased, specifically Down syndrome confers a 150-fold increased risk of acute myeloid leukaemia (AML). Children with significant congenital anomalies are at higher risk of cancer than other children, e.g. there is an increased risk of Wilms' tumour in children born with Beckwith-Wiedemann syndrome, such that screening is recommended for children with this syndrome. This increased risk of malignant disease in children with congenital anomalies suggests a common cause to these conditions, and that the origins of many childhood cancers may lie in the period preceding birth. It is possible that peri-conceptual or gestational exposures may be important in affecting the genome, the epigenome or the proteome and, hence, increase susceptibility to cancer in childhood.

Although the potential time period for children to experience a carcinogenic exposure is short, because of the tremendous rate of growth and development during the post-conceptual period, there is potential for greatly increased vulnerability. In the transmigration from fertilized egg to adult human, there are some 42 sequential cell divisions, over 90% of which occur *in utero* and during the first months of life. This period of extensive DNA replication reflects a period of genomic sensitivity and certainly the carcinogenic effect of radiation exposure is greatly enhanced in the foetus and the child.

Leukaemia

Leukaemia, and in particular acute lymphoblastic leukaemia (ALL), has been the most studied childhood malignancy from an epidemiological/aetiological perspective. There are several reasons for this. First, leukaemia is the most common malignancy of childhood, which means that from an epidemiological point of view it is the easiest to study. Secondly, it has a striking age incidence pattern – peaking at the age of around 4–6 years and then declining rapidly. Thirdly, this age peak emerged in the developed world over a period of several decades during the twentieth century, and is continuing to emerge in the developing world, where it was previously absent. This changing epidemiology, with a growing number of cases, has increased awareness and concern about this disease. In addition, the observation in the 1980s of apparent clusters of childhood leukaemia led to intense interest in the possibility of an environmental factor, causing childhood leukaemia, and the search for this factor has been the object of a great deal of research. It should be noted that because many epidemiological studies were retrospective, relying on historical ascertainment of cases, they were not able to necessarily distinguish between the various subtypes of childhood leukaemia and some also included non-Hodgkin lymphoma. In general, however, the leukaemias in this age group are predominantly

acute lymphoblastic leukaemia, the main thrust of the hypotheses outlined below.

Radiation

Ionizing radiation

Ionizing radiation has been recognized as a potent carcinogen for over a century and exposure is known to cause leukaemia in adults. A higher rate of leukaemia was observed in the radiation-exposed survivors of the bombs at Nagasaki and Hiroshima. Because of this and because one of the largest and most persistent 'clusters' of childhood leukaemia was reported in the village of Seascale adjacent to the Sellafield nuclear installation in Cumbria, the role of ionizing radiation and electromagnetic fields has been much studied in childhood leukaemia.

There is agreement that *in utero* X-ray exposure increases the risk of all cancer, including leukaemia, in children born subsequently by around 30%. However, it is not an important cause of cancer in children in the UK or elsewhere where X-ray exposure during pregnancy is limited. Exposure to natural background radiation (due predominantly to radon exposure) has not been found to be strongly associated with childhood leukaemia. Studies of the role of paternal exposure to radiation have been equivocal, but since such exposures are now generally low due to vigilant radiation protection regimens, any increased risk they may bring makes a very small contribution to the overall burden of childhood leukaemia in the population.

Non-ionizing radiation

Studies of non-ionizing radiation, such as electromagnetic fields (emf) from electric power lines or appliances suggest that exposures greater than $0.4\mu\text{T}$ may increase the risk of childhood leukaemia. However, there are concerns about the reliability of these studies and again, even if this finding was accepted, such high exposures to emf are uncommon, implying that the vast majority of ALL cases are not caused by such exposures.

Other environmental exposures

Studies of other environmental exposures, such as agrochemicals, have had equivocal results, but there is some evidence that exposure to these agents is associated with small increased risks of leukaemia, especially in those who are genetically susceptible.

Clustering and infection

A characteristic of the occurrence of ALL is its tendency to 'cluster', i.e. there are places where, for a period of time, there are more cases than would be expected by chance alone. This has led to the generation of hypotheses around the role of community and individual infection in the aetiology of childhood leukaemia. Kinlen has studied many circumstances where there has been unusual population mixing, such as new towns, commuter towns, and war time evacuation of children from cities to rural communities. He found high rates of childhood leukaemia associated with many of these phenomena, leading to the hypothesis that high levels of circulating infections in circumstances, where herd immunity is low, leads to childhood leukaemia as a rare and unusual response to a common infection. There is some evidence that this explanation could account for more than half of all cases, and it is consistent with many of the current and historical features of the epidemiology of childhood leukaemia.

Solid tumours

In general, solid tumours have not been studied as much as leukaemias from an epidemiological point of view, the major reason being the challenge of studying these very rare diseases.

The causes of most solid tumours remain unknown. Retinoblastoma can arise from an inherited or a new mutation, and it is estimated that slightly less than half of retinoblastoma arising in the UK is inherited. While, as noted above, some characteristic congenital conditions increase the risk of solid tumours (such as Wilms' tumour), the vast majority of solid tumours are not inherited. As for leukaemia, there is evidence that *in utero* exposure to X-rays can increase the risk of solid tumours, but since very few women receive such investigations, this plays almost no causal role at a population level.

Implications for primary prevention and screening

For the vast majority of childhood cancers, the cause or causes remain unknown. This means there is currently little prospect of primary prevention of childhood cancer, although the role of infection and maturation of the immune system in leukaemia may point to a role for vaccination as an immune system maturation device. Breast feeding (exclusive and of long duration) protects against the development of leukaemia, probably by playing a similar role.

Screening for Wilms' tumour is recommended for children with Beckwith-Wiedemann syndrome and a few other rare congenital conditions.

Attempts were made to screen for neuroblastoma using urine catecholamine measurements in infants. While some cases of neuroblastoma were found by this approach, which was implemented throughout Japan for a number of years and investigated in research projects in North America, Germany, France, and the UK, it was eventually concluded that such screening did not reduce mortality and may have increased morbidity from this disease.

Definitions

Incidence

Incidence rate

This is the rate of occurrence of new cases of disease within the population. Generally, for childhood cancer, the incidence is reported as the number of cases per year per million population within a specific group, with respect to age and sex. For example, during 1971–1980 in England and Wales, the incidence rate of childhood cancer in boys aged 0–14 years was 114.1 per million per year.

Age-adjusted incidence rate

Age-adjusted incidence rate takes into account the fact that the age distribution of the population being studied may be different from that of a population with which you may wish to compare it. Commonly, a standard European or World population is used for the adjustment, which then allows direct comparison of rates between countries that may have different proportions of younger and older individuals. For example, during 1971–1980 in England and Wales, the age-adjusted incidence rate of childhood cancer in boys aged 0–14 years was 119.6 per million per year.

Cumulative incidence rate

The cumulative incidence rate is the risk aggregated over several years – typically up to age 14. For example, during 1971–1980 in England and Wales, the cumulative incidence rate of childhood cancer in boys up to age 15 years was 1310 per million or 1.3 per 10000.

Mortality

Mortality rate

The mortality rate is the number of deaths within a specific population during a specific time period – typically a year. Thus, for childhood cancer, the mortality rate would typically be reported as 20 per million per year.

Standardized mortality rate

The standardized mortality rate, like the adjusted incidence rate, takes into account the differences in age and/or sex distribution between populations, and allows direct comparison of mortality rates between different populations.

Standardized mortality ratio

For estimation of the standardized mortality ratio (SMR), the mortality rate in a reference population is considered to be equal to 100 and the SMR of the study population is the ratio of the observed number of deaths to the number that would be expected if the mortality rate was the same as that of the reference population. Populations with mortality rates lower than the reference population will have SMRs less than 100, while populations with rates higher than the reference population will have SMRs higher than 100.

Survival rate

The survival rate is the proportion of those diagnosed with the disease who survive for a given period of time. Typically, for childhood, ALL 5-year survival is around 85%.

Prevalence

The prevalence of disease is a measure of the number of people within a specific population who have the disease at any one time. Prevalence depends on both the incidence of disease and the duration of symptoms. For acute illness, prevalence is less than incidence, but for chronic disease, the prevalence may be higher.

The prevalence of childhood cancer is typically around 400 per million.

Measures of effect**Relative risk/risk ratio**

The relative risk (or risk ratio, RR) is a comparison of the risk of disease in an exposed population with the risk of disease in an unexposed population. True relative risk estimates are only available from cohort studies. OR (see below) are used as an approximation to the RR, although they can overestimate the magnitude of the effect in small studies.

Odds ratio

The odds ratio is directly calculable from case-control studies and is the effect estimator from logistic regression analyses. It is the ratio of the odds of exposure in the diseased vs. the disease-free population. It is used as an estimate of the RR, but the two measures are not necessarily the same.

Confidence interval

Confidence intervals are a probabilistic window around a measured rate or point estimate of effect (OR or RR, for example) within which the true point estimate is likely to occur. 95% CI are typically reported; these encompass 95% of all probable values of the point estimate given the dataset scope and limitations. The width of the 95% CI depends on both the size (and statistical power) of the study and the heterogeneity of the exposure measurements. A narrow 95% CI implies a more robust study finding than a wider one.

Study design***Case-control study***

Case-control studies capture retrospective data on exposure and compare exposure histories in the diseased group (cases) with a disease-free group (controls). Case control studies are more efficient for the study of rare diseases, such as childhood cancer.

Cohort study

Cohort studies may be retrospective or prospective and involve capturing exposure data on a large population from which the cases will (or have) emerge(d). For rare diseases, such as childhood cancer, cohort studies must capture information on huge populations (typically, several hundred thousands or even millions of person years) for a sufficient number of cases to arise to make the observations robust. Cohort studies are generally more expensive and resource intensive than case-control studies, although they may be less prone to bias.

Clustering analysis/incidence rate heterogeneity studies

There are several different approaches used to determine whether there are differences in the rates of disease between places and between different time periods. Space–time clustering investigated whether cases are closer in space and time than would be expected by chance. This would occur, for example, if an infection agent was involved in the aetiology of the disease. Childhood leukaemia cases tend to demonstrate space–time clustering, especially when place and time of birth (vs. diagnosis) are considered. Other statistical tests compare rates between one place and another, and between one time period and another. This addresses other hypotheses of causation, such as whether there may be more cases in one place due to an environmental factor, such as a source of pollution.

