The Epidemiology of Childhood Cancers

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Abstract

In this article, the recent epidemiological literature on childhood cancer is reviewed. This includes findings from descriptive, case-control and cohort studies. The aetiology of most childhood cancers is unclear. Both genetic and environmental factors are likely to contribute. Increasing incidence, findings of clustering and seasonality in the incidence of certain cancers support a role for environmental agents in aetiology. The evidence concerning putative risk factors is considered and suggests that the aetiology is likely to be multifactorial and involve a number of different agents. These include infections, ionising radiation, certain chemical exposures, parental smoking, parental alcohol consumption and hair dyes. Conversely, breastfeeding and certain dietary supplements may convey protection. Recent findings regarding electromagnetic fields suggest that this factor is not likely to have a major role in aetiology.

Keywords

Aetiology, childhood cancer, descriptive epidemiology, incidence, trends, space–time clustering, spatial clustering, seasonality, environment

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In this article, the epidemiology and aetiology of childhood cancer are reviewed. The aetiology of childhood cancer is not clear. Both genetic predisposition and environmental agents are likely to be involved. There is a vast amount of literature on the subject, and PubMed (www.ncbi.nlm.nih.gov/PubMed) has been utilised to find key references. This review also synthesises and updates findings from articles that have been discussed in previously published reviews.[1–4]

Descriptive Epidemiology

Studies of descriptive epidemiology are important for providing clues to aetiology. The main findings are summarised in *Table 1*.

Incidence

Childhood leukaemia comprises three main sub-types: acute lymphoblastic leukaemia (ALL), acute non-lymphocytic leukaemia (ANLL) and chronic myeloid leukaemia (CML). Childhood leukaemia is dominated by ALL, whereas CML is rare in this age group.

There is a marked variation in the incidence of ALL between countries, with a general trend for the incidence to be lower in less affluent populations and higher in more affluent populations. An incidence peak of ALL is found in more affluent populations in those one to four years of age and mainly comprises cases of the precursor B-cell subtype.[1–4] This pattern is consistent with three recent aetiological hypotheses related to infections.[5–8] Earlier exposure to infections may provide early priming of the immune system and consequently greater protection. In more affluent populations there is a general tendency for delay in exposure to infections compared with less affluent populations. The geographical patterning of ANLL is less clear.[1–4]

In contrast to leukaemia, the incidence of Hodgkin's lymphoma (HL) is higher in less affluent populations. Burkitt lymphoma (BL) is associated with the Epstein-Barr virus (EBV) and is prevalent in certain malaria-endemic parts of sub-Saharan Africa and Papua New Guinea. Other types of non-Hodgkin's lymphoma (NHL) do not show clear geographical patterns.[1,3,4]

Central nervous system (CNS) tumours display the highest incidence in North America, Europe, Australia, New Zealand, Israel and Japan and the lowest incidence in Africa. Sympathetic nervous system tumours have the highest rates in Europe, North America, Australia and Japan and are very rare in Africa. Retinoblastoma has the highest rates in Africa and South America. Wilms' tumour has the highest incidence in Africans and African-Americans. The highest incidence of osteosarcoma occurs in US African-Americans, Italy, Brazil, Germany and Spain, whereas the highest incidence of Ewing sarcoma is found among white Caucasian populations. The highest incidence of soft-tissue sarcoma is found in Africa, France, the US and Israeli Jews. The incidence of germ cell and gonadal tumours displays heterogeneity between countries, with the highest rates in certain Pacific communities. Hepatic tumours and carcinomas are rare in children.[1,3] The incidence of hepatic tumours is related to the prevalence of exposure to hepatitis viruses.[9,10] Caution should be exercised when making geographical comparisons between the reported incidence

Table 1: Summary of Key Findings from Descriptive Studies

Incidence
Higher incidence of leukaemia, CNS tumours and sympathetic nervous system tumours in more affluent populations
Higher incidence of lymphomas (especially HL), Wilms' tumour and retinoblastoma in less affluent populations
Trends
Increases for leukaemia, attributable to precursor B-cell ALL in the childhood peak
Increases for CNS tumours, sympathetic nervous system tumours, hepatic tumours, germ cell and gonadal tumours
Space–time Clustering
Observed for leukaemia, HL, NHL, CNS tumours, soft-tissue sarcoma, osteosarcoma and Wilms' tumours
Spatial Clustering
Observed for leukaemia, soft-tissue sarcoma and Wilms' tumour
Seasonality
Observed for leukaemia, HL, BL, CNS tumours, rhabdomyosarcoma and hepatoblastoma

ALL = acute lymphoblastic leukaemia; BL = Burkitt lymphoma; CNS = central nervous system; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma.

rates. Data quality, completeness of ascertainment and methods of diagnosis may all play a role. This might at least partly explain some of the disparities. For example, some of the heterogeneity in incidence of CNS tumours may be due to differences in methods of diagnosis, such as the availability of magnetic resonance imaging.[11] Geographical variations in incidence may also result from differences in possible competing risks of early death from infectious diseases (before potential diagnosis of cancer). In developing countries, such competing risks are likely to be much greater than in resource-rich countries.[12–14]

Trends

Recent reports have found marked increases in the incidence of specific childhood cancers.[1–4,15,16] Increases in the incidence of precursor B-cell ALL are consistent with an increasing tendency for less opportunity for early exposure to infections in more affluent societies.[17] There have been recent increases in the incidence of lymphomas, especially HL.[18–21] Increases have also been reported for CNS tumours, which cannot be explained as diagnostic artefact.[20–23] Increases in the incidence of sympathetic nervous system tumours, hepatic tumours and germ cell and gonadal tumours have been reported from a number of more affluent countries.[14,21,23,24] Increases for retinoblastoma have been reported from Africa and India and may be linked with the increased prevalence of HIV infection.[1,3] Increases in thyroid cancer have been reported from Belarus during the period following the Chernobyl nuclear accident.[25] It is possible that some of the apparent increases in incidence may be due to the improved efficiency of cancer registration, changes in methods of diagnosis and reduction in competing risks of dying from other causes.[11–14]

Space–Time Clustering

Space–time clustering is observed when excess numbers of childhood cancer cases occur within highly localised geographical areas for very limited periods of time and these excesses are not attributable to general excesses in those areas or at those periods. Statistically significant space–time clustering among cases of childhood leukaemia (especially cases of ALL occurring at one to four years of age) has been observed in a number of studies from Europe, Australia and the US.[1–4,26–39] Also, significant space–time clustering has been found for childhood solid tumours, including HL, NHL, CNS tumours, soft-tissue sarcomas, osteosarcoma and Wilms' tumours.[36,37,40,41] In addition, one study found cross-space–time clustering between cases of leukaemia and CNS tumours.[42]

The positive space–time clustering found for leukaemia is consistent with current hypotheses relating to infections.[5–8] Space–time clustering for lymphomas is consistent with a directly transforming infection. Putative agents include EBV, hepatitis C, human herpes virus 8 (HHV8), HIV and *Helicobacter pylori*.[43–45] The finding of space–time clustering for CNS tumours is also consistent with an infectious aetiology, as has been suggested by other epidemiological studies.[46–49] The space–time clustering for both soft-tissue sarcoma and osteosarcoma suggests the possibility of an infectious aetiology. It is noteworthy that studies in adults have found a causal association between HHV8 and Kaposi's sarcoma (with involvement of HIV).[50] Animal studies have shown that simian virus 40 is causal in the induction of osteosarcoma.[51,52] For Wilms' tumours there is little evidence to support a role for infections in aetiology.[1] Cross-clustering between leukaemia and CNS tumours suggests the possibility of a common environmental aetiology for some cases of these two diseases.[42]

Spatial Clustering

Spatial clustering is seen when excess numbers of cases of childhood cancer occur within highly localised geographical areas for a sustained temporal period. These excesses are widespread and not limited to one small area.

A number of recent studies from Europe, Hong Kong and New Zealand have found spatial clustering among cases of childhood leukaemia.[53–60] Other studies have not found spatial clustering of childhood leukaemia.[38,61,62] Recent studies from the UK have also found spatial clustering among certain solid tumours, namely soft-tissue sarcoma and Wilms' tumour.[59,63]

Spatial clustering for childhood leukaemia is consistent with an infectious aetiology, with persistent occurrence in areas of high or unusual population mixing.[6,7] Clustering of soft-tissue sarcoma may be linked with infections or another environmental agent. However, clustering of Wilms' tumours may arise from other spatially heterogeneous environmental exposures, including hydrocarbons, lead, boron and pesticides.[1]

Seasonality

Seasonal patterning in incidence has been reported for a number of childhood cancers, including leukaemia, HL, BL, CNS tumours, rhabdomyosarcoma and hepatoblastoma.[1–4,64–66] The presence of seasonality is consistent with an environmental aetiology and the possible involvement of seasonally variable environmental agents such as infections and pesticides.

Genetic Risk Factors

Overall, known genetic risk factors account for only a small proportion of all childhood cancer cases.[1,3,67] However, certain genetic syndromes are linked with a higher risk of specific childhood cancers. For leukaemia these include Down's syndrome, neurofibromatosis type 1, ataxia telangiectasia and Fanconi anaemia. For CNS tumours these include neurofibromatosis types 1 and 2, tuberous sclerosis, Gorlin syndrome and Turcot syndrome. For Wilms' tumour these include Denys-Drash,

Beckwith-Wiederman, Wilms' tumour, aniridia, genitourinary anomalies and mental Retardation (WAGR) and Perlman syndromes. Soft-tissue sarcomas are associated with Li-Fraumeni syndrome and neurofibromatosis type 1. Hepatoblastoma is associated with familial adenomatous polyposis.[1,3] Forty per cent of retinoblastoma cases are heritable.[68] An association between congenital anomalies and increased risk of neuroblastoma has been identified.[3,69]

Environmental Risk Factors (Case-control and Cohort Studies)

The major findings are summarised in *Table 2*.

Ionising Radiation

A recent review of 12 ecological studies and seven case-control studies suggested the possibility of a weak association between domestic exposure to radon and childhood leukaemia.[70] Another study from Denmark suggested that domestic radon exposure increases the risk of ALL.[71] By contrast, most recent studies have found no associations with domestic exposure to gamma radiation.[1,3,4] A case-control study from Sweden found a positive link between gamma radiation and increased risk of leukaemia.[72] Another study from Germany found an association between residential radon exposure and increased risk of solid tumours (mainly due to CNS tumours).[73] A recent study has suggested that around 20% of childhood leukaemia cases in the UK may be attributable to natural background ionising radiation.[74]

Most studies have found no associations with living close to a nuclear plant.[1,3,4,75–77] Two recent case-control studies found a higher risk of leukaemia associated with residential proximity to nuclear plants.[78,79] Another study from Belarus found a strong association between thyroid cancer and fallout from the Chernobyl accident.[80]

Some positive associations have been reported with parental occupation exposures. However, a number of other studies, including a major UK government investigation, have found no links between parental occupational exposures and subsequent occurrence of a malignancy in the offspring.[1,3,4]

Only one recent study has found an association between pre-conceptional paternal X-ray examinations and increased risk of leukaemia in offspring.[81] Most other recent studies have found no associations between childhood cancer and maternal (preconception or intrauterine) or paternal (preconception) exposures. It should be noted that levels of intrauterine exposure have been radically reduced in recent years.[1,3,4]

One recent study found an increased risk of leukaemia associated with more than two diagnostic X-rays of the child.[82] However, other recent studies found no associations with childhood diagnostic exposures.[1,3,4] This is undoubtedly due to a restriction in use of diagnostic radiation for children in recent years.

Electromagnetic Fields

Recent studies, including a pooled analysis (of nine studies of childhood leukaemia) and a meta-analysis (of 13 studies of childhood CNS tumours), found increased risks of childhood leukaemia and CNS tumours associated with estimated residential magnetic field exposures of at least 0.4 micro-Tesla.[1,3,4,83–85] A recent review suggested that extremely strong low-frequency magnetic fields (≥100 micro-Tesla) may interact with other chemical and physical environmental agents and thereby enhance carcinogenic effects.[86] Other studies have shown no associations with lower levels of residential exposure. Some studies have shown an increased risk of childhood leukaemia associated with living close to an overhead power line, but these studies may be prone to high levels of exposure misclassification.[1,4,87]

Table 2: Summary of Major Findings from Environmental Studies

Factors Associated with Increased Risk
Ionising radiation (very limited evidence for leukaemia and thyroid cancer)
Electromagnetic fields (leukaemia and CNS tumours, but only for exposures ≥0.4 micro-Tessla)
Pesticides (leukaemia, lymphoma, CNS tumours, neuroblastoma, Wilms' tumour)
Solvents, benzene and other hydrocarbons (leukaemia, HL, CNS tumours)
Parental smoking (leukaemia, NHL, CNS tumours, hepatoblastoma)
Parental alcohol consumption (leukaemia, CNS tumours)
Vitamins, especially vitamin K (leukaemia, lymphoma)
Contaminated drinking water (leukaemia, astrocytoma)
Hair dyes (CNS tumours)
High birth weight (ALL, astrocytoma, Wilms' tumour, germ cell tumours)
Low birth weight (hepatoblastoma)
Delayed exposure to infections (leukaemia)
Direct exposure to infections (HL, CNS tumours, bone tumours)
Factors Associated with Decreased Risk
Breastfeeding (leukaemia, HL, neuroblastoma, Wilms' tumour)
Diet including fresh fruit and vegetables (leukaemia)
Folate supplements (leukaemia)
Iron supplements (precursor B-cell ALL)

ALL = acute lymphoblastic leukaemia; BL = Burkitt lymphoma; CNS = central nervous system; HL = Hodgkin's lymphoma.

Pesticides and Fungicides

Exposure of a child or parent (via occupational exposure) to pesticides has been linked with an increased risk of a number of childhood cancers, including leukaemia, lymphoma, CNS tumours, neuroblastoma and Wilms' tumour.[1,3,4,88–92]

Solvents, Benzene and Other Hydrocarbons

A numbers of recent studies have found an increased risk of leukaemia associated with exposure to solvents.[1,3,4,93–97] An increased risk of leukaemia, HL and CNS tumours has also been linked with exposure to benzene and other hydrocarbons (often from vehicular emissions).[98–100]

Parental Smoking

Reliable assessment of parental smoking in childhood cancer studies is problematic. A tendency for under-reporting among parents of case children has been demonstrated[101] and may contribute to the inconsistency between studies. Although most recent studies have not found any associations with childhood ALL,[102] some have reported positive associations for childhood leukaemia, NHL, CNS tumours and hepatoblastoma.[100–109] In one of these studies, a higher risk of leukaemia was associated with interaction between parental smoking and certain genetic polymorphisms.[103]

Parental Alcohol Consumption

A number of studies have found an increased risk of childhood leukaemia (mainly AML) associated with maternal alcohol consumption.[1,3,4,110,111] Another study found a decreased risk of ALL associated with maternal consumption of alcohol during pregnancy, but

an increased risk associated with interaction between parental alcohol consumption and certain genetic polymorphisms.[112] An increased risk of CNS tumours has been associated with paternal use of alcohol prior to conception.[113] An increased risk of neuroblastoma has been linked with maternal alcohol consumption during pregnancy.[114]

Breastfeeding

This topic has previously been reviewed extensively. Overall, there is evidence that breastfeeding is protective for childhood leukaemia, HL, neuroblastoma and Wilms tumour.[1–4,115–118]

Diet

Consumption of vegetables, fruits and protein sources during the year immediately preceding pregnancy, and regular consumption of oranges or bananas and orange juice before the age of two years has been found to be protective against leukaemia.[1,3,4,119–120]

Vitamin and Folate Supplements

Four case-control studies from the UK have shown a link between neonatal administration of vitamin K and higher risk of leukaemia or lymphoma in offspring, although several other studies (including a pooled analysis of six case-control studies) have found no association.[3,4] Recent evidence suggests that maternal folate intake may be protective against onset of leukaemia in the offspring,[121] but with interactions between folate intake and certain genetic polymorphisms determining the level of protection.[122–125] One study also found that maternal use of iron or folate supplements during pregnancy was protective against precursor B-cell ALL in the child.[4] Another study (of Down's syndrome children) found that there was no overall association with regular use of multivitamins and leukaemia, but there was an association with prolonged use.[126]

Drinking Water

Case-control studies have found an increased risk of leukaemia associated with consumption of drinking water contaminated with trihalomethanes, chloroform and zinc.[3,127,128] An association between nitrite in drinking water (consumed by mothers during pregnancy) and astrocytoma in the child has also been reported.[3,129]

Hair Dyes

Mothers' use of hair dyes during pregnancy has been found to increase the risk of a brain tumour in offspring.[3,130]

Birth Weight

Increased risk of ALL, astrocytoma, medulloblastoma, Wilms tumour and germ cell tumours is associated with high birth weight.[1,3,131–134] Conversely, an increased risk of hepatoblastoma is linked with very low birth weight.[135]

Viral and Bacterial Infections

An increased risk of childhood leukaemia has been consistently linked with greater affluence and unusual population mixing. Conversely, lower risk has been associated with immunisation and early day care attendance.[1–4,136] Although there is inconsistency between studies of social contact,[137–139] the time of occurrence of early infectious exposures may be an important factor.[140,141] Specific agents that have been linked with a higher risk of childhood leukaemia include *Mycoplasma pneumoniae*, *Helicobacter pylori*, EBV and adenovirus.[142–144]

An increased risk of HL has been linked with early measles infection.[145] Early infectious exposures (*in utero* or around the time of birth) have been associated with a higher risk of the child developing a CNS tumour.[46–49] Exposure of both the mother and the child to farm animals (indicating greater opportunity for exposure to infections) has also been shown to lead to an increased risk of a CNS tumour.[146,147] Childhood infections and day care attendance provide protection for neuroblastoma.[148] An increased risk of childhood bone tumours has been associated with frequent change of residence, mumps, living on a farm and parental occupations involving social mixing.[149–151]

Conclusions

Increasing incidence and findings of clustering and seasonality in the incidence of certain cancers (including leukaemia and CNS tumours) suggest a role for environmental agents in aetiology. The evidence concerning putative risk factors suggests that the aetiology is multifactorial. Both genetic predisposition and a number of environmental agents are likely be involved. These include infections, ionising radiation, certain chemical exposures, parental smoking, parental alcohol consumption and hair dyes. Conversely, breastfeeding and certain dietary supplements may convey protection. Recent findings concerning electromagnetic fields suggest that this factor is not likely to play a major role in aetiology. Future research should investigate putative mechanisms and evaluate the combined effect of different environmental agents. ■

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