Although the study of environmental factors in the causation of childhood cancers has been ongoing for a number of years, there is very little conclusive information on the relationships between environmental agents and childhood cancer risk. Past studies have been hampered by a lack of understanding of etiologically significant disease subtypes, difficulties in obtaining sufficient numbers of cases to study, problems in assessment of environmental exposures, and information on the biological mechanisms that would lead to the development of cancers in childhood. In recent years, using new classifications of childhood cancers and improved methodologies in large collaborative epidemiologic studies, more information is available on the potential factors affecting the risk of childhood cancers. Much further research is required, however, since in many areas of study, specific agents have not been conclusively identified, mechanisms of carcinogenesis have not been determined, and exposure assessment that could provide information on relevant timing, quantity, and modes of exposure is lacking. This review of chemical exposures (including use of medications and other drugs, dietary agents, and second-hand exposure to tobacco smoke, alcohol, and industrial chemicals), exposures to ionizing radiation and electromagnetic fields, and exposures to infectious agents, summarizes the current literature on childhood cancer risk and identifies future directions in this area of research.

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Descriptive epidemiology of childhood cancers

Cancer in childhood is a rare disease, with an incidence rate of approximately 157 cases per million under 15 years in Canada. Overall incidence of childhood cancer does not vary markedly around the world, ranging from 75 to 160 per million, although the rates of specific types do vary in different regions. However, it is a significant cause of childhood morbidity and mortality in industrialized countries, being the most common cause of death due to disease in the age range 1 to 14 years. Approximately 910 new cases of cancer are diagnosed each year in Canada in children between 0 and 14 years of age, and 170 deaths from cancer are recorded annually in this age group.

The types of cancer seen among children are very different from those seen in adults, being mainly hematopoietic and embryonal type cancers rather than epithelial cancers. Recent Canadian data (Table I) demonstrate that the leukemias are the most common type of paediatric cancer, accounting for 31% of new cases and 32% of deaths. Between 75% and 80% of childhood leukemia cases are acute lymphatic leukemias. Brain tumours are the next most frequent type, accounting for 19% of new cases and 27% of deaths from childhood tumours. About 50% of childhood brain tumours are astrocytomas, and 17% are medulloblastomas, otherwise known as primitive neuroectodermal tumours (PNET). Lymphomas rank third in frequency, with 12% of new cases and 6% of deaths. Hodgkin’s disease accounts for just over one third of childhood lymphomas. Although mortality for leukemia is decreasing due to major advances in treatment, the incidence is apparently increasing in
several jurisdictions, including the U.S., Canada, and parts of Europe. The incidence of childhood brain tumours also appears to be increasing.

Etiologic factors for childhood cancers are generally not known or not well understood. The study of risk factors has been difficult because of the rarity of these conditions, as well as difficulties in pathologic differentiation of tumour subtypes that are biologically similar and therefore would be expected to be influenced by similar risk factors. Environmental exposures are also difficult to assess among children, because of problems in monitoring for personal exposure in children’s environment, and because many exposures are ubiquitous but at low levels. Recent advances in pathologic classification, and the development of collaborative studies, mean that the newer studies are now more informative than in the past.

Although genetic factors appear to be influential for some types of childhood cancers, known genetic factors account for only a small proportion of total cases, and environmental factors can also be important in determining risk. The world-wide variation in incidence for some cancer types is suggestive of greater environmental influence in risk for those types. The major environmental factors hypothesized to influence the risk of developing cancer in childhood are: ionizing radiation (from both manmade and natural sources); chemical exposures, from drugs or medications, diet, and secondary smoking or occupational exposure; and low-frequency electromagnetic field exposure. Children can be exposed both directly and indirectly (via family members and associates), and at different periods in development: before conception (because of inherited susceptibility or the influence of various agents on the father’s or mother’s germ cells), during pregnancy (via the mother’s exposures), and after birth. Various possible mechanisms of causation of childhood cancer, originally proposed for occupational exposures by Peters and Preston-Martin, are outlined in Table II.

### TABLE I

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Cases Incidence Rate (1989-1993)*</th>
<th>Percent of All New Cases</th>
<th>Deaths Mortality Rate (1991-1995)*</th>
<th>Percent of All Cancer Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>48.1</td>
<td>30.7</td>
<td>9.39</td>
<td>32.2</td>
</tr>
<tr>
<td>Acute lymphocytic</td>
<td>38.3</td>
<td>24.4</td>
<td>4.22</td>
<td>14.5</td>
</tr>
<tr>
<td>Acute non-lymphocytic</td>
<td>6.0</td>
<td>3.8</td>
<td>2.22</td>
<td>7.6</td>
</tr>
<tr>
<td>Brain &amp; Spinal</td>
<td>29.6</td>
<td>18.9</td>
<td>7.91</td>
<td>27.1</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>15.7</td>
<td>10.0</td>
<td>1.70</td>
<td>5.7</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>5.2</td>
<td>3.3</td>
<td>1.76</td>
<td>6.0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>19.1</td>
<td>12.2</td>
<td>1.62</td>
<td>5.6</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>8.0</td>
<td>5.1</td>
<td>0.13</td>
<td>0.5</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>5.6</td>
<td>3.6</td>
<td>0.34</td>
<td>1.9</td>
</tr>
<tr>
<td>All other lymphomas</td>
<td>5.5</td>
<td>3.5</td>
<td>0.95</td>
<td>3.2</td>
</tr>
<tr>
<td>Sympathetic Nervous System</td>
<td>12.8</td>
<td>8.1</td>
<td>3.65</td>
<td>12.5</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>9.9</td>
<td>6.3</td>
<td>2.40</td>
<td>8.2</td>
</tr>
<tr>
<td>Renal Tumours</td>
<td>8.7</td>
<td>5.5</td>
<td>0.75</td>
<td>2.5</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>7.5</td>
<td>4.8</td>
<td>0.47</td>
<td>1.6</td>
</tr>
<tr>
<td>Bone</td>
<td>7.2</td>
<td>4.6</td>
<td>1.58</td>
<td>5.4</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>6.2</td>
<td>3.9</td>
<td>0.10</td>
<td>0.3</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>3.7</td>
<td>2.4</td>
<td>0.03</td>
<td>0.1</td>
</tr>
<tr>
<td>Other Cancers</td>
<td>2.1</td>
<td>1.3</td>
<td>0.54</td>
<td>1.9</td>
</tr>
<tr>
<td>Hepatic Tumours</td>
<td>2.0</td>
<td>1.3</td>
<td>0.74</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td>156.8</td>
<td>100.0</td>
<td>29.19</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* Rate per million children aged 0-14 years, standardized to the 1991 Canadian population.

### TABLE II

<table>
<thead>
<tr>
<th>Mechanisms of Childhood Cancer Causation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception maternal and paternal exposures:</td>
</tr>
<tr>
<td>• could result in transmissible genetic effects that could cause childhood cancer</td>
</tr>
<tr>
<td>Prenatal maternal exposures:</td>
</tr>
<tr>
<td>• could result in in utero exposure of the developing infant to substances that cross the placental barrier and cause genetic or teratogenic effects, either directly to the mother or indirectly via transmission of exposures from other individuals in surroundings</td>
</tr>
<tr>
<td>Postnatal maternal exposures:</td>
</tr>
<tr>
<td>• maternal exposures during the neonatal period, either direct or from other exposed individuals in surroundings, could result in transmission of exposures in breastmilk</td>
</tr>
<tr>
<td>Postnatal exposures of child:</td>
</tr>
<tr>
<td>• child could be exposed directly, or indirectly through others in surroundings</td>
</tr>
</tbody>
</table>

the sources used for these studies (birth and death certifications, parental interview, or proxy information). Lastly, the mechanisms by which direct and indirect exposures to various chemicals at different periods could lead to cancer in childhood are generally not known. Due to the lack of experimental evidence, many of these studies have based their hypotheses on positive investigations in the adult literature.

**Chemical exposures due to parental occupation**

Paternal employment in hydrocarbon-related occupations (including but not limited to occupations such as service station attendants, motor vehicle mechanics, machinists, and automobile and truck repairmen) was first associated with excess overall childhood cancer risk, risk of leukemia and risk of brain tumours, in a Canadian study by Fabia and Thuy. A positive association with childhood leukaemia was reported in studies by Vianna et al.15 Buckley et al.16 (for solvents, petroleum products and acute lymphocytic leukaemia) and McKinney et al.17 (specifically for benzene). Paternal machine-repair work was associated with excess risk of brain tumours in Finland. Wilkins and Sinks19 reported an elevated risk of brain cancer with jobs presumed to have moderate to heavy exposure to several compounds including hydrocarbons, and in a large study reported by Cordier et al.,20 primitive neuroectodermal tumours were identified as being at excess risk with paternal hydrocarbon exposure. Risk of a brain tumour was related to solvents,21 paints,21,22 and employment in the aerospace industry,15,21,23,24 which appears to be related to solvent exposure. Kwa and Fine26 reported an association between hydrocarbon occupations and Wilms’ tumour, Buckley et al.27 found an association between occupationally related paternal exposure to paints and petroleum products and risk of hepatoblastoma, Spitz and Johnson28 reported an excess risk of hepatoblastoma, and Hicks et al.23 found a relationship with lymphomas and rhabdomyosarcoma. Many of the relationships with rarer cancers, however, have been based on small and therefore unstable numbers.

However, there have been many negative studies as well, including investigations by Hakulinen et al.,28 Sanders et al.,29 Zack et al.,30 and Feingold et al.,31 which failed to observe any association for all cancer cases combined. No association between hydrocarbon-related paternal occupations and leukemia risk was found in studies by Shaw et al.32 and van Steensel-Moll et al.,33 and studies of childhood brain tumours were negative.4,5,34,35 Bunin et al.36 and Wilkins and Hundle17 found no relationship with neuroblastoma, and the study by Wilkins and Sinks38 found no association with Wilms’ tumour.

Paternal occupational exposures to metals have also been reported as leading to risk of childhood cancer,31 specifically Wilms’ tumour,39-41 acute nonlymphocytic leukemia,16 hepatoblastoma,27 brain cancer,39,42 and solid tumours.43 A study by Wilkins and Sinks38,44 did not find a relationship with Wilms’ tumour. Non-significant excess risk of childhood leukemia or acute lymphoblastic leukemia, the most common subtype, was found for fathers who were farmers or who worked in an agricultural occupation during the index child’s gestation in two of six studies reporting odds ratios, with values ranging from 0.3 to 1.8,18,33,45-48 Presumed paternal occupational exposure to pesticides during the gestation period was associated with an odds ratio of 1.9 in a Childrens Cancer Group study of acute non-lymphocytic leukemia.16 This study also reported an elevated risk of 1.8 for presumed paternal occupational exposure to pesticides during the index child’s childhood, and an odds ratio of 1.7 for paternal exposure prior to the child’s conception. One study of paternal agricultural occupation after the birth of the index child showed no relationship with risk of childhood leukaemia,33 whereas another showed a significant excess risk of 5.6.34 Four studies of childhood brain tumours reported elevated odds ratios of between 1.0 and 1.8 with father’s occupational exposure during the child’s gestation period;18,19,42,49 two of these studies also observed increased odds ratios of 2.719 and 1.849 for fathers who worked in an agricultural setting prior to conception of the index child, although they did not observe an effect after the child’s birth. A relationship between brain tumour risk and paternal occupational exposure to pesticides, with time period not specified, was reported in studies by Kristensen40 and Cordier.20 Studies of other cancers have very small numbers of cases, and therefore odds ratios are imprecise. Two studies of Ewing’s sarcoma,50,51 a study of germ-cell tumours,52 and a study of Wilms’ tumours53 reported elevated risks with father’s agricultural occupation or pesticide exposure during the pregnancy; other studies of all cancers,5,29 Wilms’ tumours54 and of neuroblastoma55, 56,57 failed to find a relationship with agricultural occupations during pregnancy. Increased childhood cancer risks have also been observed with paternal employment in pulp and paper manufacturing,6,24,25,56,57 manufacturing industries, and exposure to wood dust,7,37 and the medical and dental professions.40

Results from studies of maternal occupational exposures are generally less stable, due to smaller numbers of exposed individuals. The risk of all childhood cancers was elevated with mother’s occupation as a farmer’s wife, pharmacist, or factory worker.18 Increased risk of childhood leukaemia has been reported with maternal employment in domestic/personal service, hotel and catering occupations,24,33 chemical-related occupations,33,58 hydrocarbon-related occupations,59 metal-related occupations,58 physicians or pharmacists,58 and occupational exposure to dusts.27,59 Two of three studies examining maternal occupational exposure to pesticides during pregnancy with the index child and risk of leukaemia or acute lymphatic leukaemia found elevated risks of between 1.4 and 3.5;58,59 an elevated risk of 2.4 was reported for risk of acute non-lymphocytic leukaemia.58 A relationship with risk of brain tumours has also been seen with inhaled chemicals,21 and solvents.20 Maternal occupations in medical and dental care were associated with increased risk of Wilms’ tumour.60

**Residential chemical exposures**

Several studies have also examined children’s exposure to chemicals in the home—in particular residential pesticide use—and risk of childhood cancers. Studies of childhood leukaemia found elevated risks of between 1.1 and 3.8 with use
of no-pest strips and home use of pesticides, but generally no excess risk with professional extermination or garden pesticide use. Similar results were seen in studies of brain tumours, where, with the exception of the study by Davis, who calculated risk by type of pesticide, professional extermination or garden pesticide use did not result in higher odds ratios, but use of no-pest strips and home use of pesticides during the mother’s pregnancy or during childhood resulted in excess odds ratios of between 1.0 and 5.2. Residence on a farm resulted in excess risk for brain tumours, primitive neuroectodermal and non-astrocytic neuroepithelial tumours in three studies, but not for astrocytic gliomas.

Studies of other cancers suffered from lack of sufficient cases for reliable risk estimates. One study observed increased risks of childhood Wilms’ tumours, neuroblastoma, retinoblastoma, and non-Hodgkin’s lymphoma with farm residence, although timing of exposure was not specified. Leiss and Savitz reported an excess risk of soft tissue sarcoma with childhood exposure to garden pesticides, but not with pregnancy exposure. Home extermination during childhood did lead to increased risk of Wilms’ tumours and lymphomas in two other studies.

Medications and other drugs

Several studies have examined the possibility of links between medications taken by the mother during pregnancy, and development of childhood cancers. Three studies reported a positive relationship between the use of antinausea medications during pregnancy and the development of acute nonlymphocytic leukemia, retinoblastoma, or astrocytoma; however, two other studies found no association. The evidence for a relationship between various types of drugs affecting the central nervous system is contradictory. Four of seven studies reported an increased risk of brain and nervous system tumours with maternal use of neurally active drugs such as barbiturates and other types of sedatives; Gold et al. van Steensel-Moll et al., Kramer et al., and Schwartzbaum showed positive results; Goldhaber et al., Kuijten et al., and McCredie et al. found negative results. Studies of anaesthetic drugs administered during labour showed a relationship with brain tumours and childhood leukemia; however, other studies failed to support these findings. The narcotic pethidine, administered during labour, showed an association with increased risk of childhood cancer in a study by Gilman et al., however, this finding was not supported in a later study by Golding et al.

A large study of barbiturate exposure after birth and risk of central nervous system tumours found an increase in risk after adjustment for epilepsy-related use; further research was recommended.

Maternal alcohol consumption during pregnancy has been reported to increase the risk of neuroblastoma, acute nonlymphocytic leukemia, and infant acute myeloid leukemia. However, other studies of all cancers, leukemia, hepatoblastoma, and brain tumours did not find any association with alcohol use. At this time, the information available does not provide a convincing case for a causal relationship between prenatal alcohol consumption and excess risk of childhood cancers.

Chemical exposures due to parental smoking

Because there are known carcinogens in cigarette smoke that can cross the placental barrier, and there are other health risks for children associated with maternal smoking during pregnancy, several investigations of childhood cancer have examined the possibility of a causal link with parental smoking.

Several studies found that mother’s smoking during pregnancy was linked to excess risk of childhood cancer, acute leukemia, brain tumours, lymphomas, Ewing’s sarcoma, and neuroblastoma. Some studies reported a relationship with father’s smoking during the prenatal period and childhood cancer, acute leukemia, lymphomas, brain tumours, and rhabdomyosarcoma.

However, other studies found no relationship with childhood cancer risk and maternal prenatal smoking. Other studies of both maternal and paternal smoking reported an absence of excess risk either for all childhood cancers or for specific types (Gold et al., Howe et al., Kuijten et al., and McCredie et al. reporting on brain tumours; van Steensel-Moll et al. reporting on leukemia). Other investigations negative for a link with paternal smoking included Buckley et al., Bunin et al., reporting on retinoblastoma, Birch et al., and Gold et al. reporting on central nervous system tumours, Holly et al., reporting on Ewing’s sarcoma, Severson et al., reporting on acute myeloid leukemia, and Olshan et al. reporting on Wilms’ tumour.

The odds ratios for these studies are generally not high (less than 3), and results for smoking by dosage and timing during pregnancy were not consistent. Therefore, these data provide very little support for the hypothesis of increased risk, but the difficulties in exposure assessment preclude definitive conclusions.

Diet and childhood cancer

There is experimental evidence that some N-nitroso compounds, present in processed and cured meats and some other foods and beverages, can cause brain tumours in several animal species, but that the ingestion of vitamins C and E blocks the carcinogenic process. Other sources of these compounds include smoke from burning incense or cigarettes, facial cosmetics, diuretics, and antihistamines.

Several studies have reported an increased risk of childhood brain tumours with N-nitroso compounds, most consistently through maternal consumption of cured meats during the child’s pregnancy. Beer consumption (a beverage known to contain nitrosatable compounds) by the mother during pregnancy resulted in higher risk of PNET in a study by Bunin et al. and in another study of all types of childhood brain tumours by Howe et al. However, McCredie et al. and Carozza et al. found no association between maternal consumption of nitrosatable drugs and brain tumours. A large recent study by Preston-Martin et al. confirmed an increased risk in all three major groups of brain tumours (astroglial tumours, PNET and other histologies together), through maternal consumption...
of processed and cured meats during pregnancy, and also found an increasing risk with increased consumption. Risk was lower with use of prenatal vitamins.

Development of childhood leukemia was associated with maternal consumption during pregnancy of preserved and cured meats in one study, and with paternal consumption of hot dogs in another (recognizing that pre-conception intake is the only relevant exposure).

The evidence for a relationship between dietary consumption of some N-nitroso compounds and excess risk of brain tumours is very suggestive. More studies are needed to further explore the mechanisms involved; to further qualify and quantify the critical components of diet and modes of exposure to these compounds that are of greatest importance; and to explore the possible relationship with risk of leukemia and possibly other paediatric cancers through studies of the complete diet of mothers during pregnancy and of children before diagnosis. Laboratory studies of the effects of various dietary components can provide additional hypotheses to test.

**Ionizing radiation**

The types of childhood cancer most susceptible to the effects of ionizing radiation are acute lymphoblastic leukemia, brain tumours, thyroid cancer, and bone and soft tissue sarcomas.

A very small number of children have been exposed to high doses of ionizing radiation, either gamma radiation from the atomic bombs at Hiroshima and Nagasaki, radioactive iodine nuclides from the Chernobyl nuclear power plant accident, or high-dose therapeutic x-irradiation. Other groups of children have been exposed at low doses due to nuclear fallout from atmospheric testing of atomic bombs, one in Utah and one in the Nordic countries, failed to provide convincing evidence of an increase in risk. Studies of postnatal diagnostic x-ray exposure have also failed to demonstrate a relationship with childhood cancer. In all these studies, dose information is lacking or uncertain, but is probably very low. Marshallese Island children, heavily exposed to nuclear fallout, demonstrated increased rates of thyroid cancer.

However, in several studies of children therapeutically exposed to x-irradiation, where doses were higher, increased risks for childhood cancers, including leukemia, brain tumours, thyroid cancer, and bone cancer were observed. Cohorts studied included children treated for benign disease (including timea capitis and thyroid disease), and children receiving radiotherapy for cancer.

Reports of a cluster of childhood leukemia cases near an English nuclear power facility in the mid-1980s, and a subsequent study by Gardner in 1987, led to speculation that fathers’ pre-conception exposure to ionizing radiation in the power plant could result in leukemia in their offspring. Increased incidence rates of childhood leukemia were observed near nuclear facilities at Dounreay, and Egremont in the British Isles; nonsignificant excesses were observed in West Berkshire, Ontario (Canada), and La Hague (France), and a further study in Scotland failed to find a relationship. After further investigation and inquiry, it was concluded that the increases at Seascale and Dounreay could not be explained by paternal occupation exposure, specifically pre-conception exposure to radiation. The possibility of increased risk due to later exposure to viruses and other infectious agents coupled with immune susceptibility, as a result of community mobility, has been proposed as a possible explanation for the observed clusters.

In summary, although ionizing radiation is an established risk factor for many types of childhood cancer both prenatally and postnatally, the characterization of the risk relationship particularly at low dosage levels is not well defined.

**Extremely low-frequency electromagnetic fields**

Despite almost two decades of epidemiological and experimental research into the question of whether or not there are health effects related to exposure to power-frequency magnetic and electric fields, the issue is still not resolved. This is in part due to inconsistent evidence, and in part due to limitations of earlier studies. Much of the research has focused on cancer in children, as this is the disease outcome for which the first study by Wertheimer and Leeper found an effect, and where there has been additional suggestive evidence. Several reviews have been published on the findings to date (e.g., Ahlbom et al., Hardell et al., Miller et al.), methodological issues, and priorities for research. The U.S. National Research Council has recently published a report on possible health effects of exposure to residential electric and magnetic fields.
Electric fields are present in all lines carrying electricity; magnetic fields are generated whenever there is electric current flowing in a line. The North American electric power system uses 60-Hertz power, an extremely low electromagnetic frequency, which means that the current alternates back and forth in a line 60 times per second. All components of the electric power system, and all electrically powered machines, generate power-frequency electromagnetic fields (EMF); these fields are too weak to produce ionizing radiation or thermal effects.

An initial retrospective case-control study of children who died of cancer in the Denver area between 1950 and 1973, by Wertheimer and Leeper,133 found that children who died of leukemia or brain tumors were two to three times more likely to have been living in homes with nearby powerlines with configurations suggestive of higher magnetic fields inside the homes, as indicated by their powerline configuration classification into categories of “underground”, “very low”, “ordinary low”, “ordinary high”, and “very high” magnetic fields (the “Wertheimer-Leeper classification” and wire codes).

In a subsequent study, Savitz et al.142 found elevated but not significant associations with risk of leukemias and either wire-codes or measured magnetic fields in the home, as proxies for personal exposure. London et al.143 found a positive association with leukemia in childhood using the Wertheimer-Leeper wire coding, but no association with measured fields. Feychtling and Ahlbom,144 in a cohort study carried out in Sweden, reported a link with calculated magnetic fields based on residential proximity to higher-voltage lines and historic power load estimates. Neither Verkasalo et al.145 in Finland, nor Olsen et al.146 in Denmark, found any link with calculated magnetic fields in their cohort studies. The most recent reported U.S. study, by Linet et al.147 did not see this relationship. Many of the studies on this question have major methodological problems, including non-representativeness of the controls, non-response especially for measurements, and inadequate control for potential confounders, but the major problem has been in the identification of the true risk factor and the use of surrogate measures. Interpretation of results is therefore difficult. Alternative hypotheses have been proposed, for example that excess risk is related to some other, not-measured, aspect of magnetic fields, or that risk is associated with some aspect of the neighborhood environment that is confounded by certain wiring patterns. Several studies are currently underway, in Canada, the United Kingdom, and Europe, in an attempt to further explain the findings observed so far.

Savitz et al.142 did identify a positive association for brain tumour risk using the Wertheimer-Leeper wire coding, but brain tumour risk according to strength of measured fields was not elevated. A study by Preston-Martin et al.150 was negative both for a relationship with wire codes or with measured magnetic fields. The Scandinavian studies144,146 also failed to find any relationship with calculated magnetic fields and brain tumours.

Elevated risk of lymphomas was seen in the studies by Savitz et al.142 and Olsen et al.146 Savitz et al. also found a higher risk of soft tissue sarcomas, but this finding has not been replicated in other investigations of all childhood cancers.

A meta-analysis of risk of leukemias, lymphomas, and brain tumours carried out by Washburn et al.151 determined that risks of leukemias and lymphomas were elevated but did not achieve statistical significance, whereas the risk of brain tumours relative to EMF exposure were statistically higher than controls.

Overall, the inconsistencies and generally low risks reported mitigate against the hypothesis of a relationship between exposure to power-frequency EMF and risk of childhood cancer. The consistency of the finding of a relationship of leukemia with wire-codes is not explained, although it is notable that the large, well-designed study by Linet et al.147 did not see this relationship. Many of the studies on this question have major methodological problems, including non-representativeness of the controls, non-response especially for measurements, and inadequate control for potential confounders, but the major problem has been in the identification of the true risk factor and the use of surrogate measures. Interpretation of results is therefore difficult. Alternative hypotheses have been proposed, for example that excess risk is related to some other, not-measured, aspect of magnetic fields, or that risk is associated with some aspect of the neighborhood environment that is confounded by certain wiring patterns. Several studies are currently underway, in Canada, the United Kingdom, and Europe, in an attempt to further explain the findings observed so far.

Viruses and other infectious agents

Observations of leukemia clusters and results from several epidemiologic investigations have led to the hypothesis that risk of childhood cancer, particularly leukemia, could be increased due to the effect of an infectious agent. An association between gestational infection with influenza and risk of childhood leukemia was reported in several studies;152-155 several other studies did not find a relationship.156-159 Viral infection during the perinatal period or early infancy resulted in an increased risk of leukemia or lymphoma in two studies,159,160 and in an excess of germ cell tumours164 and hepatoblastoma.17 Other studies reported a protective effect for acute lymphocytic leukemia.165 Childhood immunization was also found to be protective for childhood cancer in this and other studies.166,167 Several studies did not observe any associations with infections in early childhood166,167 or bacillus Calmette-Guerin (BCG) vaccination.168,169

A protective effect of breastfeeding, due to the immunological components of human breastmilk, was postulated as the result of one study reporting a significantly lower risk of childhood cancer among children breastfed for more than six months.170 No association with breastfeeding was observed in several other studies, however.71,74,171,172

Childhood environments that alter the usual time of exposure to infections have been suggested as factors that may increase the risk of some childhood cancers. Greaves has postulated that delay in exposure to general infections, and consequent alteration in the timing of antigenic challenge during infancy, may increase the risk of leukemia; a study by Petridou showing reduced risk of leukemia in children who attended day care in infancy supports this hypothesis.174 Kinlen175 has suggested that rapid population change in a community could alter the pre-existing exposure patterns and result in leukemia development in immune-susceptible individuals, and an increased leukemia risk has been observed in several such populations.176,177

An increased risk of childhood cancer has also been observed with in utero infection by herpes viruses (chicken pox or cytomegalovirus),153,180,181 or rubella.155
although no link was observed in several other studies. Epstein-Barr virus has been linked to risk of Burkitt’s lymphoma (reviewed by de-The), although this is a problem mainly seen in Africa. More research needs to be carried out in this area.

CONCLUSIONS

Relatively little is known about the role of environmental agents in the etiology of childhood cancers. Except for ionizing radiation, investigations of many environmental agents are still inconclusive, with conflicting findings and methodologic issues complicating the interpretation of the information available thus far.

For many hypothesized environmental risk factors for childhood cancer, the prevalence and levels of exposures are low. Therefore, future studies of the etiology of childhood cancers need to be of sufficient size to be able to detect and quantify risk with less uncertainty. Collaboration among investigators in developing study designs that would allow meta-analysis would enhance the value of individual investigations by improving precision and quantitative risk assessment. Detailed classification of subtypes is required in order to identify etiologically relevant subgroups. Most importantly, improved exposure assessment and additional information on potential confounders would provide the opportunity to characterize the nature and size of risk. Investigations linking job titles and duties with known exposures, and assessing likelihood and level of exposures, should enable an assessment of risk with respect to specific agents.

Studies to date on chemical exposures have demonstrated some positive results, in particular exposures to pesticides, paints, petroleum products, solvents, and metals, with excess risks generally about two-fold, but other studies have failed to find elevated associations. Ionizing radiation has been shown to be a risk factor for many childhood cancers, with risk apparently increasing linearly with dose, but the exact nature of the dose-response relationship particularly at low dosage levels is not clear, and highly exposed individuals constitute a very small proportion of the population; therefore the attributable risk is low. The several examinations of electromagnetic fields or wiring and childhood cancers, notably leukemia or brain tumours, are inconsistent, and at this time there are insufficient data to conclude a causal relationship. There are suggestive findings for infectious agents; these need to be confirmed, since the observed odds ratios are not large and the findings are not consistent. Finally, studies of maternal smoking and use of alcohol have not demonstrated an excess risk of childhood cancers, in spite of evidence from laboratory and adult studies. In summary, further large-scale epidemiologic investigations are necessary, with direct exposure assessment and categorization of disease subtypes, in order to provide additional understanding of these relationships.

Epidemiologic studies, of course, provide only part of the evidence required to determine causality. Epidemiologic studies look for patterns and statistical associations between putative factors and occurrence of disease in human populations. Laboratory studies, of cells or among animals, attempt to determine biological mechanisms of action of possible cancer-causing agents that would explain how these agents affect development of cancer. For an agent to be considered a cause of disease, both statistical and biologic evidence need to be established. Therefore, much further research needs to be done in order to identify and characterize environmental factors affecting childhood cancer development. This knowledge can then be used to develop prevention measures to lower the overall risk of these devastating diseases.

REFERENCES


