**This article was written for The Childhood Brain Tumor Foundation, Germantown, Maryland.**

# THE EPIDEMIOLOGY OF BRAIN TUMORS IN CHILDREN
# PART 2: Risk Factors

*by Melissa Singer, M.D. and Julianne Byrne, Ph.D.*

## INTRODUCTION

Central nervous system tumors in children are the most common solid tumor in the pediatric population. Although advances are being made in treatment, improving survival continues to be a challenge. Like most pediatric cancers, there is no one specific risk factor that explains a substantial proportion of brain tumor occurrence. The epidemiology of brain tumors was discussed in Part 1 while risk factors for brain tumors in children will be outlined here. The known risk factors for childhood brain tumors include ionizing radiation and certain genetic conditions. There are a variety of other risk factors for which evidence is suggestive but not conclusive. These factors include family history of a brain tumor, nutritional habits during pregnancy and childhood, environmental neurocarcinogens and electromagnetic radiation. Overall, many risk factors have been examined, although most of the information to date is inconsistent and few significant conclusions have emerged.

## RISK FACTORS

Many factors have been studied to try to delineate what genetic and environmental factors are associated with the development of brain tumors in children.

### A. Known Risk Factors

1. Ionizing Radiation: Children who undergo radiotherapy to the brain for treatment of malignancies such as leukemia are at a higher risk of developing a brain tumor, with benign tumors more likely to arise than malignant tumors. Children who underwent radiotherapy for tinea capitis (ringworm of the scalp) had a seven-fold increase in brain tumors compared to normal controls, with the highest risk for benign tumors (relative risk 33.1) compared to malignant tumors (relative risk 2.6) (Ron et al, 1988). As a result of this and other experiences, cranial radiation for diagnostic purposes and most medical reasons is now used sparingly and with much greater caution than in the past. Of interest, Japanese atomic bomb survivors of all ages exposed to a single high dose of ionizing radiation did not show a significant excess of brain tumors, either benign or malignant (Little et al, 1998).
2. Genetic Conditions: Overall, genetic conditions account for less than 5% of all childhood brain tumors (Gurney et al, 2001). Some hereditary conditions that are clearly associated with increased susceptibility to CNS cancer in children include neurofibromatosis Type 1, tuberous sclerosis, nevoid basal cell syndrome, Turcot

3. syndrome and Li-Fraumeni syndrome. Neurofibromatosis and tuberous sclerosis are neurocutaneous syndromes of unknown etiology, which can cause a variety of skin and nervous system abnormalities. Although these conditions are rare, their presence confers a very high risk of tumor development. Specifically, there is a 50-fold increase in patients with neurofibromatosis and a 70-fold increase in children with tuberous sclerosis (Gurney et al, 2001). The converse is that a child with one of these conditions has approximately a 15% chance of developing a tumor, the majority of which are gliomas. Despite the increased risk to some children, only a small proportion of pediatric brain tumors can be explained by known inherited genetic factors.
4. Gender: Males have a 24% higher incidence of invasive brain tumors than females. Compared to females, there is a male preponderance for certain brain tumors, especially medulloblastomas and ependymomas. The reasons are unknown. The predominance of males over females persists among both white and black children.

## B. Evidence Suggestive but not Conclusive

1. Family History: Other evidence for the role of genetics in the origins of childhood brain cancer comes from studies of family history. When a sibling or parent has a brain tumor, there is an increased risk for brain tumors of 3 to 9 fold (Gurney et al, 2001). Some studies show an elevated risk of brain tumors in children when a sibling or parent has certain types of seizure disorders. Similarly, a positive family history of epilepsy and mental retardation has been associated with brain tumors in some studies. In addition, there have been several studies evaluating anticonvulsant use in mothers during pregnancy with inconclusive results to date (Little, 1999).
2. Nutritional Habits: Frequent maternal consumption during pregnancy of cured meat, which contains N-nitroso compounds or precursors, has been consistently associated with a small (1.5 to 2 fold) increased risk of developing a brain tumor. It is unclear whether uncured meats alone or in combination with other dietary factors are responsible. Several studies have looked at the role of nutritional habits during gestation and childhood and brain tumor development. One study showed that increased consumption of vegetable fat in children and maternal potassium intake during gestation were associated with an increased risk of brain tumors (Lubin et al, 2000). But this same study did not find evidence to support the recent hypothesis for the role of nitrates, nitrites and vitamin C during gestation and early childhood as being associated with pediatric brain tumors. In summary it seems that specific nutritional etiologies need to be further evaluated.

## C. Evidence Inconsistent or Limited

1. Parental Occupation: Parents' work in certain industries with a variety of chemical exposures has been linked to CNS tumors in their children in some studies. Specifically, work in industries involving aircraft, agriculture, petroleum, painting, printing and chemical solvents have been implicated. One study found a two-fold elevated risk for brain tumors in children whose fathers worked in the chemical-petroleum industry or as electrical workers (McKean-Cowdin et al, 1998). Some researchers have linked brain tumors in adults with exposure to farm animals. This suggests that viruses may be involved, but this hypothesis needs further evaluation.

2. Environmental Neurocarcinogens: It has been proposed that a small part of the apparent increase in incidence of brain tumors may be due to environmental neurocarcinogens. One category of these environmental exposures, also called chemical neurocarcinogens, has attracted considerable interest, especially N-nitroso compounds. These compounds are found in diet, in alcohol, tobacco, cosmetics, lotions, antihistamines, diuretics, and rubber baby bottle and pacifier nipples (Gurney et al, 2001). In addition, the ingredients in pesticides can react with nitrite in the stomach and cause the formation of N-nitroso compounds (Inskip et al, 1995). Studies have been largely inconsistent in showing the linkage between N-nitroso compounds and brain tumors in humans. Many studies have tried to evaluate parents' exposures to these substances before, during and after pregnancy, without conclusive results (Little, 1999). However, a number of chemical compounds, including N-nitroso compounds, have been shown to cause CNS tumors in experimental animals. These animal studies have shown that susceptibility to these compounds is greatest during the in utero or early postnatal period of life in animals (NCI, 1996). Additional studies need to be done to examine the potential role of chemical neurocarcinogens in the etiology of childhood brain tumors.
3. Other Factors: Passive cigarette smoke exposure, electric blanket use and ultrasound testing during pregnancy have been studied and have not been linked to development of CNS head injuries in patients with brain tumors.

**Electromagnetic Field Radiation (EMF)**

1. Power Lines and Household Appliances: In 1979 the first published study in this area indicated that more children with all types of cancer lived near power lines than did children without cancer (Miller et al, 1997). In an attempt to replicate this observation since that time, studies have been directed toward evaluating EMF exposure. A few studies have reported a small number of children with CNS tumors living in areas with high power lines but a strong association has not yet been demonstrated (Gurney et al, 1996). Some data suggests that for children, most EMF exposure occurs in the home environment. Studies have therefore focused on the evaluation of residential power line magnetic fields and household electric appliance usage. It has been difficult to accurately and consistently measure actual EMF radiation levels in the home from power line and electrical appliance exposures. Instead, researchers commonly use surrogate ranking systems, such as the Wertheimer-Leeper code, which assigns exposure levels to houses based on the visible electric current capacity in and around the home (Gurney et al, 1996). Overall, real-time and precise measurements of exposure levels of electric and magnetic fields continues to be a difficult task and is inconsistent across studies. At the present time, it has been difficult to show the dangers of EMF radiation exposures at levels that are commonly used. For high power field radiation, there is weak laboratory evidence of increasing cancer rates and other harmful effects in animals and cell cultures. There also has been inconsistency in demonstrating dose-response relations when looking at adults in different occupations with different intensity of exposures. Furthermore, the particular subtypes of brain cancer associated with magnetic fields have not been consistent between studies in adults or children. In summary, despite numerous studies and media attention, available data has not yet

been able to consistently show that electromagnetic field radiation causes pediatric brain tumors.

2. Cellular Phones: Cellular telephones are low-power frequency radio devices that transmit and receive electromagnetic radiation at frequencies of about 1000 MHz, above the high-frequency television and below the microwave part of the electromagnetic spectrum. All of these frequency ranges are within the radio-frequency spectrum. Cordless telephones operate at a lower frequency and power than cellular telephones. The biological effect of radio-frequency signals is related to its potential to increase the temperature of exposed tissue, which has the potential to damage cellular DNA. This DNA damage has been hypothesized to play a role in causing cancer. But, most scientists agree that there is negligible heating of brain tissue by cell phones and that the energy they emit produces minimal local heating in the brain, of about 0.1 degrees Celsius (Trichopoulos et al, 2001). Therefore, it has been speculated that any carcinogenic effect of cell phones would be mediated through a non-thermal mechanism as opposed to a thermal (heating) effect.

Cellular phones were introduced into the United States market in 1984 but were not widely used until the mid-1990s. Concern has arisen that the use of hand-held cellular telephones could cause brain tumors due to the recent increased incidence of childhood brain tumors. Allegations were first voiced in the media and courts of cell phones causing cancer in 1993, leading to further interest in this area of research (Moulder et al, 1999). Questions have been raised about adverse health effects of cell phones, especially the possibility that the low-power microwave-frequency signal transmitted by the antennas on the handsets might cause brain tumors or accelerate growth of subclinical tumors (Inskip et al, 2001). Implicating cellular phones in brain tumor etiology would be a considerable public health concern given the rapidly increasing use of these devices by adults and adolescents.

Recent investigations of the use of cellular phones directly increasing the risk of brain tumors have essentially negative results. The New England Journal in 2001 published a large case-control study over a four year time period which examined cellular phone use in adults. The study found that there was no evidence that the risk of brain tumors was higher among individuals who used cellular phones for greater than 60 minutes a day or regularly for five years (Inskip, 2001). These results pertain primarily to analogue telephones at frequencies of 800 to 900 MHz while the increasingly common digital telephones operate at a lower average power and would be therefore expected to carry a lower risk. Also there was no association in the lateral location of brain tumors with the side of the head used while talking on cell phones. Well-known epidemiologist, Dr. Dimitrios Trichopoulos, was reassuring in his comments on this study and stated, “This study allays fears raised by alarmist reports that the use of cellular telephones causes brain tumors.”

Overall, there is not strong or sufficient evidence that radio-frequency radiation from cell phones causes cancer. The results of future investigations may modify this perspective. Nevertheless, many researchers feel it is highly unlikely that future studies will show any cancer-causing effect of cell phone radiation since there is a lack of theoretical basis for non-thermal effects at the involved frequencies (Inskip et al, 2001). It is understandable that cellular phone use and its potential risks of disease have been looked at due to the

growing popularity of cell phone usage in society today. Future research should continue as radiation exposure from cellular phones may cause other potential human health hazards that have not yet been recognized.

## CONCLUSION

A great deal of research is presently being conducted to further illuminate the potential role of electromagnetic field radiation and the development of brain tumors in children. This controversy about electromagnetic fields and cancer reflects the intrinsic difficulties inherent in assessment of cancer risk. Researchers need to improve electromagnetic exposure assessment methods that have so far been inconsistent and have led to difficulties in making conclusions. The etiology of brain tumors has been studied mostly in adults, but are highly concerning in pediatrics, since treatment success rates tend to fall behind that for other childhood cancers.

Scientists continue to look at potential environmental causes including in utero and early postnatal exposures. Childhood brain tumors are a growing research area since incidence is high, prognosis is generally poor and therapeutic modalities are unsuccessful. Perhaps genetic research will add to the understanding of childhood brain tumor etiology, and more importantly, add to improved treatment and survival among these young patients.

## Reference List


1. Gurney JG, Smith MA, Bunin GR; CNS and miscellaneous intracranial and intraspinal neoplasms. SEER Pediatric Monograph, National Cancer Institute 2001; 51-63.
2. Gurney JG et al; Childhood brain tumor occurrence in relation to residential power line configurations, electric heating sources, and electric appliance use. American Journal of Epidemiology 1996; 143:120-127.
3. Inskip PD, Linet MS, Heineman EF; Etiology of brain tumors in adults: Epidemiology in Review 1995; 17:382-414.
4. Inskip PD et al; Cellular telephone use and brain tumors. New England Journal of Medicine 2001; 344:79-85.5.
5. Little J; Epidemiology of Childhood Cancer; World Health Organization, 1999.
6. Little MP et al; Risks of Brain Tumour Following Treatment for Cancer in Childhood: Modification by Genetic Factors, Radiotherapy and Chemotherapy. International Journal of Cancer 1998; 78:269-275.
7. Lubin, F et al; The role of nutritional habits during gestation and child life in pediatric brain tumor etiology. International Journal of Cancer 2000; 86:139-143.
8. McKean-Cowdin R, Preston-Martin S, Pogoda JM, Holly EA, Mueller BA, Davis, RL; Parental Occupation and Childhood Brain Tumors: Astroglial and Primitive Neuroectodermal Tumors. Journal of Occupational Environmental Medicine 1998; 40(4):332-339.
9. Miller RD, Neuberger JS, Gerald KB; Brain cancer and leukemia and exposure to power-frequency (50- to 60-Hz) electric and magnetic fields. Epidemiologic Reviews 1997; 19:273-290.

10. Moulder JE et al; Cell Phones and Cancer: What Is the Evidence for a Connection? Radiation Research 1999; 151:513-531.
11. National Cancer Institute; Cancer rates and risks. National Institutes of Health 1996.
12. Ron E et al; Tumors of the Brain and Central Nervous System After Radiotherapy in Childhood. The New England Journal of Medicine 1988; 319(16):1033-1039.
13. Trichopoulos D, Adami H; Cellular telephones and brain tumors. New England Journal of Medicine 2001; 344:133-134.