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Editors: Julie A. Ross, PhD, Logan G. Spector, PhD and Stella M. Davies, MD, PhD

email: pedsepi@tc.umn.edu

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Fluoride foofaraw

Although fluoride conspiracy theorists are easy fodder for satire (see *Dr. Strangelove*), sincere public concerns about the safety of drinking water fluoridation must be taken seriously. Last year, for instance, the citizens of Bellingham, Washington voted to reject fluoridation of municipal water supplies. Since fluoride deposits mainly in calcified tissues the possibility of its affecting risk of osteosarcoma has received particular attention. Most studies have not supported an association of fluoride with osteosarcoma, but employed unsatisfactory study designs or collected insufficiently detailed exposure histories. Moreover, most have not focused on exposure to fluoride during childhood, when bone growth is rapid. A re-analysis of a case-control study of osteosarcoma has recently filled in this gap in evidence [Bassin EB et al. *Cancer Causes and Control* 2006; 17: 421-428]. Cases of osteosarcoma diagnosed at < 40 years of age during 1989-1992 were identified at eleven United States teaching hospitals. Controls were chosen from the orthopedics departments of the same institutions, matched by date of diagnosis, age, sex, and distance of residence from hospital. Subjects (or parental proxies, for cases < 18 years of age) were interviewed by telephone regarding their residential histories, usual sources of drinking water (municipal, well, or bottled water), and use of fluoride supplements. The level of drinking water fluoridation was estimated for each residence with municipal water either from the Centers for Disease Control (CDC) Fluoridation Census of 1985 and 1992 or from each individual water system.

This painstaking process was detailed in a separate publication [Bassin EB et al. *J Public Health Dent* 2004; 64: 45-49]. Samples of water were obtained from residences with wells and fluoride levels estimated by a colorimeter. A level of fluoridation was assigned to bottled water based on a sampling of leading brands. Fluoride intake for subjects who reported drinking mainly bottled water was estimated as the average of bottled water and residential water fluoridation. Each estimate was standardized to the CDC recommended target level of fluoridation for locale, which takes into account variation in water consumption by climate. Lastly, an estimate of drinking water fluoride intake was calculated for each single year of age, up to 14, and categorized into those reaching < 30%, 30-99%, and >99% of target fluoride levels. Conditional logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) relating drinking water fluoride intake during each single year of age to risk of osteosarcoma, with interaction terms to identify sex-specific effects. This analysis was limited to the 103 cases who were

< 20 years of age at diagnosis and their 215 matched controls. For females, ORs comparing the intermediate and high drinking water fluoride intake categories to the lowest category were weak and not significant. ORs among males were stronger, ranging from 2 to 5, and were significant for fluoride exposure at seven years of age. The ORs comparing risk of osteosarcoma with fluoride consumption of 30-99% and > 99% of target levels to < 30% at seven years of age were 3.36 (95% CI: 0.99-11.42) and 5.46 (95% CI: 1.50-19.90), respectively, among males. Corresponding ORs among females were 1.39 (95% CI: 0.41-4.76) and 1.75 (95% CI: 0.48-6.35).

COMMENT: This study is the most thorough examination of fluoride intake and pediatric osteosarcoma, yet is still less than ideal. The investigators admirably attempted to quantify a remarkably complex exposure. However, there still is substantial potential for misclassification of fluoride intake. For instance, water may be imbibed in school or elsewhere that has variable fluoride content and fluoride intake from food and other beverages besides water was not assessed. Other shortcomings include the hospital-based study design and small number of cases. Whether these findings are real, artifactual, or the result of chance we cannot know without replication. In fact, an accompanying editorial [Douglass CW and Joshipura K. *Cancer Causes and Control* 2006; 17: 481-482] mentions that the present results do not appear to have been replicated in preliminary analysis of data collected from a separate set of cases and controls as part of the extended study. Other studies that use different study designs and perhaps even more intensive exposure assessment will be needed to definitively confirm or refute these results. Logan G. Spector

Send in the clones!

Leukemia relapse occurring after allogeneic bone marrow transplant in what are clearly donor cells is a rare but well described event. The mechanism is poorly understood, with hypotheses such as somatic cell fusion (fusing of a donor cell with a residual host leukemia cell) or a "leukemia-promoting" microenvironment having been suggested. A flurry of recent case reports have described leukemia occurring in unrelated donor umbilical cord blood cells [Ando T et al, *Leukemia* 2006; 20:744-745; Matsunaga T et al, *Am J Hematol* 2005;79:294-298; Fraser CJ et al, *Blood* 2005; 106:4377-4380]. In these cases the leukemia was a new occurrence in the affected child, not a relapse of a previous malignancy, ruling out the cell fusion hypothesis.

In a letter to the editor, [Leukemia 2006; 20:1633-1634] **Mel Greaves** suggests that with the recognized high (around 1% for TEL-AML1) frequency of putative pre-leukemic clones in cord blood, the risk of donor derived leukemia in the recipient might be increased in cord blood transplantation. The proliferative stimulus of transplantation might well be enough to allow emergence of a malignant clone that might remain dormant or be extinguished in the donor child. Professor Greaves suggests that it should be possible to go back to material from the original graft to determine if pre-leukemic cells were present in that product. It should certainly be possible to systematically identify cases of cord blood donor derived recipient leukemia. The availability of sample for "back-tracking" is more challenging as all of a cord blood unit is typically used for transplantation; small aliquots can be kept for HLA or genetic testing and might be available in the future for such a very interesting investigation. Stella M Davies

Babes of Botox

Advanced maternal age has been associated with certain childhood cancers in several studies, although the data are conflicting. Fewer studies have explored advanced paternal age- partly because mom's and dad's age are often highly correlated. Moreover, many studies have explored this association using a case-control approach, which may be biased as older educated individuals are more likely to serve as controls. In this report, **Yip BH et al [Int J Epidemiol 2006; published online September 26]** link the Swedish Cancer Registry with three other national registries (Multi-generation Registry, National Census, and Death Notification) to investigate parental age and childhood cancer. During the period 1961-2000, a total of 7844 childhood cancers were diagnosed under the age of 15 years within a cohort of 4.3 million parents and their children. The overall mean parental age at birth increased for both moms and dads; 27.0-29.6 years and 30.6-32.6 years, respectively. Maternal and paternal age were also strongly correlated ($r=0.74$). The authors used multivariate Poisson regression to obtain incidence rate ratios (IRR) and 95% confidence intervals (CI). Since childhood cancer rates increased during this time period, they adjusted for period and age. They found an increased risk of retinoblastoma with advancing maternal age (IRR=2.39, 95% CI=1.17-4.85 for maternal age > 40 years at birth compared to maternal age < 25 years at birth); this association was maintained after adjustment for paternal age. For childhood leukemia, there was a significant 44% increased risk with maternal age over 40 years, which was still elevated but no longer significant when adjusted for paternal age. Advanced paternal age (> 40 years) was associated with an increased risk of CNS tumor, especially after adjustment for maternal age (IRR=1.69; 95% CI=1.21-2.35). This association with CNS tumors was particularly apparent for astrocytomas in which case there was a 95% increased risk with paternal age > 40 years. Interestingly, associations with parental age were confined to children diagnosed < 5 years of age. With the exception of CNS tumors, there was no evidence of a period effect when comparing the 1961-1980 to 1981-2000. For CNS, the significant results with paternal age were confined to the later period. -

COMMENT: The authors acknowledge that they lacked information on other potential risk factors that may be associated with parental age (e.g., high birth weight, smoking, in vitro fertilization). Nevertheless, this is one of the largest analyses of parental age and childhood cancer and

does offer some potential avenues for further investigation. The authors point to the usual speculation that aging germ cells could be contributing to these increased risks. However, the positive associations found with only one parent (e.g., advanced maternal age and retinoblastoma and advanced paternal age and astrocytomas) are particularly intriguing and may suggest different etiologies. It will be of interest to see whether other national registries can duplicate these findings. Julie A. Ross

Moles on the Mark

Hydatidiform moles (HMs) are fascinating aberrations in nature. Moles usually arise from fertilization of an anuclear egg by one chromosome X-containing sperm (or sometimes two sperm (both X, or one X and one Y)). The egg subsequently divides and develops into a mass of cells entirely of paternal origin (complete HM). Interestingly, these complete HMs are 46 diploid (normal chromosome count) and either XY or XX, but never YY. Alternatively, a partial HM can develop that includes one set of maternal and two sets of paternal chromosomes (triploid). In either instance, the resultant HM "conceptus" is not viable. Some of our understanding of genomic imprinting (differential expression of certain genes depending on the parent of origin) has arisen from studies of HM. Until now, no one has examined the possible relation between HM and childhood cancer. In this brief report, **Roman E et al [Human Fertility 2006; 9:171-174]** utilize medical record data from the United Kingdom Childhood Cancer Study (UKCCS) to identify prior pregnancies that resulted in HM. Obstetric records from 1764 case mothers and 3220 control mothers who had at least one pregnancy prior to the index child's birth were included. A total of 21 mothers had a previous molar pregnancy including 12 (0.68%) case mothers and 9 (0.28%) control mothers. After adjusting for child's sex, month of birth and region of residence, there was an increased risk of childhood cancer with a previous molar pregnancy (OR=2.5; 95%CI=1.1-.6.1). While the ORs were generally elevated across diagnostic subgroups, significantly elevated findings were found for common acute lymphoblastic leukemia (OR=5.2; 95%CI=1.9-14.7) and sarcomas (OR=6.2; 95% CI=1.3-30.3). They speculate that HM may arise along a continuum of epigenetic alteration, with childhood cancer at the extreme end. They note that although most research has tended to focus on genetic rather than epigenetic mechanisms, "epigenetic predisposition to cancer may be a consequence of genetic variation".

COMMENT: As a first report, it will be interesting to see if others can replicate it. One strength is the comprehensive collection of medical and birth records (nearly impossible in the United States), which eliminates recall bias. It was somewhat surprising that maternal age was not evaluated as a confounder. Advanced maternal age would increase the opportunity of having a previous HM pregnancy and is associated with an increased risk of childhood cancer. Nevertheless, the initial finding is of interest. Besides genetic variation influencing epigenetic phenomena, it is important to consider evidence that the environment (e.g., diet) can play a role. As we noted (**See C3 Vol 14, No 4**), animal studies of maternal dietary manipulation of folate show permanent alteration of gene methylation in offspring. This is an exciting time to consider the intersection of epidemiology and basic science. Julie A. Ross