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CAUSES OF CHILDHOOD CANCER NEWSLETTER

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Vol 17 No 6

(website: <http://www.cancer.umn.edu/page/risk/c3main.html>)

December 2006

Osteosarcoma- a growing concern?

Peak incidence of pediatric osteosarcoma (OS) coincides with the pubertal growth spurt, prompting a number of investigations which have sought to determine whether cases are taller or develop differently than controls [see **C3 Vol. 15, No. 4 for an example**]. The latest report is derived from a hospital-based case-control study [Troisi R et al *Br J Cancer* 2006; 95: 1603-7]. Cases of OS were recruited from ten orthopedic departments across the United States; controls were patients seen at the same departments for ailments other than cancer and were matched on age, sex, department, and distance of residence from the hospital. Data on growth and pubertal development were obtained via interview of parents and participants for those < 20 and ≥ 20 years of age, respectively. Pediatric growth records were also acquired for participants 9-21 years of age. Developmental milestones for cases and controls in each matched set were recorded only prior to the cases' date of diagnosis. Percentile values for current height and birth weight were calculated using national standards. Unconditional logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) relating anthropometric variables to risk of OS. This analysis was restricted to 169 cases and 144 controls <40 years of age. Current height was not associated with OS, but cases were significantly less likely to report having been shorter than their peers at 9 or 10 years of age (OR = 0.56; 95% CI: 0.30-1.0). In regards to secondary sexual characteristics, there was no association of disease with having reached menarche among females but male cases were less likely to have started shaving than were male controls (OR = 0.41; 95% CI: 0.18-0.89). Lastly, a greater proportion of cases weighed > 4000 grams at birth than did controls (OR = 3.9; 95% CI: 1.7-10).

COMMENT: The descriptive epidemiology of OS is a conspicuous clue to etiology that continues to drive interest in this cancer. The current investigation, like others, hinted at a role for patterns of growth in development of the disease. The observation that cases had higher birth weight contradicts two previous studies but could signal the importance of prenatal factors or be a marker for later accelerated growth. However, due to the small sample size, power was limited overall and

potentially interesting subgroup analyses, for instance of cases with tumors of the femur (where most longitudinal growth during puberty occurs) or of cases < 20 years of age, could not be performed reliably. It may be preferable in the future simply to compare a series of cases to national anthropometric standards, given the easy availability of such statistics. Logan G. Spector

Checkpoint ChALLie

The G₁/S checkpoint is the critical branch in the cell cycle at which a cell commits to divide or remain intact. Cyclin-dependent kinases are intracellular molecules that move cells into S, or division, phase in response to extracellular signals. As the name implies, cyclin-dependent kinase inhibitors (CDKNs) counterbalance promotive signaling to keep cells in the G₁, or resting, phase. This cycle is frequently dysregulated in cancer cells, in favor of cell division, so it is reasonable to investigate whether polymorphic germline variation in cell cycle genes influences cancer susceptibility. Researchers recently reported on a potential role for CDKN1A, CDKN1B, CDKN2A, and CDKN2B in the etiology of childhood acute lymphoblastic leukemia (ALL) [Healy J. et al. *Blood* 2006; prepublished online September 28th]. In an ongoing hospital-based case-control study in Montreal, investigators collected DNA from 240 children with pre-B ALL and 277 healthy controls recruited from other clinical departments. Parental DNA was also available for 135 cases. Ten single nucleotide polymorphisms (SNPs) in CDKN gene promoter regions, which could potentially affect protein expression, were selected for study. Odds ratios (ORs) and 95% confidence intervals (CIs) comparing cases to controls were obtained using logistic regression. Deviation from expected inheritance of alleles from parents to child (a.k.a. transmission disequilibrium) was assessed using the Family Based Association Test (FBAT). SNPs were examined separately and as estimated haplotypes. One SNP was significantly associated with ALL after correction for multiple testing; the CDKN2A -222A allele was more frequent in cases than in controls (OR = 2.2; 95% CI: 1.2-4.0). Two other alleles (CDKN1B -1608G and CDKN2B -593A) were significantly associated with ALL before but not after accounting for multiple testing. The CAG haplotype for variants at positions -1270, -593, and -287

of the CDKN2B promoter region was associated with an increased risk of ALL (OR = 1.7; 95% CI: 1.2-2.4), which corroborated the single locus analysis of the -593A allele. Applying the FBAT to the subset of case-parent trios revealed significantly elevated transmission of the CDKN2A -222A ($p = 0.009$) and CDKN2B -593A ($p = 0.005$) alleles.

COMMENT: Two strengths support the results of this analysis. The relative genetic homogeneity of the French-Canadians under study reduced the potential for spurious findings due to population stratification (i.e. dissimilarity of ancestry in case and control groups). Also, the case-parent study design is inherently robust to population stratification and is valid even in highly selected case series, so it is reassuring that the case-parent and case-control analyses concurred. On a side note, this sort of validation is expected to become more common in studies of childhood cancer, since parents are often available and willing to participate in research. One caveat to the current study is that the SNPs associated with ALL may only be linked to causal variants rather than being causal themselves. As the authors noted, the CDKN2A -222T>A polymorphism is in complete linkage disequilibrium with the non-synonymous coding SNP Ala148Thr. Further examination of these genes with a dense set of SNPs is thus warranted. Logan G. Spector

An infectious gasp!

Childhood ALL occurs much more frequently in industrialized countries than in developing ones, especially B cell precursor common ALL (cALL), which accounts for the majority of the 2-5 year age peak. As noted previously (see C3 Vol 16, No 2), this observation has led to two not mutually exclusive theories: the first, by Leo Kinlen, postulates that childhood leukemia may arise as a consequence of exposure to an infectious agent, which could be fostered by population mixing. The second, by Mel Greaves, suggests that a lack of exposure to infections in early life followed by an infectious challenge later on may account for the age peak in childhood ALL. Proxy measures of early life infection such as time in attendance at day care and birth order have shown an inverse association with leukemia, though not entirely consistently. In this report, investigators from the UK [Roman E, et al. *Am J Epidemiol* 2006; online; December 20] evaluate Greaves hypothesis in a case-control study. Children 0-14 years of age diagnosed with ALL in Great Britain between 1991 and 1996 were eligible. Two controls (matched on age, sex, and region) were randomly recruited from primary care registries for each case. Parents of cases and controls were asked for permission to collect medical records from birth to diagnosis; these were subsequently abstracted using standard forms. In this analysis, the investigators restricted cases to those diagnosed between the ages of 2 and 5 years (to focus on the age peak) and evaluated evidence of infections in the first year of life as reported in the medical records. A total of 422 cases were diagnosed with ALL in this age group, including 342 with cALL. In comparison to 1,031 controls, children with ALL were significantly more likely to visit a general practitioner with an infection or symptoms of an infection in the first year of life (mean 4.5 visits compared to 3.9, $p < 0.05$). Further,

18% of controls and 24% of cases were diagnosed with at least one infection in the first month of life (OR=1.4; 95%CI=1.1-1.9). ORs were elevated for all types of infection except lower respiratory tract. However, the types of infection varied by age, which influenced the magnitude of the risk. For example, fungal infections in the first month of life (neonatal period) were associated with a higher risk of ALL (OR=1.9; 95% CI=1.1-3.2) than fungal infections diagnosed in the first year (OR=1.4; 95%CI=1.1-1.9). There were no differences for other medical consultations (e.g., diaper rash, feeding problems, etc). Interestingly, children who developed ALL and were seen for infection more than once in the neonatal period were diagnosed on average 7 months earlier than children with one or no infections.

COMMENT: Rather than rely on maternal recall, the investigators used medical records with careful abstraction. Further, events were restricted to the first year of life, while cases and controls were restricted to children aged 2-5 years. Over 90% of cases were ascertained in the area, and the controls were similar with respect to socioeconomic indicators. All of these factors contribute to a rigorous study design that is absent of recall or reporting bias. The authors acknowledge that this report runs contrary to several studies including their own that have used proxy measures of infection such as early life attendance in day care, etc. They speculate that genetic susceptibility may result in an abnormal immune response, which would imply that timing of infection may not be that important in some cases. However, it is also possible that overt clinical symptoms of infection that warrant a visit to a physician may not be the same as priming the immune system with subclinical infections via exposure to children in day care or through older siblings. Along this same line, it is not clear whether the authors took into account birth order. Mothers of first born children (who have been found to be at an increased risk of ALL) would likely take their child to the physician for an evaluation of minor ailments while mothers of second and subsequent children might tend to let problems resolve on their own. This potential bias could also contribute to the findings observed here. Julie A. Ross

Briefly Noted: Clones of diminishing returns

TEL-AML1 translocations are the most common chromosomal abnormalities reported in childhood ALL (see C3 Vol 13 No 3) and have been found in neonatal blood spots of children who later develop leukemia. TEL-AML1 is also found in about 1% of cord blood samples from healthy children suggesting that the translocation is not sufficient for leukemia development. Olsen M et al [*J Pediatr Hematol Oncol* 2006; 734-740] screened a total 2005 healthy blood donors (ages 18-65 years) for TEL-AML1 using real-time and nested reverse transcription PCR. Ten samples (0.5%) tested positive, including 5 males and 5 females between the ages of 23 and 58 years. The authors conclude that prenatal clones of TEL-AML1 diminish with age and likely reflect the lower incidence of TEL-AML1 leukemia in adults compared to children. However, a few questions remain. It is not clear whether 0.5% is really that different from 1%. Further, it is not clear whether TEL-AML1 can be acquired later in life. Julie A. Ross