

C³

CAUSES OF CHILDHOOD CANCER NEWSLETTER

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

email: pedsepi@umn.edu

Vol 18 No 4

(website: <http://www.cancer.umn.edu/c3>)

August 2007

IFG2R + OS = OMG!

Researchers have long suspected that pediatric osteosarcoma (OS) is somehow related to growth during puberty, since incidence of the disease peaks at the time of the adolescent growth spurt. However, it has been difficult to establish clear and consistent differences in height or growth between cases and controls in interview- or record-based studies [see C3 Vol 16, No.6; C3 Vol 15, No 4]. In a new report, investigators attempted to circumvent the limitations of other study designs by examining single nucleotide polymorphisms (SNPs) in genes that regulate bone growth [Savage S et al. *Cancer Epi Biomark Prev* 2007; 16:1667-1674]. DNA was obtained from the blood of 104 cases of OS and 74 controls that participated in a hospital-based case-control study previously described [see C3 Vol 16, No 6]. Fifty-two SNPs in 13 genes involved bone growth regulation were typed. Associations of SNPs with OS were examined using the chi-square test under both dominant and additive (i.e. gene-dose) models of action. Haplotypes were also estimated and analyzed similarly.

Two synonymous exonic SNPs (Ex16+88G>A; Ex45+11T>C) and one intronic SNP (IVS16+15C>T) in the insulin-like growth factor 2 receptor (*IGF2R*) were significantly associated with OS ($p=0.01$, 0.008 , and 0.44 , respectively). SNPs in other candidate genes showed no association with disease. Haplotype analysis suggested that a small block of linkage disequilibrium between Ex16+88G>A and IVS16+15C>T had the most important effect on risk of OS, with an odds ratio of 2.04 (95% confidence interval: 1.29-3.24) comparing the AT to the GC haplotype. Examination of bioinformatic databases suggested that Ex16+88G>A resides in a CpG island, which are regions of the genome regulated by methylation.

The percent methylation at this site was examined in 23 subjects using a bisulfite assay. GG homozygotes presented 85% methylation compared to 54% among heterozygotes and 0.2% among AA homozygotes.

COMMENT: This pilot study offers preliminary evidence in favor of a biologically plausible hypothesis. The data would have been more compelling with a larger sample size, which would offer reassurance that other associations were not missed, and, while study

participants ranged in age from 7 to 77 years, one would expect associations of OS with variants in genes regulating bone growth to be strongest during adolescence. However, results from even the soundest of molecular epidemiologic studies require replication in order to be credible. As it happens, the Children's Oncology Group has recently initiated an investigation of 500 case-parent triads which will examine many of the same genes as the present study and will offer the chance of replication. Logan G. Spector

EBV and Hodgkin Lymphoma: Not a MONolithic proportion

Studies have shown that 30-40% of Hodgkin lymphoma (HL) cases in the western world and a far higher proportion in some developing countries carry the Epstein Barr virus (EBV) in the malignant Reed Sternberg cells. EBV infection is an early event in the development of HL as the viral genomes are monoclonal, indicating that infection of the tumor cells occurred before their clonal expansion. Genetic association studies in sporadic and familial cases include a large number of significant associations with HLA, and the occurrence of HL in children with impaired immunity supports a role for the immune response in susceptibility to HL. In a new study, Niens M et al [*Blood*, epub ahead of print, July 13, 2007] demonstrate that the HLA locus HLA-A*02 is protective against HL, while HLA-A*01 increased susceptibility to EBV-associated disease. There was no effect in EBV negative disease. The authors speculate that the protective effect arises because HLA-A*02 can present EBV-derived peptides and evoke an effective immune response. It should be noted that HLA-A*02 is frequent in Caucasians populations, being present in about 50% of people, and could in part explain the relative infrequency of HL among this population.

COMMENT: Immune responses have been implicated in susceptibility to HL for years. What is novel about this study is the definition of cases as EBV positive or negative to define the role of HLA. This study illustrates the importance of looking at as homogenous and well-defined a population as possible when performing disease susceptibility studies; important associations will be missed if populations are mixed. Stella M Davies

The ALL-SARS game

In 2003, the severe acute respiratory syndromes (SARS) outbreak hit Hong Kong particularly hard. As part of the public health response, all schools were closed for two months and, upon reopening, followed strict infection control protocols for another six months. For instance, all students were required to wear masks at school and those with signs of illness were not allowed to attend. Apart from these formal measures, many people also avoided public areas during the outbreak. The sudden drop in interpersonal contacts created a situation with which to test Kinlen's and Greaves' hypotheses of acute lymphoblastic leukemia (ALL) etiology. Briefly, these hypotheses maintain that ALL results from an abnormal response to delayed infection in childhood or from altered infection dynamics following population mixing [see **C3 Vol. 16, No. 2**].

Li, CK and colleagues [Leukemia 2007; 21:1353–1356] examined cancer incidence in Hong Kong among children 1-14 years of age during 1994-2005. Cases of childhood cancer, excluding central nervous system tumors, were gathered from the Hong Kong Cancer Registry and classified into standard risk ALL (according to National Cancer Institute criteria), other ALL, and non-ALL. Incidence of each cancer group was modeled using a wavelet-based smoothing technique to produce visual plots. In addition, the minimum m-estimation regression method was used to test for changes in cancer incidence during the SARS outbreak.

The number of ALL cases in 2003, 25, was somewhat lower than the 28-41 yearly cases recorded in the other years of the study. Only 7 cases of common (CD10+ B-lineage) ALL were seen among children 1-10 years of age in 2003 compared to 11-23 in 1993-2002 and 2004-2005. Statistical testing indicated that incidence was significantly lower during the SARS period for each type of ALL, with the respective p-values being 0.01 and 0.04. By comparison the respective numbers of cases of childhood cancers other than ALL were 51 in 2003 and 42-75 in other years. The investigators also examined data on reportable communicable diseases, which supported the contention that infections were less common in general while people avoided contact. For example, the number of chicken pox cases in 2003 was 6,780 compared to yearly totals between 8,556 and 16,727 during 1999-2002 and 2004-2005.

COMMENT: The SARS outbreak in Hong Kong comprised a fascinating natural experiment. The data seem to support a decline in common ALL incidence in Hong Kong in 2003, although the small numbers of cases each year, which limits statistical inference and examination of subgroups, is a caveat. Assuming the decline was real, it may indicate that events relatively close to diagnosis precipitate ALL. It will also be of interest, as the authors point out, to determine the cancer incidence among children born during the superhygienic SARS era, although to do so will take several more years and would possibly require pooling data with other affected cities.

EDITORS' NOTE: Children's Oncology Group Epidemiology Committee is hosting the scientific symposium in Denver, Colorado

The Epidemiology Committee is hosting the COG Groupwide Scientific Symposium in Denver on Thursday, October 18 from 9am-noon. With advances being made using a transdisciplinary approach (i.e., the intersection of basic, clinical, and population research), and our increasing knowledge of the importance of the in utero period in the etiology of childhood cancer, the theme for this year's symposium is: **"In Utero Exposures and Childhood Cancer: A Transdisciplinary Approach"** This symposium is being partially supported by the Children's Cancer Research Fund, a non-profit organization that provides research support to the University of Minnesota Divisions of Pediatric Hematology, Oncology and BMT, and Epidemiology & Clinical Research in the Department of Pediatrics. The symposium agenda is below.

"Epidemiology of childhood cancer- Current evidence & future directions"

Julie A. Ross, Ph.D.
Chair, COG Epidemiology
Professor, Department of Pediatrics
University of Minnesota

"The developmental basis of disease: The paradigm that changes everything"

Jerrold Heindel, Ph.D.
Scientific Program Administrator
National Institute of Environmental Health Sciences
Organ and Systems Pathobiology Branch

"Do genotoxicants initiate neoplasms in human fetuses? Mechanistic considerations from animal models"

Lucy F. Anderson, Ph.D., D.A.B.T.
Chief, Cellular Pathogenesis Section
Laboratory of Comparative Carcinogenesis
National Cancer Institute

"Little footprints- Biomarkers of prenatal exposures"

Cynthia F. Bearer, M.D., Ph.D.
Associate Professor
Pediatrics, Neurosciences, and Environmental Health Sciences
Case Western Reserve University
Attending Neonatologist, Rainbow Babies & Children's Hospital

"Chemical exposures and childhood leukemia"

Martyn T. Smith, Ph.D.
Professor of Toxicology
University of California at Berkeley