

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 3

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

June 2007

All ribbing aside- you can count on me!

Congenital anomalies have been noted in pediatric cancer patients and may reflect abnormalities in developmental processes associated with malignancy. In this report, **Loder RT et al [Spine 2007; 32:904-910]** examined chest radiographs of children treated for pediatric malignancy (n=218) at Riley Children's Hospital in Indiana from 2001-2005 and compared them to children (n=200) presenting at the hospital for trauma or abuse. Radiographs were reviewed by one radiologist. Overall, rib number was normal, 24 ribs, for 363 children (86.8%). Of the remaining 55 children, 44 had 22 ribs, 10 had 23 ribs, and 1 had 26 ribs. Three children had rib fusions and 1 child had a rib bifurcation (all 4 were in the malignancy group). When the authors compared rib count (normal/abnormal; 24/not 24) between the control and malignancy group, 92% of controls had a normal rib count whereas only 82.1% of cases did (p=0.003). Interestingly, differences in rib count number among cancer cases was most apparent in children with neural malignancies (35% abnormal) compared to lymphoproliferative (15% abnormal) and solid malignancies (13% abnormal). When the authors compared control children with each of the three malignancy groups in a logistic regression model, the odds ratios (OR) and 95% Confidence Intervals (CI) were 6.2 (2.7-14.5), 2.0 (1.0-4.1), and 1.9 (0.8-4.3) for neural, lymphoproliferative, and solid tumors, respectively. The authors speculate that disruption in certain homeobox genes, which help in body organization and rib sequencing, may also play a role in the development of these malignancies.

COMMENT: This is a remarkable chart review that could be conducted at other centers given the ease of obtaining these readily available data. Importantly, the authors are cautious in stating that while this association is interesting, an abnormal rib count should not give parents too much concern since 8% of healthy children also have abnormal rib counts. This observation raises several key considerations about how we may be overlooking the broader picture when studying etiology. Perhaps childhood cancer does represent a continuum of abnormal development, and etiologic studies, particularly of neural tumors, need to consider congenital and other developmental abnormalities in the process. Julie A. Ross

Random digit dialing: hanging on (and up) the telephone

As we noted in a previous C3 (Vol 15, No 3), the use of random digit dialing (RDD) for nationwide control selection is no longer viable. With the increased use of cellular phones (at the expense of land lines), along with the ubiquitous use of caller identification and answering machines, reaching individuals for interviews via RDD is nearly impossible. Moreover, for those individuals who are reachable (and willing to take part in a telephone interview), there is substantial concern of bias as they represent a diminishing proportion of a population that is difficult to characterize. The Children's Oncology Group Epidemiology Committee recently published an analysis of secular trends in using RDD among case-control studies in the former Children's Cancer Group and the current COG, which seems to have sealed the fate of RDD use nationally in the United States [**Bunin GR, et al; Am J Epidemiol; online April 27**]. During the period 1982-2003, epidemiologists conducted 17 case-control studies that used RDD; data from 8 and 13 studies were available for calculating RDD and field response rates, respectively. [Note: RDD response rates are calculated from the product of the contact rate (percentage of households called in which a household member answers the telephone) and the cooperation rate (percentage of households who participate in screening among those in which someone answered the phone) Field response rates are the proportion of potential controls who participated in a study interview among those screened and found eligible]. Over the period, the contact rate declined by about 2.5% per year from above 90% in the 1980s to between 63-69% in the most recent studies. The response rate similarly declined, from above 80% in the 1980s to between 50-67% after the mid-1990s. Field response rates, in contrast, have declined more modestly. Importantly, however, the overall response rate (product of RDD response and field response) has decreased by about 2.4% per year, and indicates potential for substantial selection bias.

COMMENT: As recognized by the 2002 site visit reviewers for the COG Epidemiology Grant, one of our biggest challenges was the identification of an appropriate alternative control group. To address this

challenge, we held a workshop in 2002 to discuss the pros and cons of different types of control groups that may be viable for nationwide studies. National experts in control selection were invited to give input. Based partially on the success of Dr. Patricia Buffler and colleagues' work in the Northern California Childhood Leukemia Study, the Epidemiology Committee concluded that birth certificates may provide the best alternative to RDD for control selection on a national basis [Ross JA et al *Am J Epidemiol* 2004; 159:922-924]. A survey of all vital statistics registrars in the United States was conducted by the Epidemiology Committee in 2003 (Canada does not allow use of birth certificates). Thirty-two states, providing a sample close to 75% of young children in the United States, agreed to provide birth certificate controls for recruitment. Two COG studies (AE24-Phase 2 and AEPI04C1), funded through the NCI, are utilizing this method to recruit controls under the age of six years. This is no small effort as several of these states have their own regulatory boards and varying requirements under legal statutes. However, both of these studies are successfully tracing birth certificates, and nearly 150 interviews with mothers have been completed. Unlike RDD, an advantage is that non-responders can be characterized through information on the birth certificates as well as through geocoding. Finally, a grant proposal was recently funded (NCI R01 CA108934, Greta Bunin, Ph.D) to test the feasibility and validity of using birth certificate controls up to the age of 15 years. Julie A. Ross

Oh forbidden fruit!

Infant leukemia, diagnosed in the first 12 months of life, often presents with a rearrangement of the *MLL* gene that occurs during fetal development. Approximately 80% of infant acute lymphoblastic leukemia (ALL) and 65% of acute myeloid leukemia (AML) have this rearrangement. Since therapy-related AMLs associated with DNA topoisomerase II inhibitors (e.g., etoposide) also can present with *MLL* gene rearrangements, we speculated that maternal exposure to DNA topoisomerase II inhibitors could be associated with infant leukemia [Ross JA et al, *JNCI* 1994; 86:1678-1680]. There is a growing body of evidence from epidemiological studies that *MLL*-rearranged infant leukemias, particularly AMLs, are associated with maternal exposure to DNA topoisomerase II inhibitors found in diet, medications, and other products. Laboratory evidence also supports this contention. As an example, flavonoids, including quercetin found in apples and onions, and genistein found in soy, are known to be DNA topoisomerase II inhibitors from cell culture studies. However, it has been unknown to what extent this could be extrapolated to humans. Further, although there was some preliminary work to suggest that flavonoids could cause *MLL* gene rearrangements [Strick R et al, *PNAS* 2000; 97:4790-4795], additional follow-up work was necessary. Two independent studies addressing these issues were recently published. The first, by Bandele OJ and Osheroff N [Biochemistry [April 27, 2007], provides data that support the hypothesis that flavonoids function as potent DNA topoisomerase II inhibitors in humans. The authors investigated the activity and mechanism of action for three major classes of bioflavonoids against human topoisomerase II α and II β . They found evidence that genistein was the most active flavonoid, stimulating a 10-

fold increase in enzyme-mediated cleavage. Almost all of the flavonoids tested enhanced DNA cleavage mediated by topoisomerase to some degree. The authors conclude that further physiological research in the benefits and deleterious consequences of flavonoids is needed. Another piece of evidence comes from Doorn-Khosrovani SW et al [Carcinogenesis, May 3, 2007]. Here, the authors investigate double-strand break formation in CD34+ cells isolated from cord blood following exposure to quercetin, kaempferol (also found in apples and onions among other foods) and genistein. Double-strand breaks were frequently observed following exposure to flavonoids. Moreover, *MLL* rearrangements occurred following a rest period for cells to allow for DNA repair. Using an inverse PCR method, *MLL* rearrangements in intron 11 and 12 were found, which is a hot spot for infant and treatment-related leukemias. Notably, the levels of flavonoids used in these experiments would be similar to blood levels achieved after consuming a 220g serving of onions. The authors call for caution in marketing flavonoid supplements as they may contribute to the development of infant leukemia.

COMMENT: These studies are helpful in understanding some of the biological mechanisms by which maternal DNA topoisomerase II inhibitor exposure could lead to infant leukemia. However, there is still much to be understood, given the rarity of the malignancy and the ubiquity of exposure. We would be reluctant to call for caution in marketing flavonoid supplements due to their potential role in infant leukemia based on current evidence. Assessment of gene-environment interactions in humans will likely help in addressing more. The Children's Oncology Group is completing the second phase of a molecular epidemiology study of infant leukemia (COG AE24). We expect to have both DNA (maternal and infant) and interview data available from over 400 cases. Julie A. Ross

UNIVERSITY OF MINNESOTA
Post Doctoral Research Fellowship
Pediatric Cancer Epidemiology
T32 CA 099936

<http://www.med.umn.edu/peds/epi/Fellowships.html>

One postdoctoral slot will be available in the fall of 2007. This program provides opportunities to enhance research training and experience in pediatric cancer across an interdisciplinary environment. Trainees have the opportunity to work in a variety of research settings including molecular and cellular biology, animal studies, prevention and etiology, clinical outcomes including late effects, and exposure and behavior assessment. Graduate Faculty offer courses in epidemiology, genetics, cancer epidemiology, behavioral epidemiology, cancer biology, genetic epidemiology, nutrition, methods, and human experimental studies. Students have opportunities for supervised research in basic biology, human laboratory research, study design, analysis, and grant writing. The post-doctoral trainee can choose to obtain an M.S. in Clinical Research through the Graduate School. Trainees who graduate from this program will be able to undertake pediatric cancer epidemiologic research across a spectrum of disciplines. Trainees participate in weekly research topic meetings, an annual retreat, and present their own research at national meetings. All trainees receive instruction in the responsible conduct of research. Women and minorities are especially encouraged to apply. Applicants must be United States citizens or permanent residents. **Eligible trainees include pediatric fellows who have completed their clinical training and are beginning a research training period and recent Ph.D. recipients in health sciences (laboratory, clinical and epidemiology).** Criteria for selection include academic performance and a career orientation toward independent research in an academic, clinical, or public health setting.