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CAUSES OF CHILDHOOD CANCER NEWSLETTER

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Vol 19 No 1

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

February 2008

No deficit here--it got my attention!

As we summarized previously [see C3 Vol 16, No 2], a few have raised concern that methylphenidate (MPH) used to treat attention-deficit disorder may raise the risk of cancer in children. Part of this evidence comes from a 1995 study in mice where administration of MPH resulted in hepatic tumors; however, a similar study in rats found no risk [Dunnick JK et al, *Toxicology* 1995; 103:77-84]. Additional evidence came from El-Zein RA et al [Cancer Letters 2005; 230:284-291], who conducted a cell mutagenicity study using blood samples of children before and after MPH therapy. They reported an increased frequency of cytogenetic aberrations following MPH. However, that study was limited in scope and had some flaws as noted in our comments. Here, Oestriecher N et al [Pharmacoepidemiology and Drug Safety 2007; 16:1268-1272] conduct a surveillance study linking data from a health maintenance organization's pharmacy database and cancer registry data. MPH use was ascertained from Kaiser Permanente Medical Care Program's (KPMCP) Pharmacy Information Service, an electronic database that provides outpatient prescriptions dispensed at KPMCP pharmacies beginning in 1991. There are over 3 million members of KPMCP, which is based in the greater San Francisco Bay area and Central Valley area of California. The dataset used here contained records from 1991-2003; the authors have data to suggest that over 90% of patients with a pharmacy drug benefit who are members of KPMCP fill their prescriptions at a KPMCP pharmacy. They were interested in examining childhood cancer risk following prescribed MPH therapy. Standardized mortality ratios (SMRs) were calculated (cases observed to cases expected) to examine the association between drug use and subsequent cancer development. Expected numbers were calculated based on age-sex-calendar specific incidence rates in all subscribers. Follow-up time was calculated from the time the drug was dispensed until cancer diagnosis, disenrollment from KPMCP, or the end of 2003, whichever came first. Dose was estimated from the number of prescription dispensings. Cases had to be free of cancer prior to drug dispensing and younger than 20 years of age at first prescription. Malignancies were identified through the Northern California Cancer Registry. There were about 35,400 children identified at risk (MPH user) during the follow-up period; 23 children developed cancer versus 20.4 expected (SMR=1.13, 95% CI=0.72-1.70). For site-

specific SMRs, there was a positive association for 7 sites, a negative association for 10 sites, and no association for one site. Lymphocytic leukemia was the only diagnosis that had a statistically significant excess risk with 8 cases observed but only 3 expected (SMR=2.64; 95%CI=1.14-5.20). In subsequent analysis to evaluate a possible lag effect (use of the drug to treat early symptoms of cancer prior to diagnosis), the authors reported SMRs of 2.64, 3.67, and 4.51 for an unlagged, 1-year lag, and 2 year lag analysis, respectively, based on 8, 8 and 7 observed cases, respectively. These results suggest that there was a notable lag time between MPH prescription and lymphocytic leukemia diagnosis. Overall, the authors conclude that their results are consistent with 'no moderate or strong association between MPH use and cancer risk in children.' However, they caution that the finding with lymphocytic leukemia needs to be investigated further.

COMMENT: This type of research question could be asked within the context of a typical case-control study, but would be subject to the usual concerns regarding recall bias (type of drug prescribed and when prescribed, etc) if medical records were not readily available. Linking easily accessible databases is a complementary approach that can help ask relevant questions important to childhood cancer etiology. Many have linked birth certificates with cancer registries and have found interesting results. In this pharmacy linkage study, limitations include small numbers of cases (and some lost to follow-up), inability to adjust for unmeasured risk factors, and the possibility that not all prescriptions were filled at a Kaiser-associated pharmacy. The positive finding with lymphocytic leukemia (presumably mostly ALL) is likely due to chance and could be easily ruled out by further vetting within other case-control studies. Julie A. Ross

To err in humans

Several childhood cancer studies have focused on the prevalence of major congenital abnormalities and minor anomalies because these errors in morphology may provide important clues about relevant genetic underpinnings (See Roganovic J et al *Med Pediatr Oncol* 2002; 38:128-130; Mehes K et al, *Eur J Pediatr* 1985; 144:243-249 and Am J Med Genet 1998; 75:22-27). Further, associations between genetic syndromes

and childhood cancers have long been recognized by clinicians and confirmed by population-based studies, such as the increased risk of leukemia in children with Down syndrome. A recent study by **Merks J et al [JAMA 2008; 299:61-69]** takes things a step further by performing comprehensive physical examinations on 1,073 children with cancer and 1,007 school-aged controls. Additionally, they attempted to tease out patterns of abnormalities indicating novel tumor predisposition syndromes. They report that major and minor age-independent abnormalities were significantly more common among childhood cancer cases (26.8% and 65.1%, respectively) than the school-aged controls (15.5% and 56.2%, respectively). Cases were also more likely to have both >1 major and >1 minor abnormality than controls. These associations held after 42 individuals with recognized genetic syndromes were excluded. Fourteen individual malformations were statistically significantly related to pediatric cancer; all but two (port-wine stain and scoliosis) were minor anomalies. In addition, the authors identified two novel syndromes of minor anomalies, although no associations within a specific cancer type were found; blepharophimosis (narrow eyelid openings) appeared to be a common characteristic of one novel syndrome ($n_{\text{cases}}=13$, $n_{\text{controls}}=0$), while asymmetric lower limbs ($n_{\text{cases}}=21$, $n_{\text{controls}}=2$) defined the second. Interestingly, the asymmetric lower limb pattern was observed more often among male cases (19 males versus 2 females, $p=0.001$). Cancer survivors made up a large proportion (84%) of the cases, introducing the potential for bias. The authors partially addressed the issue of survival bias by showing the distribution of cancers was similar among survivors and newly diagnosed patients. There may also have been bias in ascertainment of malformations, since the control group was much younger than the case group. For this reason, they analyzed only age-independent abnormalities and took additional steps in the pattern analysis. Additionally, one investigator examined all cases and another examined all controls, which may have contributed to differences in ascertainment. The authors addressed this by replication of a subset of examinations by a clinical geneticist; the interobserver agreement was relatively high in both groups ($K_{\text{cases}}=0.93$, $K_{\text{controls}}=0.85$).

COMMENT: A major strength of this study is the use of thorough physical examinations, allowing for high ascertainment rates of minor anomalies, which are unlikely to be reliably identified via registries, medical record review, or interview. It is also the largest study of its kind. It should be noted that they examined only morphology that could be readily measured (and not abnormalities of internal organs, for example.) Minor anomalies are defects of phenogenesis and can be thought of as extreme values on the continuum of normal phenotypes existing in a population; however, the etiological inference for minor anomalies may be very different than that of common variants, particularly when multiple anomalies are present [**Opitz JM Eur J Pediatr 1985; 144:252-254**]. Associations with congenital malformations may therefore implicate disruptions in morphogenesis in pediatric cancer development. Unfortunately, all childhood cancers cases were grouped together; it would be of interest to see the distribution of malformations by diagnosis. It would also be interesting to learn whether minor anomalies in case siblings are more common than in control siblings. (Note: **JM Opitz** predicts they will not be.) Natural extensions of this study include replication in another population, which is no small undertaking, and exploration of genes relevant

to the fourteen abnormalities and two novel tumor predisposition syndromes identified. Amy M. Linabery

EBV, malaria, and Burkitt lymphoma - Uganda regret it!

Burkitt lymphoma (BL) is infrequent in industrialized countries but relatively common among children in the equatorial nations of Africa. Epstein-Barr virus (EBV) is recognized as a cause of BL, since cases frequently have higher antibody titers than do unaffected children and the EBV genome has been found to be integrated into BL cells. Involvement of malaria in development of BL has also long been suspected, since this infection is endemic in the "lymphoma belt" of Africa, but direct evidence addressing this hypothesis has been lacking until the publication of a recent report [**Carpenter LM, et al; Int J Cancer 2008; 122:1319-1323**]. The investigators enrolled 399 children diagnosed with BL at ≤ 15 years of age in three hospitals in Kampala, Uganda during 1994-1999; analyses was restricted to the 325 children found to be human immunodeficiency virus (HIV) negative. Controls were 579 HIV negative children being treated at the same hospitals for non-malignant surgical conditions ($n = 447$) or for childhood cancers other than BL ($n = 132$). Information on potential risk factors was gathered by parental interview. Blood was obtained from children and a subset of mothers to test for antibodies to EBV and malaria, although losses in transit resulted in fewer subjects with serology available. Odds ratios (OR) and 95% confidence intervals (CI) describing the association between putative risk factors and BL were calculated using unconditional logistic regression. Analysis of interview data indicated independent, significant associations of BL with residential insecticide use (OR = 0.2; 95% CI: 0.1-0.4) and treatment for malaria three or more times in the previous year (OR = 1.8; 95% CI: 1.2-2.8). As would be expected, there was a strong association of BL with the presence of EBV antibodies (OR = 4.5 comparing high to low levels; 95% CI: 2.3-8.7). The level of antibodies to malaria was also associated with BL, with ORs of 3.4 (95% CI: 2.3-8.7) and 2.5 (95% CI: 1.6-3.6) comparing high and low levels, respectively, to no antibodies. The OR for high levels of antibodies to both pathogens compared to no/low levels (OR = 5.0; 95% CI: 2.8-8.9) was higher than one would expect based on exposure to malaria (OR = 1.1; 95% CI: 0.5-2.4) or EBV (OR = 1.0; 95% CI: 0.5-2.2) alone. Mothers of children with BL were not more likely than mothers of control children to have high levels of antibodies to EBV (OR = 1.6; 95% CI: 0.6-4.7) or malaria (OR = 0.3; 95% CI: 0.1-0.8).

COMMENT: Despite the difficulties of performing a case-control study in a poor nation (e.g. 2/3 of blood samples were lost in transit!), this report offers preliminary evidence supporting a role for malaria in development of BL. Certainly it was reassuring that the investigators found a strong association of EBV antibodies with BL, as would be expected, and that the interview data seemed to corroborate an association with malaria. However, it was unclear from the text whether the OR for malaria antibody positivity was adjusted for EBV serostatus and the evidence for synergy between the two pathogens was very tentative given the wide confidence intervals. As every scientist has written at some point, "...more research is needed." Logan G. Spector