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Never meta-analysis I didn't like... until now

Meta-analysis has the goal of summarizing results across studies. At their best, meta-analyses produce highly regarded estimates of disease-exposure associations by increasing statistical power and diluting the idiosyncrasies of individual studies. A recent meta-analysis of maternal prenatal multivitamin use and pediatric cancer, however, added little to the literature. **Goh YI et al [Clin Pharmacol Ther 2007; 81: 685-91]** turned up 61 articles by searching biomedical databases for relevant case-control or cohort studies. Two reviewers then scored each article for possible inclusion in the meta-analysis. In the end, seven articles were included, of which three reported results for acute lymphoblastic leukemia (ALL), two for neuroblastoma (NB), and three for central nervous system (CNS) tumors. (One reported on both ALL and CNS). Odds ratios (ORs) and 95% confidence intervals (CIs) for maternal prenatal vitamin supplementation and cancer were summed for each diagnosis separately. Summary ORs were 0.61 (95% CI: 0.50-0.74), 0.53 (95% CI: 0.42-0.68), and 0.73 (95% CI: 0.60-0.88) for ALL, NB, and CNS, respectively.

COMMENT: Several factors undermine the credibility of this meta-analysis. First and foremost, very few articles were summed for each type of cancer. There is little benefit to summing the results of studies that share flaws, which is more likely when a small number of articles are combined. Two studies were arbitrarily excluded because the authors combined multivitamin use with iron supplementation. In addition, some articles (e.g. **Bunin GR et al. NEJM 1993; 329: 536-541**) were excluded because raw data were not available in the manuscripts. However, the meta-analysts could have contacted the authors, many of whom are easy to locate and known to be collegial, to obtain these data. This meta-analysis does not close the lid on the still-interesting hypothesis that maternal vitamin supplementation reduces the risk of childhood cancers. Logan G. Spector

This mortal coil?

Li-Fraumeni syndrome (LFS) is a rare inherited cancer syndrome resulting from a mutation in the p53 tumor suppressor gene. Carriers are predisposed to develop several types childhood tumors, including choroid plexus carcinoma, rhabdomyosarcoma, adrenocortical carcinoma, and osteosarcoma, as well as adult-onset cancers. Mechanisms that explain the highly variable age at onset of cancer in LFS are beginning to be elucidated. For instance, it

has recently been demonstrated that SNP309 variant of the MDM2 gene, which influences p53 protein degradation, promotes tumor formation at a younger age in conjunction with the 72Arg variant of p53. Investigators in Toronto hypothesized that shortening of the tightly coiled ends of chromosomes, called telomeres, may also influence the age of onset of cancer in LFS carriers [**Tabori U et al, Cancer Res 2007; 67: 1415-1418**]. Short telomeres promote cell senescence and genomic instability. Moreover, the heritability of short telomeres may contribute to anticipation, which is the phenomenon of earlier and or more severe disease onset in successive generations, in some LFS families.

For the current study, the researchers obtained blood from 45 members of nine LFS families and 15 individuals with known wild type (WT) p53 genes. The presence and type of P53 mutations, as well as of MDM2-SNP309 and p53-72Arg variants, was determined among LFS family members by sequencing and restriction fragment-length polymorphism analysis. Telomere length (in kilobases (kb)) was determined for all subjects using the commercial TeloTAGGG assay. There were 17 cancers, including 10 in children (< 18 years of age), among the 23 members of LFS families who were p53 mutation carriers. Among children in LFS families, mean (standard deviation) telomere length was 7.8 kb (0.46), 9.0 kb (0.26), 9.1 kb (0.6), respectively, among affected carriers, unaffected carriers, and WT relatives. Corresponding figures for adults in LFS families were 6.8 kb (0.45), 7.7 kb (0.72), and 8.6 kb (0.9). Mean telomere length was significantly lower ($p < 0.01$) in affected carriers compared to WT relatives in both age groups.

COMMENT: This elegant study has important implications for the clinical care of LFS. The results require replication in an independent and larger sample, but if confirmed may provide a risk-prediction model for age at onset that takes into account telomere length and variants such as MDM2-SNP309 and p53-72Arg. Screening regimens for p53 mutation carriers could thus be tailored to individuals' yearly risk of developing cancer. On a more existential note, it is not clear whether all LFS patients could bear knowing precisely when they may be afflicted, when most of us are comfortable being spared such knowledge. It is also interesting to note that telomere attrition appears accelerated even in unaffected carriers. One reason may be that mutant p53 tends to direct cells towards apoptosis less often, thus allowing shorter telomeres to become prevalent. Logan G. Spector

A growing conception for leukemia risk

Disentangling potential mechanisms of why high birth weight is associated with childhood leukemia, especially acute lymphoblastic leukemia (ALL), is of importance. Many studies have simply evaluated either categorical or continuous definitions of birth weight and new studies are suggesting that information may be lost with these limited explorations. As we recently reported [**C3, Vol 17, No 3**], **McLaughlin CC et al [Br J Cancer 2006; 94:1738-1744]** found that maternal weight influenced the association between birth weight and childhood leukemia risk. Here, **Milne E et al [Am J Epidemiol 2007; online April 18, 2007]** evaluate the risk of childhood leukemia associated with fetal growth. The authors used the impressive Western Australia Data Linkage System, which links data across different population-based registries including inpatient hospital data, midwives' notifications, death registrations, electoral roll, mental health services data, birth registrations and cancer notifications. Linkages are also made with birth defects registries and the reproductive technology transfer registry. Birth registrations from 1980-2004 and cancer registrations in children diagnosed between 0 and 14 years of age during the period 1980-2005 were linked along with midwife records, hospitalizations, and birth defects. Data available included birth weight, length, gestational age, sex, plurality, birth order, maternal/paternal age, maternal height, maternal ethnicity, selected pregnancy complications, and pre-existing maternal medical conditions. Optimal birth weight was calculated, which takes into account gestation duration, maternal height, parity, and infant sex and is derived from a reference population of singleton births without any risk factors for intrauterine growth retardation. After various exclusions, the final data set included 243 cases of ALL and 36 cases of AML. These cases were compared to over 576,000 non-cases. Risk of ALL was positively associated with the proportion of optimal birth weight such that a 1 unit increase was associated with a 25% increase in ALL risk for children under the age of 5 years. Importantly, among children less than 5 years of age who would not be classified as 'high birth weight', there was an approximately 40% increased risk of ALL with each one unit increase in optimal birth weight. The authors indicate that this suggests accelerated in utero growth, rather than just high birth weight, is associated with an increased risk. They found no consistent associations with AML, likely because of small numbers.

COMMENT: This study is important on several fronts. The analysis approach, using optimal birth weight, suggests a larger number of ALL cases that are associated with altered growth patterns in utero. Simply evaluating high birth weight would have missed several cases that reflect abnormal growth. Second, this study confirms that the association with growth is stronger among children diagnosed at earlier ages. Third, the authors have a worthy discussion that reflects on mechanisms that may be important. We first suggested back in 1996 that the association between high birth weight and childhood leukemia may be due to insulin-like growth factor-1 (IGF1) [**Ross JA et al Cancer Causes Control 1996; 7:553-559**]. IGF1 is associated with increasing birth weight and is an important regulator of hematopoiesis. Assuming that many childhood leukemias experience the first initiating event in utero (e.g., reflected in translocations detected in neonatal blood spots), higher levels of circulating IGF1 may increase the probability of additional genetic alterations and lead to frank leukemia. However, high birth weight is also associated with a larger number of at-risk cells, so we also speculated that high birth weight may contribute in that way. This study suggests that the former may be more likely, although this

type of hypothesis might be best answered in an animal model. Julie A. Ross

Nothing to sneeze at

Allergic history has been evaluated in several studies of malignancy with the thought that an abnormal immune response (either overactive or underactive) may be associated with risk. The results are somewhat inconsistent, but lean toward protection for many types of cancer including childhood leukemia for persons with allergies. Importantly, however, relying on questionnaire data for report of allergies can be problematic since one person's interpretation of an 'allergy' may be different than another. In this report from the United Kingdom Childhood Cancer Study (UKCCS) (detailed in **C3 Vol 16 No 5 and 6**), researchers [**Hughes AM, et al Int J Cancer, published online March 27, 2007**] evaluated the relation between allergic history and childhood leukemia from both parental report and primary care medical records. Analyses were restricted to cases and controls that had systematic abstraction of medical records. Additional exclusions included children with Down syndrome, children less than 3 months of age, and children with allergies reported within 3 months of diagnosis (equivalent date for controls), leaving 839 leukemia cases and 1337 matched controls available for analysis. About a third of children had at least one allergy diagnosed. A history of eczema (questionnaire report) was associated with a 30% decreased risk (OR=0.70; 95% CI=0.51-0.97) of ALL, while there was over a 50% reduced risk associated with hay fever (OR=0.47; 95% CI=0.26-0.85). Similar reductions were observed for the most common type of ALL (c-ALL). Parental report of selected allergies was compared to medical records. Importantly, asthma was reported with high accuracy between case and control mothers ($\kappa > .80$), but there was a higher proportion of true negatives among controls compared to cases. For eczema, there was more under-reporting by mothers and a higher proportion of unsubstantiated reports, producing only moderate agreement ($\kappa=46\%$). However, misreporting did not differ between cases and controls. When the authors calculated the influence of these discrepancies on the OR, some intriguing results followed: Using report of eczema from the interview resulted in an OR of 0.77, while report of eczema from the records resulted in an OR of 0.89 (only the interview-derived OR was significant). For asthma, the interview-derived OR was 0.74 and statistically significant whereas the medical record-based OR was 1.01, suggesting no association with asthma. Thus, while the agreement between the two data sources was higher with asthma, the influence of bias due to differential reporting had a greater influence on misclassifying the true OR.

COMMENT: Epidemiologists continually fret over exposure misclassification since questionnaires are typically our mainstay. Studies such as this, which can evaluate the validity of report through a more precise measure (e.g., medical records) can reveal how bad (or good) our questionnaire approach is. For many exposures, we often rely on the premise that misclassification is equally "bad" for cases and controls, and thus would bias the OR toward the null value. The analysis by Hughes suggests that this is not necessarily the case. These results emphasize the importance of considering sensitivity analyses within any study that relies solely on questionnaire data to calculate the OR. Julie A. Ross