Assessing parental contributions to childhood cancer risk

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We now strongly suspect that most cases of childhood cancer initiate some time prior to birth. Reviews of the evidence in support of this supposition are plentiful, and need only be recounted briefly here [1–3]. Circumstantially, the young age at diagnosis [4] and undifferentiated cells of some types of childhood cancer [5–7] favor the presumption of early development. Furthermore, proof-of-principle exists in that diverse tumor types have occasionally been diagnosed prenatally [8–12], and leukemia-specific chromosomal translocations have been identified in specimens obtained at birth [1]. These observations imply that there must be parental influences on childhood cancer risk. How might we assess them?

First, it should be made clear that we are primarily concerned with maternal influences. There are specific instances of *de novo* mutations that arise in the paternal germline [13,14], in which case investigators are rightly interested in determining the genotype of the father and his exposures to mutagens around the time of conception. However, *de novo* mutations are presumed to account for a minority of cases of most types of childhood cancer. As mothers provide the gestational environment in addition to genes, they are more often the focus of etiological investigation.

The risk factors that interest epidemiologists can be roughly described as exogenous or endogenous. The latter category currently, and perhaps permanently, offers the greater opportunity to identify parental influences on the risk of cancer owing to limited options in study design. Whereas one would ideally conduct cohort studies to study etiology, the rarity of childhood cancer, especially considering that each type is presumed to have unique causes, would necessitate impractically large sample sizes. Even the long-planned, 100,000-strong National Children's Study in the USA does not have pretensions to evaluate childhood cancer risk [15], while an effort to pool data

from several existing pediatric cohorts is powered primarily to examine only leukemia, the most common form of malignancy in children [16]. Thus, the case-control study shall remain the workhorse of childhood cancer epidemiology. Unfortunately, this means that many of the classes of exposure we might wish to investigate, which can only be obtained by parental report, such as diet, drug-taking or occupational exposure, are subject to misremembering and differential recall by disease status. Although these phenomena tend to cloud interpretation of exogenous exposures, all is not lost (more on this later).

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Endogenous risk factors are somewhat less problematic to assess. Insofar as complications of pregnancy are well-documented and medical records obtainable, these provide unbiased glimpses into the *in utero* environment. However, studying maternal genotypes, which determine substantial proportions of many pregnancy phenotypes, is ultimately the more powerful approach. Surprisingly, given the likelihood of there being maternal genetic effects on the risk of childhood cancer, few studies reported so far have considered genotypes other than those of the children themselves [17,18], although for some gene variants there are already more than a dozen studies [19]. As genetic epidemiology diffuses further into pediatric cancer research, this gap will surely be filled, aided by the fact that family-based designs provide additional flexibility to study parent-of-origin (i.e., imprinting) and maternal genetic effects [20–22].

An aside regarding the utility of the genome-wide association study (GWAS) in childhood cancer is appropriate here [23]. A few examples of the use of arrays to assay common single

nucleotide polymorphism markers across the genome have appeared recently for acute lymphoblastic leukemia [24] and neuroblastoma [25], which have turned up relative risks in the order of 1.5–2. These associations were detected with high confidence, even with relatively small sample sizes, but account for a small proportion of cases, as has been the situation for many GWAS of adult-onset diseases [26]. Moreover, ever larger studies (that are not, in any case, especially feasible for rare diseases such as childhood cancers) will likely turn up only variants with ever smaller relative risks. It would seem that GWAS, while they have a place, are not likely to explain a large proportion of childhood cancer causation until, one hopes, arrays begin to include a substantial share of rare variation. In the meantime targeted, well-justified candidate gene studies conducted in an iterative process with data from traditional case–control studies are more likely to bear fruit. The putative roles of maternal folate intake during pregnancy and birth weight in childhood cancer etiology provide instructive examples.

An Australian report nearly a decade ago suggested that maternal folate supplementation during pregnancy may decrease the risk of acute lymphoblastic leukemia in offspring [27]. Hopes that a preventative measure for childhood leukemia had been found drove interest in the finding. However, the response from the scientific community consisted mainly of studies that examined well-known variants in the 5,10-methylenetetrahydrofolate (*MTHFR*) gene [19], and only one small study that examined its interaction with maternal folate intake [28]. Given that *MTHFR* variants seem to exhibit an effect only in the presence of folate deficiency [29], and that the maternal *MTHFR* genotype is likely to help determine bioavailability of the nutrient to the fetus, it now appears that the proper follow-up to the initial, provocative findings have been lacking. To be fair, ongoing studies that could rigorously address the issue of maternal folate intake and metabolism should soon produce informative results [30,31]. When they and others that examine strong hypotheses involving

gene–environment interaction (e.g., *NQO1* and dietary topoisomerase II inhibitors in infant leukemia [32,33]) do appear, they may provide a remedy to the biases of concern when relying on maternal recall. That is, survey response is generally presumed to be independent of genotype, and thus demonstrated gene–environment interactions tend to reinforce the credibility of the underlying environmental associations assessed by survey alone.

Parental influences on childhood cancer risk have already been indirectly supported in studies of birth characteristics. Incidence of several tumor types increases with rising birth weight [34–37]; an analysis of birth weight in the Medical Birth Registry of Norway attributed approximately 20% of the variance in this complex trait to maternal genetic effects [38]. As the knowledge of maternal and fetal genetic variants that influence birth weight advances, these variants should be considered candidate genes for childhood cancer as well. Other birth or pregnancy characteristics that have been associated with childhood cancer less solidly, such as pre-eclampsia, may nonetheless point to further candidate genes.

Elegant studies over the last several decades point to an *in utero* or preconceptional origin of a majority of childhood cancers and, in turn, strongly suggest that exposures to parents during these critical windows of risk, or their intrinsic characteristics, may affect their children's risk of cancer early in life. This fact should be exploited to design well-conceived epidemiologic studies that examine parental and fetal influences in pediatric cancer causation.

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