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Children's Oncology Group's 2013 Blueprint for Research: Epidemiology

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Abstract

Investigators worldwide have for over forty years conducted case-control studies aimed at determining the causes of childhood cancer. The central challenge to conducting such research is the rarity of childhood cancer, thus many studies aggregate cases through clinical trials organizations such as COG. Rarity also precludes the use of prospective study designs, which are less prone to recall and selection biases. Despite these challenges a substantial literature on childhood cancer etiology has emerged but few strong environmental risk factors have been identified. Genetic studies are thus now coming to the fore with some success. The ultimate aim of epidemiologic studies is to reduce the population burden of childhood cancer by suggesting preventive measures or possibly by enabling early detection.

Keywords

Epidemiology; etiology; prevention

INTRODUCTION

Investigators worldwide have for over forty years conducted case-control studies aimed at determining the causes of childhood cancer, initially focusing on environmental risk factors but more recently examining genetics. The central challenge to conducting such research is the rarity of childhood cancer, thus many studies aggregate cases through clinical trials organizations such as COG. Rarity also precludes the use of prospective study designs, which are less prone to recall and selection biases. Despite these challenges a substantial literature on childhood cancer etiology has emerged and few strong environmental risk factors have been identified. Genetic studies are thus now coming to the fore with some success. The ultimate aim of epidemiologic studies is to reduce the population burden of childhood cancer by suggesting preventive measures or possibly by enabling early detection.

STATE OF THE DISCIPLINE

Our knowledge about the etiology of childhood cancer is still quite limited. One reason is the continued reliance on the case-control study design. Although the design is efficient for

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the study of rare diseases it is potentially more susceptible to recall and selection biases than the cohort design [1, 2]. The number of studies of each type of childhood cancer is roughly proportional to incidence, with dozens having been conducted in acute lymphoblastic leukemia [3] and only a handful having been conducted in Ewing sarcoma [4, 5], for instance. Most epidemiologic studies of childhood cancer have been conducted in Europe and North America, with COG and its predecessor groups contributing the bulk of research from the latter [6]..

The first generation of epidemiology studies gathered mainly by parental interview and medical record abstraction [6]. However, more recent studies have adopted the case-parent triad design for both practical and scientific reasons discussed below. This design allows estimation of genetic association, maternal genetic effects, and gene-by-environment interaction while avoiding the need to obtain a control group, which has become increasingly difficult in the last decade in many locales. Accordingly, many investigators now concentrate mainly on molecular epidemiology.

MAJOR RECENT ADVANCES

Epidemiologic research is by nature incremental, as careful replication of results is a hallmark of causality [7]. Consequently many recent advances in the field have been methodologic, such as aggregating cases through clinical trials networks [8], trying new methods of control selection [9–11], adopting new study designs, and improving exposure measurement [12–14]

Aggregating cases

In many jurisdictions, including European countries [15] and individual states in the U.S. [16], childhood cancers are centrally registered. In many instances cases may be contacted for research through registries, however few single jurisdictions are large enough to recruit adequate numbers of cases to studies. Hence, it is desirable to aggregate cases through national or international clinical trials organizations. The Childhood Cancer Research Network of COG provides a paradigmatic example.

Previously the conduct of epidemiologic studies within COG required local institutional IRB approval and physician permission before contacting patients, which resulted in a heavy administrative burden and a substantial loss of potential participants. In recognition of these difficulties, a pilot protocol was developed and activated at a 10% random sample of COG institutions in North America [8] involving two upfront consents for parents (and children, if age eligible). The first consent allowed name and contact information to be released to the COG registration system. In addition to this first consent, the second consent involved agreement to be potentially contacted in the future to consider taking part in a non-therapeutic study. These future studies would then be separately consented by the investigators conducting the study. By the end of the pilot study, over 2,200 individuals had been approached; 96% agreed to both levels of consent and only 1% refused both consent levels. Given the success of this pilot the CCRN opened groupwide within COG in late 2007 and as of mid-2012 there were over 27,000 registrations on the CCRN in the United States and Canada (Table I). Among CCRN registrants, ~93% gave permission for contact for future non-therapeutic research. For many tumors, the CCRN is the only entity worldwide that aggregates enough cases to enable a study.

Control selection

Control selection has become increasingly difficult on a nationwide basis in the United States [11] and elsewhere [17]. This has been documented by the Children's Cancer Group (CCG)/COG, which conducted a number of case-control studies with control selection by

random digit dialing over a twenty-five year period [11]. They found a significant decline in participant response, which mirrors many investigators' recent experience [18–23]. Alternatives to random digit dialing include recruited through birth registries, friend controls, and genetic epidemiologic study designs [24]. Birth certificate controls were used in two recent COG studies [9, 10, 25] and were found to be comparable to random digit dialing controls there is a substantial administrative burden to dealing with more than thirty state birth registries. Hence, there is practical appeal to adopting the triad design discussed below.

Case-parent triad design

Due to the difficulty of recruiting controls as well as increasing interest in genetics, many have adopted the case-parent triad design [26, 27]. Scientifically the triad design is appealing because of its validity and flexibility; there are several statistical models by which one may analyze triad data, but all examine whether the inheritance of alleles by affected children deviates from Mendelian expectation [28–36]. The design allows estimation of risk ratios associated with alleles or haplotypes while being robust to confounding by ancestry (i.e., population stratification). It also allows the estimation of maternal genetic effects, parent-of-origin effects (i.e., imprinting), and gene-by-environment interaction. By adopting this design one precludes examination of environment only, however it is likely that the effect of most environmental factors is mediated through genetics.

Exposure assessment with dried blood spots

Dried blood spots (DBS) are stored for up to twenty years by a number of jurisdictions [37, 38] and have the potential of providing an unbiased assessment of exposures in late pregnancy. For instance, DBS have been used to examine prenatal exposure to tobacco[39] and folic acid [40], among many other possible analytes [41]. However, the ability to obtain DBS for childhood cancer research across multiple jurisdictions has not been tested. A pilot study in the United States was able to obtain written consent for release of DBS from 32% of participants, with the remainder being passive refusals or losses-to-follow-up. Five states sent DBS upon receipt of signed consent forms and the remainder did not provide them, either because they have been destroyed or because DBS release is not allowed [42]. It is thus possible to incorporate DBS into epidemiology studies for a small but useful fraction of patients in jurisdictions that retain them and allow release.

KEY INITATIVES

Exogenous risk factors

Many epidemiologic studies have sought to establish whether exogenous or environmental factors influence childhood cancer risk. Exploratory investigations in fact comprise the bulk of the literature for many types of childhood cancer [3, 43–45] and most candidate exposures have shown no strong associations. A few specific exposure-disease relationships based on strong hypotheses are however being investigated.

De novo infant leukemia frequently manifests MLL gene rearrangements, similar to secondary acute myeloid leukemia following etoposide therapy, leading to the hypothesis that maternal exposure to DNA topoismerase II inhibitors during pregnancy increases the risk of infant leukemia harboring MLL gene rearrangements [46], This hypothesis has been explored preliminarily in the United Kingdom [47] and Brazil [48], each of which found some associations of infant leukemia with maternal medication use during pregnancy. However, the most common source of exposure to DNA topoisomerase II inhibitors is diet. A single United States study has examined maternal intake of foods containing DNA topoismerase II inhibitors, which found a suggestive, but not significant, trend of increasing

risk of MLL-rearrangement positive acute myeloid leukemia with increasing consumption [49].

Recent evidence indicates increased risk of hepatoblastoma in low (1,500–2,500 grams) and especially very low (<1,500 grams) birth weight infants [50]; among the smallest infants rates are as much as 20-fold higher than background. The association of hepatoblastoma with low birth weight has been reported in the United Kingdom, the United States, the Nordic countries, China, and Japan [45], suggesting a widespread exogenous risk factor. The most obvious possibility is that hepatoblastoma is initiated or promoted by iatrogenic exposures in neonatal intensive care units [51]. This hypothesis has been explored in two Japanese studies, which enrolled too few cases to credit the results [52, 53]. A much larger and more comprehensive case-control study of hepatoblastoma has been conducted by COG[54], the results of which will be available in the near future.

Genetic risk factors

A largely endogenous etiology is suggested for several types of childhood cancer. For instance, the close correlation of osteosarcoma incidence with the childhood growth curve, the earlier peak in incidence in females, and the frequent occurrence of tumors in the long bones of the leg suggest that the etiology of pediatric osteosarcoma is linked to bone growth [55, 56]. The implication of this descriptive epidemiology is that children with a more rapid or sustained growth spurt have a higher risk of osteosarcoma. As the timing and extent of adolescent bone growth are under substantial genetic control a number of investigations have concentrated on germline genetics in osteosarcoma [57, 58]. The largest such study was recently conducted by COG and initial analyses focused on 798 single nucleotide polymorphisms in 42 genes involved in estrogen metabolism and the insulin-like growth factor/growth hormone axis [26]; three variants were significantly associated with osteosarcoma after correction for multiple comparisons.

Risk of germ cell tumors also appears to be influenced largely by inherited propensity of germ cells to survive and resist apoptosis during prenatal migration. Compelling pilot data suggests that genes associated with adult testicular germ cell tumors, *KITLG*, *SPRY4*, *BAK1* and *DMRT1,* are also associated with pediatric germ cell tumors in both sexes [59], and COG is currently investigating this hypothesis in a much larger ongoing study.

Ewing sarcoma occurs with an incidence of greater than 9:1 in children with European ancestry compared to those with primarily African or Asian ancestry [60]. While a recent genome-wide association study (GWAS) in France has identified single nucleotide polymorphisms (SNPs) associated with Ewing sarcoma in Europeans [61], it is unlikely that these explain such a wide gap in incidence between ancestries. Admixture mapping [62] of cases with African-American or Hispanic ancestry is likely to uncover additional loci that Ewing sarcoma cases inherited in common from European ancestors. In addition, recent data suggests that the length of microsatellites which are binding sites of the of EWS-FLI1 fusion protein influences downstream expression of Ewing sarcoma signaling pathways [63], suggesting that cases will have inherited a large number of consecutive GGAA-repeats in specific EWS-FLI1 transcriptional target genes. Both hypotheses are the subject of current investigation within COG.

Gene-environment interaction

Identification of gene-environment interaction can strengthen the evidence that exogenous exposures are associated with childhood cancers. For example, several studies in Europe and the United States have suggested that maternal vitamin supplementation during pregnancy may lower the risk of neuroblastoma [44, 64]. Because these associations have been

determined by maternal interview in case-control studies, they may be due to recall or selection biases. However, mothers' responses to interview should be unrelated to their genotypes- hence the appeal of studying interaction between maternal vitamin supplementation and common genetic polymorphisms involved in folate, vitamin A, and related metabolic and transport pathways in an ongoing COG study.

STRATEGIC APPROACH: ADVANCING THE DISCIPLINE

In the coming years most epidemiologic investigations of childhood cancer will incorporate genetics and further will move from mainly investigations of candidate genes to GWAS, as several have recently succeeded despite sample sizes that fall far short of recommendation [65] and despite a distinct lack of familial aggregation or twin concordance apart from known high-penetrance syndromes [66–71] (note that the high concordance for leukemia in monozygotic twins is thought to be due to *in utero* transmission rather than genetics[72]).

The apparent reason for the success of GWAS in pediatric cancers is that the magnitude of association, described by the odds ratio (OR) per allele, is greater in childhood compared to adult cancers. The median odds ratio (OR) per allele in GWAS of adult cancer was ~1.25 in a recent review [73], with 75% having an OR <1.5. In contrast, SNPs associated with four childhood cancers in GWAS have ORs per allele of between 1.4 and 2.2 [61, 74–77]. These ORs are plotted versus minor allele frequency in Figure 1; the legend includes the number of cases included in discovery and replication phases. Based on this empirical track record of childhood cancer GWAS, it is reasonable to expect a higher effect size for variants associated with other childhood cancers. Thus, although the achievable samples sizes will remain small compared to adult cancers, it is likely that the GWAS approach will to continue to succeed in pediatric tumors.

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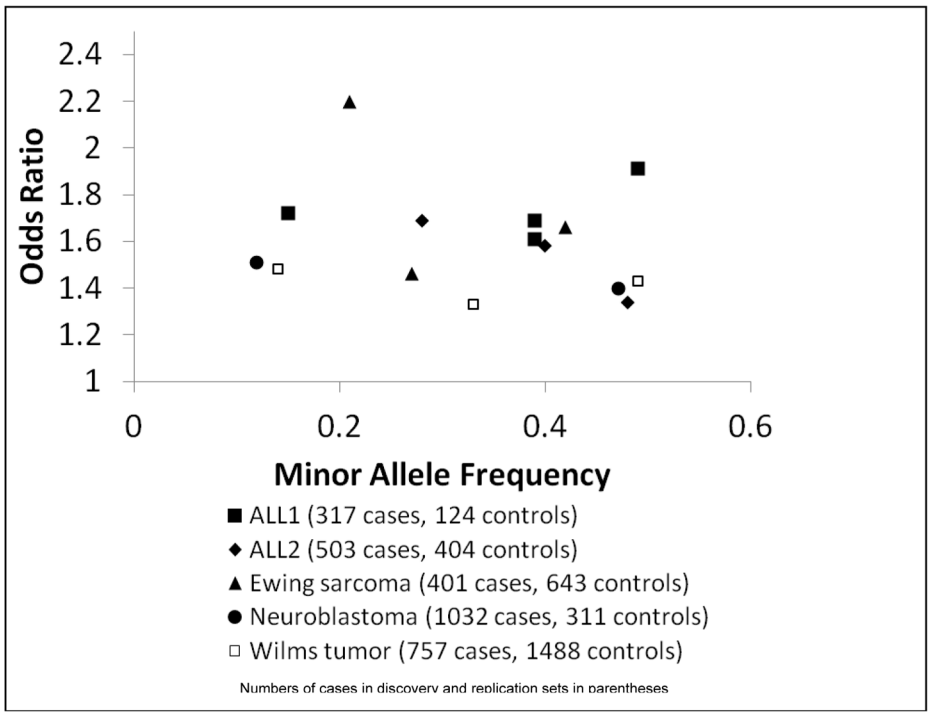

Figure 1.
Odds ratios per risk allele and minor allele frequencies for SNPs with genome-wide significance in the first five GWAS of childhood cancers.

Table I

Enrollments on the Children's Cancer Research Network (ACCRN07) protocol between July 1, 2008 and June 30, 2012

Cancer	Number	Percent
Leukemia	10109	36.81
Hodgkin lymphoma	1704	6.2
Non-Hodgkin lymphoma	1790	6.52
CNS tumors	4071	14.82
Neuroblastoma	1776	6.47
Retinoblastoma	375	1.37
Wilms tumor	1383	5.04
Hepatoblastoma	338	1.23
Osteosarcoma	884	3.22
Ewing sarcoma	547	1.99
Rhabdomyosarcoma	960	3.5
Other soft tissue sarcoma	918	3.34
Germ cell tumors	1045	3.81
Thyroid carcinoma	76	0.28
Melanoma	97	0.35
Other tumors	1390	5.06