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Genetic and nongenetic risk factors for childhood cancer

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Summary

The causes of childhood cancer have been systematically studied for several decades, but apart from high-dose radiation and prior chemotherapy there are few or no strong external risk factors. On the other hand, inherent risk factors including birth weight, parental age, and congenital anomalies are consistently associated with most types of pediatric cancer. Rare, highly-penetrant syndromes have long been known to cause a small proportion of cancers but recently the contribution of common genetic variation to etiology has come into focus through genome wide association studies. These have highlighted genes not previously implicated in childhood cancers and, surprisingly, have suggested that common variation explains a larger proportion of childhood cancers than adult. Rare variation and non-Mendelian inheritance, such as through maternal genetic effects or *de novo* germline mutations, may also contribute to childhood cancer risk but have not been widely examined to date.

Keywords

Epidemiology; etiology; genome-wide association studies; case-control studies; pediatric cancer

Introduction

The causes of childhood cancer have been systematically studied for several decades. The incidence of all cancers occurring in children under 20 years of age is about 175 cases per million in the United States (1), with the incidence of many individual types [typically grouped by the International Classification of Childhood Cancer (ICCC) schema(2)], in the low dozens (Figure 1). Rarity is thus a central fact which dictates the quality and quantity of evidence for causal associations between putative risk factors and childhood cancers. Most etiologic investigations of childhood cancer have thus of necessity used the case-control study design (3), in which the characteristics of patients with a disease are compared to those of a carefully selected group of disease-free controls. When they require participant

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involvement, as in the many studies of childhood cancer which have collected exposure information through parental interview, case-control studies are susceptible to both recall and selection biases.

Given the milieu for childhood cancer epidemiology, evidence regarding causal associations has accumulated slowly. However, for the most common types of cancer, particularly acute lymphoblastic leukemia (ALL), the body of literature is now sufficiently large to allow data synthesis through meta-analyses and data pooling. This review will only briefly discuss such analyses of external, or environmental, risk factors, as they have mainly demonstrated weak or null associations. In contrast, intrinsic characteristics or conditions of childhood cancer patients have shown stronger, more consistent associations and in the last half-decade the application of genome wide single nucleotide variant (SNV) arrays to several childhood cancers has generated surprising insights into their biology. Hence, the majority of this review for the general pediatrician will cover these topics in a broad overview to reflect their increased importance in the current understanding of childhood cancer etiology.

Demographic risk factors

Childhood cancer incidence has long been noted to vary by age, sex, and race/ethnicity. Overall incidence is highest in infancy at about 240 cases per million per year. This rate drops to a nadir of 128 cases per million at 5-9 years of age before rising to 220 cases per million at 15-19 years of age (1). Grouped incidence however obscures interesting patterns among individual cancers (Figure 1). For instance, all the embryonal tumors (neuroblastoma, Wilm's tumor, retinoblastoma, etc.) share a downward sloping incidence which starts high at birth and dissipates after about 5 years of age. ALL is notable for the incidence peak which occurs between 2 to 5 years of age, while bone sarcoma incidence peaks sharply around the time of the pubertal growth spurt in early-to-mid adolescence.

For most childhood cancers there is a slight male preponderance (Figure 2). The male-to-female ratio ranges from 1.04 to 1.64 in neuroblastoma and germ cell tumors, respectively, in cases 0-19 years of age but varies considerably by age group and more specific diagnosis. Wilm's tumor is notable for being the one major childhood cancer which is more common in females.

Childhood cancer risk also differs by race/ethnicity (Figure 3). Relative to white children in the United States the incidence of most types of cancer is lower in black, Asian, and Hispanic children. In some cases, such as the near complete lack of Ewing sarcoma among black and Asian children, the disparity is rather dramatic. In a few notable instances cancer incidence is higher in other groups compared to white children. That acute leukemia incidence is about 10% higher in Hispanic children compared to white children is particularly notable. The extent to which racial/ethnic differences are attributable to genetic versus environmental differences has yet to be determined but will surely come into focus as the genetic architecture of childhood cancer continues to be elucidated.

Environmental risk factors

High dose ionizing radiation and prior chemotherapy are accepted causes of childhood cancers, each raising risk several fold (4-7). No other environmental risk factors, by which

we mean any exposure which originates outside the body, have emerged as definitively causal for childhood cancer.

Measurement of environmental exposures poses a challenge in elucidating their effects on childhood cancer risk. Prospective studies would require hundreds of thousands, if not millions, of children to identify enough cases to generate statistically meaningful results. Thus most childhood cancer studies must rely on the case-control design, which is particularly problematic for evaluating certain types of exposures. Demographic and intrinsic factors are unambiguous, relatively easy to obtain via questionnaire, and, in such cases as parental age, race/ethnicity, and birth defects, generally not subject to recall error. In contrast, environmental factors such as parental diet, maternal medication, caffeine, and alcohol use, and pesticide and air pollution exposure, among others, are very difficult to measure accurately in a retrospective design. Although use of registries, birth and medical records and other data sources reduces some sources of bias, accurate exposure assessment remains a major barrier to determining the causal impact of environmental factors on childhood cancer risk.

For many childhood cancers findings are inconsistent or studies too few to conduct meta-analysis; moreover synthesis is hampered by the need to separately examine exposures during the preconceptional, pregnancy, and postnatal periods and the progressively finer classifications of tumors. ALL, being the most common childhood cancer, has however been the subject of several meta-analyses of putative environmental risk factors (Table 1)(8-15).

Exposure to infections has been one of the most commonly examined environmental exposures in relation to ALL risk, and there are two main hypotheses regarding the nature of this relationship. Kinlen proposes that previously isolated, and therefore immunologically naïve, populations are susceptible when exposed to specific infectious agents due to population mixing (16). A recent meta-analysis estimated an increased risk of ALL in rural settings of population mixing (17). Greaves' hypothesized that an immature and unchallenged immune system, resulting from delayed exposure to common infections, produces an unregulated immune response and leads to ALL in the presence of susceptible cells (18, 19). While direct measurement of exposure to infections and the resulting immune response is generally not feasible, several proxies have been employed, including birth order(20-22), daycare attendance(23, 24), breastfeeding(25), infectious illness histories(26), and vaccinations(27). Meta-analyses have shown protective effects for both breastfeeding (28) and daycare attendance (13), although because these are indirect exposure measures, it is unclear whether infection exposure or some other factor is driving these associations.

Several recent meta-analyses have identified increased risk for both residential (29, 30) and maternal occupational (14) exposure to pesticides. Studies of residential pesticide exposure have generally relied on self-report, which is subject to recall bias that may inflate risk estimates. Some recent studies have used residential proximity to pesticide applications (31-33), a method which is less prone to bias but still prone to measurement error which may attenuate risk estimates (34). Occupational studies typically rely on either self-report or record data. While an association between pesticide exposure and ALL is supported by the available meta-analytic data, it is difficult to estimate the true magnitude of effect, if there is

indeed a causal relationship, given the varying exposure assessment methods and the inherent biases and measurement errors therein.

Associations for other exposures examined using meta-analyses, including maternal alcohol(11), coffee(35), and vitamin use(9), and both paternal (12) and maternal (10) smoking have yielded mostly null (10, 11) or slightly elevated (12, 35) results. Maternal prenatal vitamin use was associated with a decreased risk of ALL in offspring, although the meta-analysis was based on only three studies (9). . While a causal role for these risk factors is possible, observational epidemiology is not conclusive in these circumstances. High-quality studies with a focus on accurate exposure assessment are necessary to evaluate environmental risk factors for childhood cancer.

Intrinsic risk factors

Several intrinsic characteristics of children or their parents have been consistently associated with childhood cancers. Risk of ALL(36), central nervous system tumors(37), neuroblastoma(38), and Wilm's tumor(39), among others, rises as a linear function of birth weight, to varying degrees, and recent analyses that have used alternate measures of birth size (e.g. size for gestational age, percent of optimal birth weight) have found similar results (40). Risk of acute myeloid leukemia is elevated with both low and high birth weight(41), while risk of hepatoblastoma is inversely related to birth weight and strikingly elevated among the smallest infants (42). The reasons behind the association of higher birth weight with childhood cancers have not been explored in detail, but may include prenatal growth hormone exposure (43), the underlying genetics of birth weight (44), and the greater number of cells at risk for carcinogenic transformation. The strong inverse association of hepatoblastoma with birth weight has been thought to be related to neonatal treatment, but no culprit exposure has been identified to date(45).

Advanced parental age has also been associated with most childhood cancers. A large pooled analysis of population-based record-linkage studies found significant positive linear trends in leukemia, lymphoma, brain tumor, neuroblastoma, Wilm's tumor, bone tumors, and soft tissue sarcomas with 6-15% increased risk per five years of maternal age(46). Paternal age was not associated with these cancers after adjustment for maternal age, however since the two are highly correlated it is not clear that maternal age was solely responsible. As with birth weight, the reasons behind these findings are unclear, but may include genetic or epigenetic mutations associated with advanced parental age (47).

Structural birth defects have consistently been found to increase the risk of childhood cancers, as a group, about threefold (48-50) although due to the rarity of both individual birth defects and individual childhood cancers more specific associations have not been reported to date. Undoubtedly some of this association is explained by underlying genetic causes, but as most birth defects appear sporadic(51) genetics are not likely the sole explanation for cooccurrence.

Genetic risk factors

Inherited syndromes, caused by high-penetrance germline DNA mutations(52, 53), chromosomal aneuploidy(54), or epigenetic disorders(55), are known to cause a minority of

childhood cancers. Although the proportion attributable to syndromes has rarely been precisely quantified for common childhood cancers the estimate is typically 5-10%. For especially rare cancers, such as pediatric adrenocortical carcinoma, the proportion can be much higher (56). Specific syndromes predisposing to particular childhood cancers are covered elsewhere in this issue.

Genome wide association studies (GWAS) compare the frequency of hundreds of thousands of common SNV's in those with a disease to those without(57). Due to the large number of comparisons made in GWAS a SNV-disease association must reach a high degree of statistical significance (generally $p < 5 \times 10^{-8}$) to be convincing. This requires large sample sizes not readily achievable for rare diseases. Yet, despite the *a priori* presumption that the GWAS design could not be successfully applied to childhood cancers investigations of ALL(58-64), neuroblastoma(65-74), Wilm's tumor(75), osteosarcoma(76), and Ewing's sarcoma (77), each have identified multiple variants associated with each disease (Table 2). The unexpected success of GWAS to studies of these rare cancers appears to be due to the larger magnitude of SNV-disease association among young onset cancers compared to those with adult onset, which was recently formally quantified (Figure 4) (78). An implication of this finding, besides reaffirming the applicability of GWAS to other childhood cancers not yet studied thusly, is that common genetic variation explains a greater proportion of the population attributable risk for childhood than adult cancers.

The GWAS and replication studies of ALL and neuroblastoma include diverse populations and subtype-specific analyses, giving a more mature picture of the genetic architecture of each disease than is available for those with a single GWAS to date. Two recent GWAS of ALL conducted with African-American and Hispanic cases and controls replicated many of the SNV's first identified in studies of subjects with European ancestry; SNV's in *ARID5B*, *IKZF1*, and *PIP4K2A* were associated with ALL in both ethnicities, and *CEBPE* as well in Hispanics (60). OR's per allele were similar in each group, in line with the generally high trans-ethnic replicability of GWAS results (79), however frequencies varied in directions that suggest several SNVs may explain a substantial proportion of lower incidence of ALL in African-Americans and the higher one in Hispanics compared to Europeans. *ARID5B* rs10821936 was present in 33% of Europeans, 24% of African-Americans, and 47% of Hispanics; the equivalent numbers for *IKZF1* rs11978267 were 28%, 19%, and 26%. *CEBP* rs4982731 was present in 28% of Europeans and 39% of Hispanics, as well as 38% of African-Americans in which this SNV did not replicate. Similarly, SNVs in *BARD1* replicated in a GWAS of neuroblastoma among African-Americans, while no others did, possibly due to small sample size (71).

Several SNVs in both diseases show far stronger OR's with specific subtypes, demonstrating that lumping disparate cases can dilute associations. In ALL, *ARID5B* SNVs have been more strongly associated with hyperdiploid disease(59, 80, 81) and *GATA3* SNV's with leukemias displaying a Philadelphia-chromosome-like expression pattern (63); the latter is an especially dramatic instance, with subtype-specific ORs per allele of about 3.5 versus 1.3 in total ALL. *BARD1* and *LMO1* SNVs are associated with aggressive disease in neuroblastoma (66, 67, 73), and SNVs in or near *DUSP12*, *DDX4*, *IL31RA*, and *HSD17B12* with low-risk disease (73). It seems reasonable to speculate that similarly specific

associations with subtypes of other childhood cancers will emerge as the GWAS literature expands.

Although the progress in identifying common variants associated with several childhood cancers in the past several years has been remarkable, a large portion of heritability remains unexplained. For instance, estimates indicate that about 25% of genetic variation in ALL risk was due to common variants identified by GWAS available in 2012 (82). The remainder of genetic risk may be attributable to several other plausible mechanisms which will more often be evaluated as next-generation sequencing and the inclusion of parental samples are adopted by the field. Rare variation is generally defined as that with a population allele frequency of <0.01. A recent exome-sequencing study of infant leukemia, among the first of its kind, identified compound heterozygosity for rare pathogenic variants in the *MLL3* gene as risk factors (83). Sequencing of parents and children and comparing exomes or genomes can identify *de novo* mutations which will not be apparent by other technologies(47). Lastly, since many childhood cancers are presumed to initiate *in utero*(84), maternal genetic effects may be relevant(85), but have only been examined in a candidate gene rather than genome wide context to date (86, 87).

Conclusion

The rarity of childhood cancer slows the search for their causes, but the accumulation of case-control studies and advancement of genomic technology have improved our knowledge in recent years. Few environmental risk factors for childhood cancer have been identified that exceed the capacity of observational epidemiology to distinguish causal associations from those due to bias. Inherent risk factors such as birth weight, parental age, and birth defects- as well as common genetic variation- are on the other hand consistently associated with childhood cancers.

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Key Points

- Apart from high-dose radiation and prior chemotherapy there are few or no strong external risk factors with relative risks >2.
- Inherent risk factors including birth weight, parental age, and congenital anomalies are consistently associated with most types of pediatric cancer.
- Common genetic variation has been associated with several childhood cancers in genome wide association studies, often with subtype-specificity, and explains a larger proportion of childhood than adult cancers.

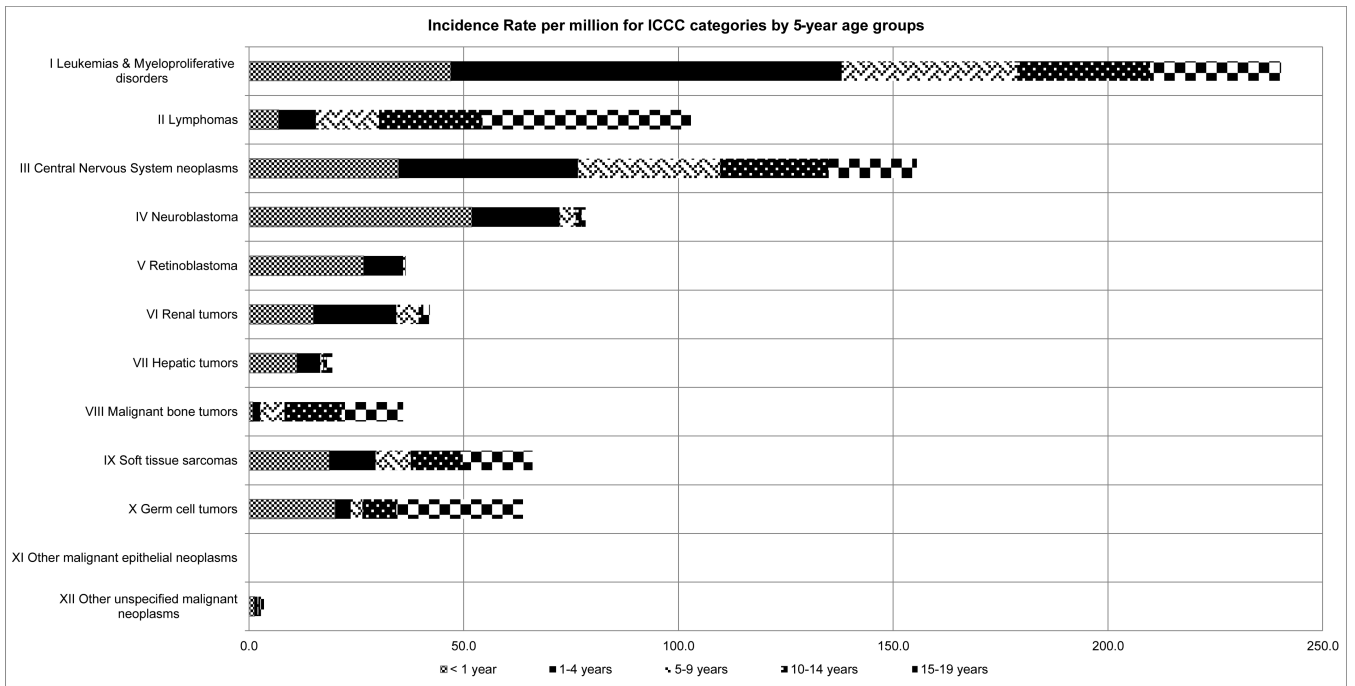


Fig. 1. Incidence rate per million for International Classification of Childhood Cancer (ICCC) categories by 5-year age groups

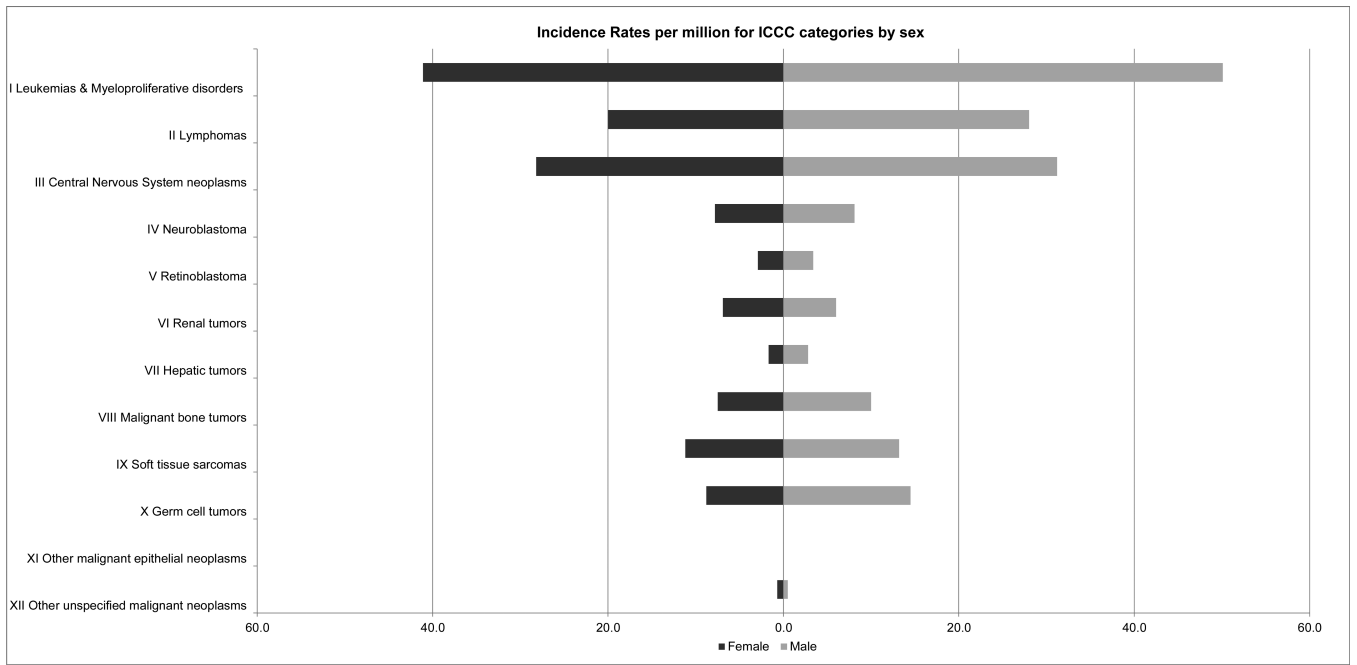


Fig. 2. Incidence rates per million for International Classification of Childhood Cancer (ICCC) categories by sex.

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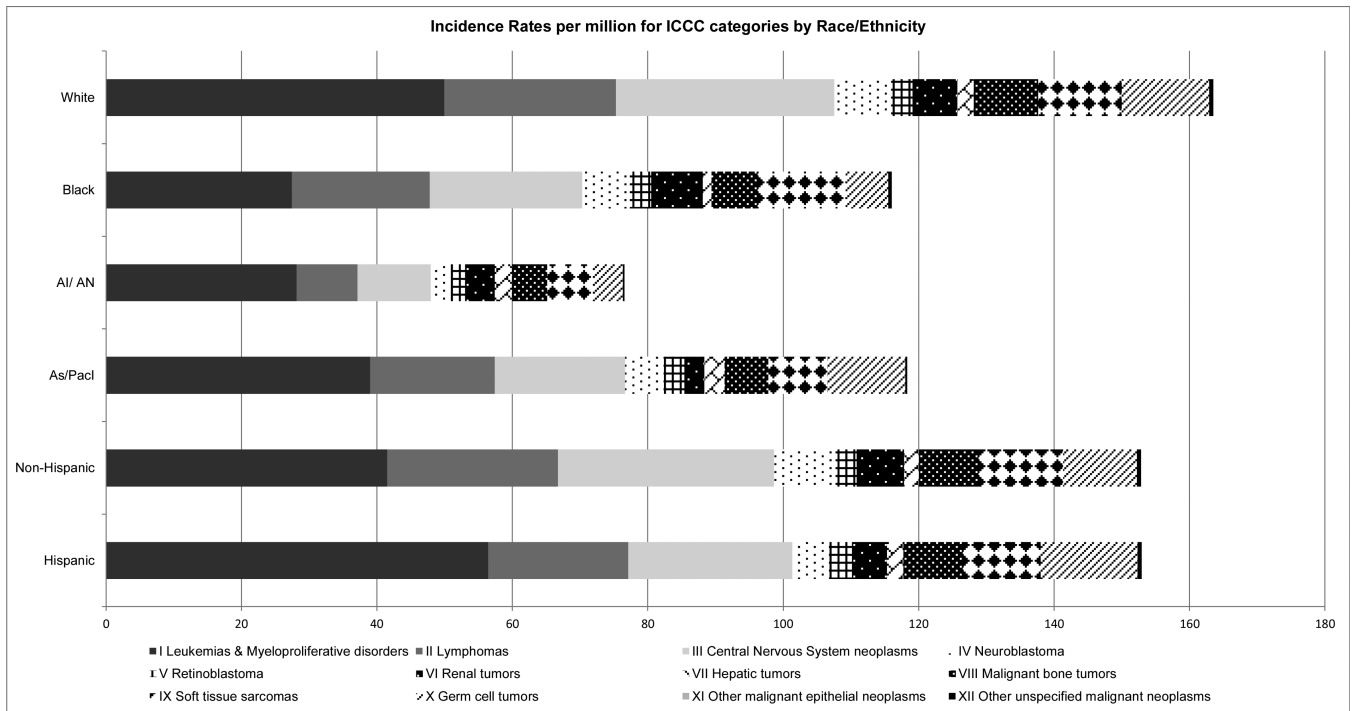


Fig. 3. Incidence rates per million for International Classification of Childhood Cancer (ICCC) categories by race/ethnicity. AI/AN, American Indian/Alaska Native; As/PacI, Asian/Pacific Islander.

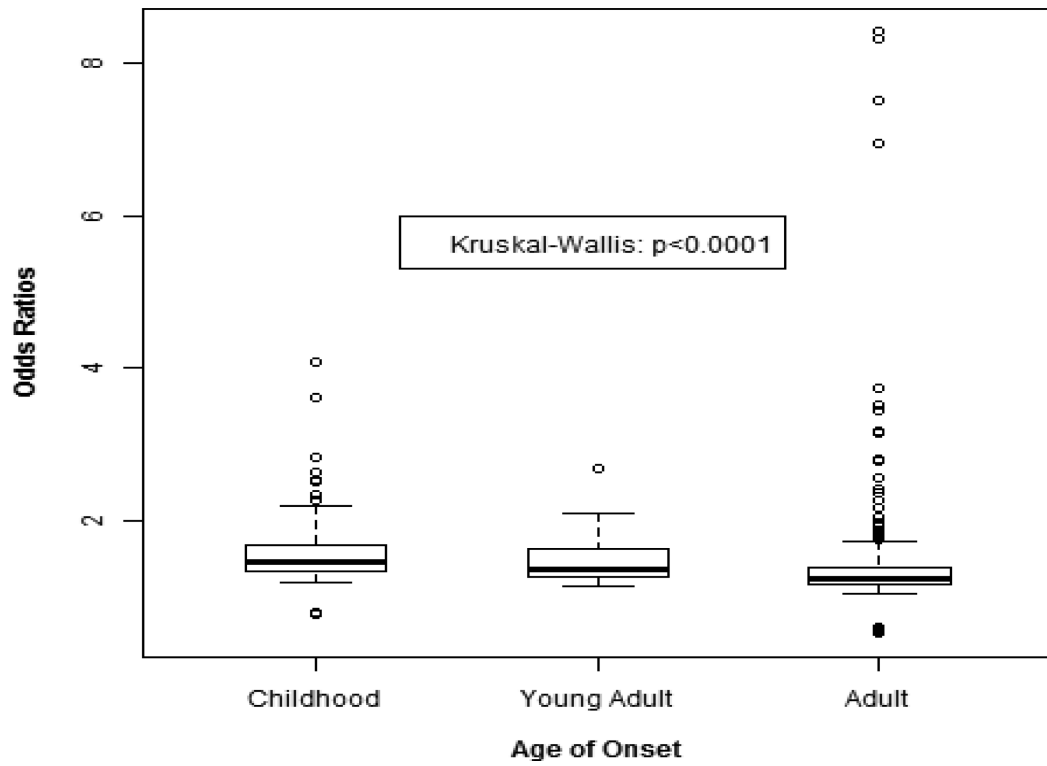


Fig. 4. Boxplot of SNV odds ratios from GWAS of cancer by age group. Dark horizontal lines represent the median and the box represents the 25th and 75th percentiles. (From Raynor LA, Pankratz N, Spector LG, et al. An analysis of measures of effect size by age of onset in cancer genomewide association studies. *Genes Chromosomes Cancer* 2013;52(9): 857; with permission.)

Table 1

Results of selected meta-analyses of environmental risk factors and childhood ALL.

Exposure	Time period	N studies	Findings	Ref
Maternal alcohol use	Pregnancy	10	No association of any alcohol use during pregnancy with ALL [mOR [*] = 1.10 (0.93-1.29)]	(11)
Maternal coffee use	Pregnancy	5	Small association of any coffee consumption during pregnancy with ALL [mOR = 1.16 (1.00-1.34)]	(8)
Daycare attendance	Postnatal	14	Small reduced risk of ALL associated with daycare attendance [mOR = 0.76 (0.67-0.87)]	(13)
Electromagnetic field exposure	Postnatal	9	No association of electromagnetic field exposure >=0.2 μ T with ALL [mOR = 1.25 (0.97-1.60)]	(15)
Occupational pesticide exposure	Pregnancy	5	Strong association of maternal occupational exposure to pesticides during pregnancy and ALL [mOR = 2.64 (1.40-5.00)]	(14)
Maternal prenatal vitamins	Pregnancy	3	Small reduced risk of ALL associated with maternal prenatal vitamin consumption [mOR = 0.61 (0.50-0.74)]	(9)
Paternal smoking	Preconception	10	Small association of any paternal preconceptional smoking with ALL [mOR = 1.15 (1.06-1.24)]	(12)
Maternal smoking	Pregnancy	20	No association of any maternal smoking during pregnancy with ALL [mOR = 1.03 (0.95-1.12)]	(10)

* mOR = meta-analytic odds ratio

Table 2

SNV's identified by GWAS of childhood cancers.

Cancer	Gene	SNV	Population	Subtype	OR	95% CI	P-value	Ref
ALL	ARID5B	rs10821936	European	Total	1.91	1.6-2.2	1.4×10^{-15}	(39)
ALL	ARID5B	rs10740055	European	Total	1.53	1.4-1.6	5.35×10^{-14}	(38)
ALL	ARID5B	rs10821936	African-American	Total	1.52	1.1-2.0	0.004	(40)
ALL	ARID5B	rs10821936	Hispanic	Total	1.95	1.6-2.4	3.78×10^{-11}	(40)
ALL	ARID5B	rs10821936	European	B-hyperdiploid	2.17	1.5-3.1	1.62×10^{-5}	(39)
ALL	CDK2NA	rs3731217	European	Total	0.71	0.6-0.8	3.01×10^{-11}	(41)
ALL	CDK2NA	rs17756311	European	Total	1.43	1.2-1.7	3.25×10^{-5}	(40)
ALL	CEPBE	rs2239633	European	Total	1.34	1.2-1.5	2.88×10^{-7}	(38)
ALL	CEBPE	rs4982731	Hispanic	Total	1.58	1.3-1.9	2.32×10^{-6}	(40)
ALL	COMMD3/BMI1	rs426962	European	Total	1.41	1.2-1.7	4.35×10^{-8}	(40)
ALL	GATA3	rs3824662	European	Total	1.31	1.2-1.4	8.62×10^{-12}	(44)
ALL	GATA3	rs3824662	European	Philadelphia-like	3.85	2.7-5.47	2.17×10^{-14}	(43)
ALL	IKZF1	rs11978267	European	Total	1.69	1.4-1.9	8.8×10^{-11}	(39)
ALL	IKZF1	rs4132601	European	Total	1.69	1.6-1.8	1.2×10^{-19}	(38)
ALL	PIP4K2A	rs10828317	European	Total	1.23	1.2-1.3	2.3×10^{-9}	(44)
Ewing sarcoma	TARDBP	rs9430161	European	Total	2.20	1.8-2.7	1.4×10^{-20}	(57)
Ewing sarcoma	EGR2	rs224278	European	Total	1.66	1.4-1.9	4×10^{-17}	(57)
Neuroblastoma	FLI22536	rs6939340	European	Total	1.40	1.3-1.6	5.82×10^{-8}	(52)
Neuroblastoma	BARD1	rs6435862	European	Total	1.64	1.4-1.9	3.19×10^{-9}	(46)
Neuroblastoma	BARD1	rs6435862	African-American	Total	1.44	1.2-1.7	1.8×10^{-5}	(46)
Neuroblastoma	HACE1	rs4336470	European	Total	1.26	1.2-1.4	2.7×10^{-11}	(49)
Neuroblastoma	LIN28B	rs17065417	European	Total	1.38	1.2-1.5	1.2×10^{-8}	(49)
Neuroblastoma	LMO1	rs110419	European	Total	1.34	1.3-1.4	5.2×10^{-16}	(54)
Osteosarcoma	GRM4	rs1906953	European	Total	1.57	1.4-1.8	8.0×10^{-9}	(56)
Osteosarcoma	Intergenic at 2p25.2	rs7591996	European	Total	1.39	1.2-1.5	1.0×10^{-8}	(56)

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Cancer	Gene	SNV	Population	Subtype	OR	95% CI	P-value	Ref
Wilm's tumor	Intergenic at 2p24	rs3755132	European	Total	1.48	1.3-1.7	1.03×10^{-14}	(55)
Wilm's tumor	Intergenic at 11q14	rs790356	European	Total	1.43	1.3-1.6	4.25×10^{-15}	(55)I