Cancer Progress and Priorities: Childhood Cancer

Philip J. Lupo[1] and Logan G. Spector[2]

Background

It is estimated that 300,000 children 0–19 years of age are diagnosed with cancer worldwide each year (1). In high-income countries, cancer is the leading cause of death due to disease in children. The absolute risk of cancer in children is, however, quite low [183 cases per million in the United States (2)], and this rarity limits attainable sample sizes and types of studies. Childhood cancers are heterogeneous and display a markedly different range of tumor types than in adults, including several classes that are largely exclusive to children. Advances in diagnostics have further split tumors into molecularly-defined subtypes that inform prognosis, therapy, and increasingly etiology. Childhood cancer epidemiology has traditionally relied on interview-based case–control studies but in recent decades has added laboratory assessment of exposure, germline DNA analysis, and molecular classification of tumors to the research repertoire.

Descriptive Epidemiology

Worldwide incidence

Accurate estimates of worldwide childhood cancer incidence are important for characterizing the impact of these malignancies and informing policy decisions. However, many countries do not have cancer registries that quantify the incidence of childhood cancer. It is estimated that 300,000 children are diagnosed with cancer annually. Data from GLOBOCAN are commonly used as a primary source to estimate the global incidence of childhood cancer. Notably, the incidence of childhood cancer is highest in North America, parts of South and Central America, Europe, and Australia with an age-standardized incidence rate (ASR) of ≥15.4 per 100,000 person-years for those 0–19 years of age (**Fig. 1A**). These patterns largely hold true for leukemia diagnosed in those 0–19 years of age as well (**Fig. 1B**). However, there are limitations to using GLOBOCAN data. For instance, data are presented according to ICD site codes, which do not reflect the major childhood cancer diagnostic groups. It is also suspected that in middle- and low-income countries poor pathology, misdiagnosis, and unascertained cases contribute to underestimation of rates. Because of this, a recent report attempted to estimate the total incidence of global childhood cancer using a simulation-based approach. In this assessment, Ward and colleagues estimated that there were 397,000 children 0–14 years of age diagnosed with cancer worldwide in 2015, a number much higher than GLOBOCAN estimates (3).

[1]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, Texas. [2]Department of Pediatrics, Division of Epidemiology & Clinical Research, University of Minnesota, Minneapolis, Minnesota.

Corresponding Author: Philip J. Lupo, Baylor College of Medicine, One Baylor Plaza MS: BCM622, Houston TX, 77030. Phone: 713-798-2960; Fax: 713-798-8711; E-mail: philip.lupo@bcm.edu

Cancer Epidemiol Biomarkers Prev 2020;29:1081–94

doi: 10.1158/1055-9965.EPI-19-0941

International comparisons of rates between high-, middle-, and low-income countries using standard registry data should therefore be interpreted with the caveat that only diagnosed cancer is counted. Overall, leukemia is the most common cancer among children ages 0 to 14 years regardless of the geographic area. However, leukemias represent a slightly higher proportion of childhood cancers in Asia, Oceania, and Central and South America, while slightly lower on the African continent. In both North Africa and Sub-Saharan Africa, lymphomas are more common than in other regions, due primarily to the high rates of Burkitt lymphoma. Soft-tissue sarcomas are much more common in Sub-Saharan Africa, due to the high incidence of Kaposi sarcoma in the region. Other notable differences include a lower proportion of CNS tumors but higher proportion of renal tumors in Sub-Saharan Africa, and a higher proportion of germ cell tumors in Asia.

U.S. incidence

Approximately 16,000 children 0–19 years of age are diagnosed with cancer in the United States (11,000 cases among children 0–14 years of age and 5,000 cases among those 15–19 years of age; ref. 4). These numbers correspond to an ASR for all cancers of 16.4 cases per 100,000 person-years for 0–14 years and 23.3 per 100,000 person-years for 15–19 (2). Notably, the incidence of childhood cancer varies by year of life (**Fig. 2**). In addition, the distribution of cancer types shifts throughout childhood and adolescence. For example, non-CNS embryonal tumors are more common in early life compared with lymphomas, whereas lymphomas become relatively more common in adolescence (**Fig. 2**).

As with many adult cancers, the incidence of childhood cancer varies by race/ethnicity. However, while non-Hispanic black adults often have a higher incidence of several cancers, non-Hispanic white children often experience a higher incidence of cancer relative to non-Hispanic black and Hispanic children. One notable exception is Hispanic children have higher rates of both acute lymphoblastic lymphoma (ALL) and acute myeloid leukemia (AML) compared with non-Hispanic white and non-Hispanic black children (2). There is emerging evidence that some of these disparities may be due to underlying genetic ancestry (5). However, this information has not been fully exploited (e.g., through admixture mapping) to better understand the etiology of childhood cancer (6).

Worldwide survival

Worldwide, more than 100,000 children and adolescents younger than 20 years of age die from cancer per year (75,000 cancer deaths among children 0 to 14 years of age and 27,000 cancer-related deaths among 15- to 19-year-olds; ref. 7). Survival is generally higher in high-income countries (HIC). Specifically, survival has consistently increased in most of Europe, North America, Japan, and Oceania (8, 9). Whereas, several countries in Eastern Europe, Southeastern Asia, and Latin America have lagged behind. As with childhood cancer incidence, it is difficult to ascertain survival in countries without robust population-based cancer registries. International data presented in The Cancer Atlas (10), which is based on data from the CONCORD program, show that for roughly the same time period (1990s to early

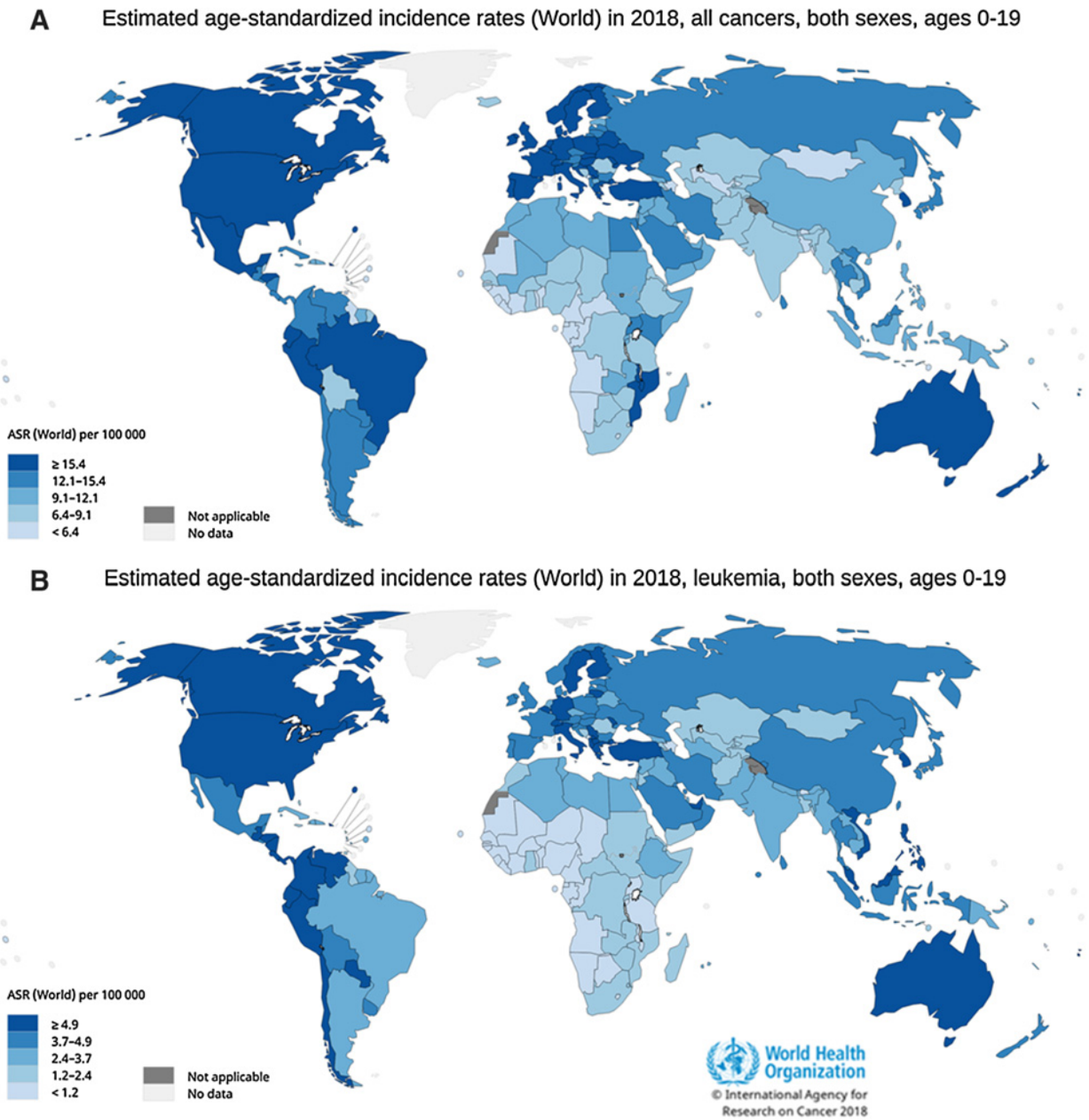

Figure 1.
Worldwide estimated age-standardized incidence for childhood cancer in 2018; panel **A** displays all cancers; panel **B** displays leukemias.

2000s), 5-year survival for childhood cancer overall was approximately 80% in high-income countries, roughly 55% in middle-income countries, and 40% in low-income countries (LIC). Furthermore, survival also differed by cancer type across those countries. Leukemia and lymphoma experience among the highest five-year survival in HICs (80% and 90%, respectively); however, in LICs only, 36% and 55% of children diagnosed with leukemia and lymphoma, respectively, survive five years after their diagnosis. The disparity is even greater for CNS tumors and neuroblastoma (which were considered together as a group in the Cancer Atlas Data). Five-year survival is reported at 71% in HICs and only 27% in LICs. These trends were also demonstrated in an assessment that used a simulation-based analysis to estimate global childhood cancer survival trends. Specifically, Ward and colleagues reported that global 5-year net childhood cancer survival is currently 37.4% (95% uncertainty interval, 34.7–39.8), with large variation by region, ranging from 8.1% (4.4–13.7) in eastern Africa to 83.0% (81.6–84.4) in North America (3).

U.S. survival

Childhood cancer remains the leading cause of disease-related mortality among children 1 to 14 years of age, with approximately 1,200 cancer-related deaths annually in the United States among

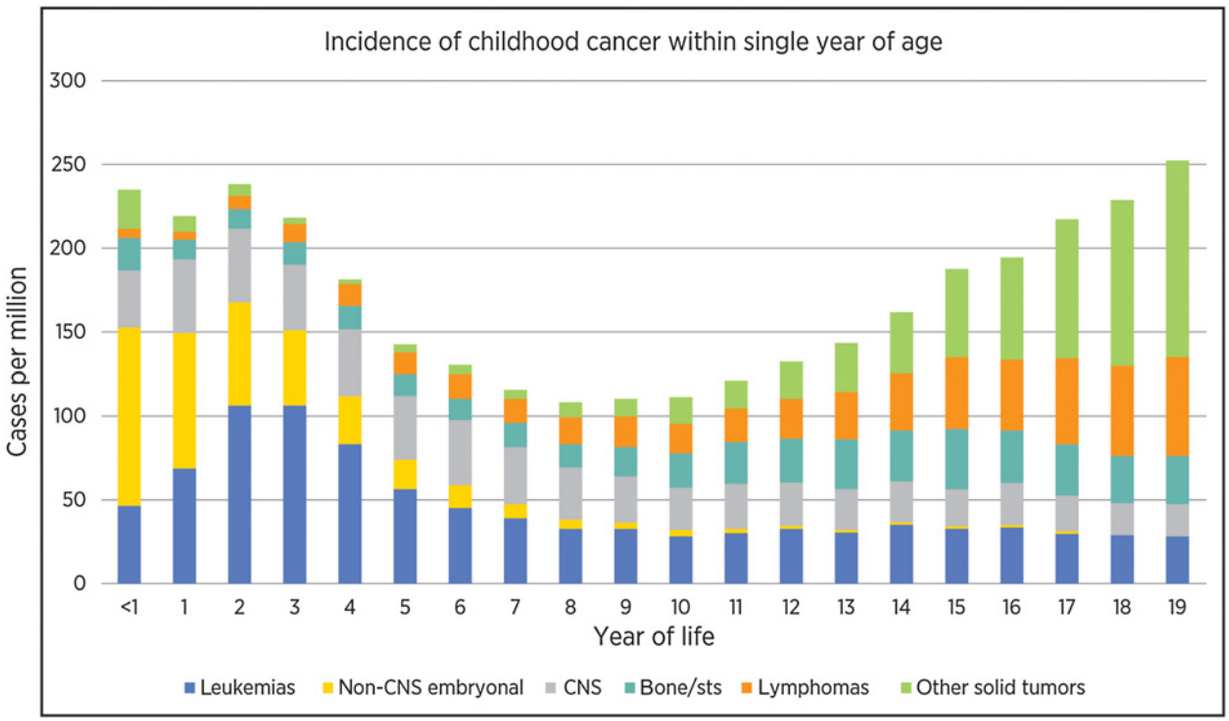

Figure 2.
Distribution of tumors across the pediatric age spectrum.

children younger than 15 years (4). The relative contribution of cancer to overall mortality for 15- to 19-year olds is lower than for the younger children, although approximately 600 deaths from cancer occur annually in this age group (11). Accordingly, death from cancer accounts for 12% of all deaths among children 1 to 14 years old, and 5% among adolescents (15–19 years old). However, survival rates for children 0–14 years of age have improved dramatically since the 1960s when the overall 5-year survival rate after a cancer diagnosis was estimated as 28% (12). Improvements in survival rates have continued into the mid-2000s in the United States, with the overall 5-year survival rate exceeding 80% for children and adolescents diagnosed during this period. In spite of this, survival does still lag for some cancer types (**Fig. 3**). For instance, as recent data from Surveillance, Epidemiology, and End Results (SEER) demonstrate, children diagnosed with CNS tumors, bone tumors, some types of soft tissue sarcoma, and hepatoblastoma have 5-year survival rates of <70%. While overall survival has improved in the United States, there remain differences based on several factors, including sex and race/ethnicity. In terms of sex, using data from SEER, investigators demonstrated that males had worse survival compared with females for several cancers, including ALL, ependymoma, neuroblastoma, and osteosarcoma (13). In addition, while non-Hispanic white children are more likely to be diagnosed with cancer, these children often have the best survival compared with other race/ethnicity groups. Specifically, data from SEER indicate that for most subtypes, non-Hispanic blacks and Hispanics have inferior survival compared with non-Hispanic whites (14–19). Differences in survival are likely to be complex, arising from several factors, including but not limited to socioeconomic status, adherence to therapy, differences in treatment, underlying tumor biology, and genetic susceptibility (20). Therefore, future studies evaluating disparities should employ a comprehensive approach to reducing the impact of these differences.

Risk Factors

Knowledge on the etiology of childhood cancers comes mainly from case–control studies and must be interpreted within the limitations of the study design. Setting must also be considered as the vast majority of analytic epidemiology of childhood cancer have taken place in high income countries and may not generalize to lower income areas with different distributions of environmental and lifestyle risk factors. Childhood cancers are heterogeneous, and it must be recognized that each tumor has its individual risk factor profile. However there are some commonalities. For instance, the incidence is higher in males in nearly all cancers and many are thought to originate *in utero*. Some risk factors, like birth weight, cut across tumors but differ in the direction and magnitude of association, while others [e.g., hernias and Ewing sarcoma (21)] are unique to a particular cancer. It is also the case that the literature on causes is roughly proportional to incidence, so that we know far more about the etiology of ALL (36 cases per million) than hepatoblastoma (2.1 cases per million). On the basis of a review of the literature and overall impressions from the state of the field, we summarize the risk factors for childhood cancer below and in **Table 1**. In addition, as there have been some reviews specifically focused on particular childhood cancers or the role of specific risk factors on a range of childhood cancers, we have also provided a table (**Table 2**) that outlines some of these efforts.

Demographics

Age, sex, and race/ethnicity each influence the risk of childhood cancer. **Figure 2** shows the distribution of tumors across the pediatric age spectrum. Leukemias, primarily ALL, display a distinct peak in incidence from age 2 to 5 years, while CNS tumors have fairly steady incidence throughout childhood. Non-CNS embryonal tumors have

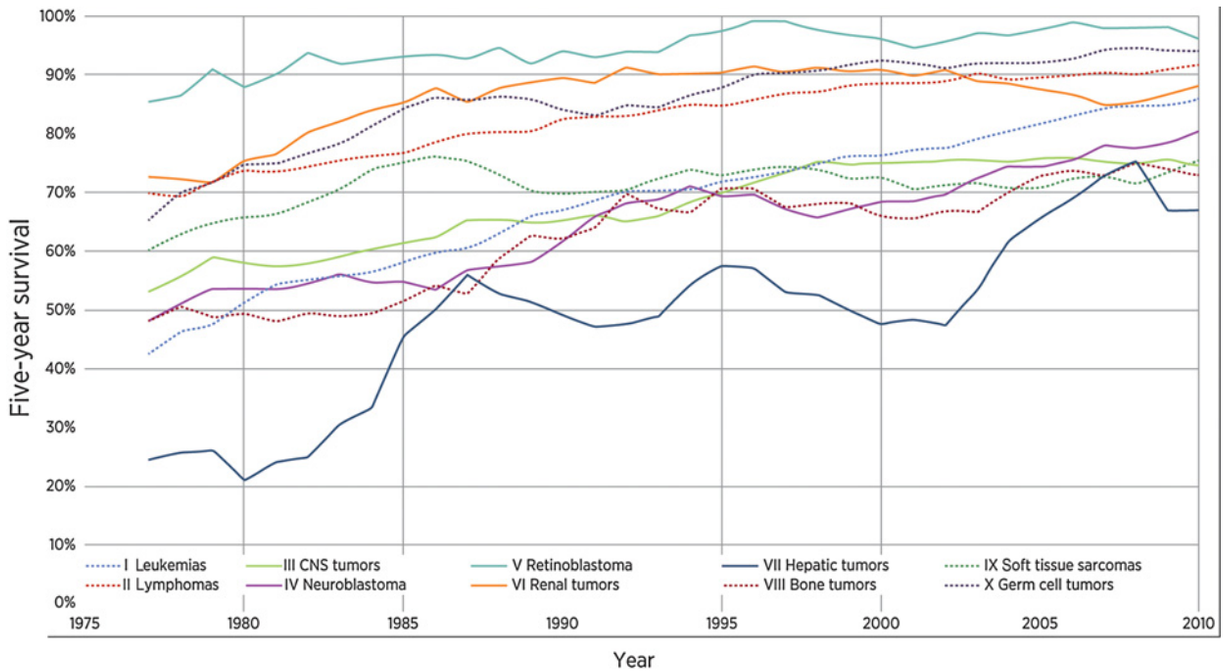

Figure 3.
Improvements in 5-year survival for childhood cancer, 1975–2010.

peak incidence in infancy, which then falls to near zero by 10 years of age. There is a peak in incidence of bone and soft-tissue sarcomas in mid-adolescence, as well as increasing incidence of lymphoma and other solid tumors that continues well into adulthood. Males have a higher risk for most childhood cancers, with rate ratios ranging from 6 for Burkitt lymphoma to 1.2 for AML; Wilms tumor, extragonadal GCT, thyroid carcinoma, and melanoma are notable for having slightly higher rates in females (22). The United States published cancer rates by race/ethnicity and so these data are often used to compare incidence. With few exceptions, the rate of childhood cancer is 25%–50% lower in black compared with white children, the rate of ALL is higher among Hispanic children but for most solid tumors lower than in white children, and incidence among Asian children is roughly similar to white children although some (i.e., neuroblastoma and Wilms tumor) have lower rates while germ cell tumors have dramatically higher rates (23).

Gestational and perinatal

Because of the young age of onset, histologic resemblance of some pediatric cancer cells to embryonal cells, and pre- or perinatal detection of multiple types of cancer, most childhood cancers are thought to initiate *in utero.* Consequently, gestation is frequently examined as a critical window of risk. Birth weight, alone or with consideration of gestational age, has been most often studied (**Table 1**). Risk of most childhood cancers rises with increasing birth weight, from 5% per 500 g increase for astrocytomas to 17% per 500 g for Wilms tumor (24); hepatoblastoma, which is strongly associated with *low* birth weight, is the exception (25). Another consistent finding is that children with structural birth defects without a reported genetic syndrome have an elevated risk of pediatric cancer (26). Risk ratios for specific birth defect–cancer combinations range from 1.5 to 6.0 and the associations are apparent for most classes of birth defects and cancer (**Table 1**). Parental age at birth of offspring is also consistently associated with most types of childhood cancer, with between 5% and 10% higher risk per 5 years of maternal age; paternal age may also be associated with higher risk of pediatric cancer, although the tight correlation with maternal age and the greater degree of missing data make it harder to assess (27–31). There is some suggestive evidence that pathologies of pregnancy, such as preeclampsia, gestational diabetes, and maternal obesity increase risk of childhood cancers but the evidence base is currently thin (32–37).

Environmental

While key environmental exposures have been identified for adult cancers (e.g., smoking, benzene), much less is known in relation to childhood cancer. A notable difference between adult cancers and childhood cancers is the latency period associated with these conditions. For instance, smoking usually starts during adolescence or young adulthood, but associated malignancies do not become apparent until many decades later. However, several childhood cancers are predominantly diagnosed in infancy (e.g., embryonal neoplasms such as neuroblastoma) or in early childhood (2–5 years of age), such as ALL. Therefore, the disruption in molecular processes that may lead to childhood cancer are likely different from those of adult cancers; at the least, the carcinogenic process in children is necessarily much shorter in time. In addition, because of the age of onset, it is reasonable to surmise that many childhood cancers result from aberrations in early developmental processes. The current evidence to support a major etiologic role for environmental or other exogenous factors in childhood cancer is minimal (**Table 1**). While there is extensive evidence that high doses of ionizing radiation are associated with childhood cancer, the prevalence of this exposure is very low (38). Relatively common environmental exposures, including pesticides (39) and air

Table 1. Confirmed and suspected risk factors for selected childhood cancers.

	ALL	AML	NB	HB	RB	WT	MB	PNET	Ependymoma	Astrocytoma	Strength of evidence
Preconception/pregnancy											
Smoking											++
Vitamins											++
Occupational exposures											++
Residential exposures											++
Coffee											+
Alcohol											++
Ionizing radiation											+++
Birth											
Maternal age											++
Paternal age											++
Chromosomal birth defects											+++
Non-chromosomal birth defects											+++
High birth weight											+++
Low birth weight											+++
C-section											+
Gestational age											+
Childhood											
Breastfeeding											+
Allergies											++
Residential chemical											+
Passive smoke											+
Irradiation											++

Note: Taken from refs. 25, 30, 31,103-266. For strength of evidence: + epidemiologic evidence with little mechanistic support; ++ can cross placenta or has developmental consequences but epidemiologicevidence is equivocal; +++ strong epidemiologic and mechanistic evidence.
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HB, hepatoblastoma; MB, medulloblastoma; NB, neuroblastoma; PNET, primitive neuroectodermal tumor; RB, retinoblastoma; WT, Wilms tumor.

Legend

Positive, effect estimate <1.5
Positive, effect estimate ≥1.5
No association
Negative, effect estimate >0.67
Negative, effect estimate ≤0.67
Inconclusive

pollution (40), have also been explored. While individual studies and meta-analyses have indicated associations between these exposures and some childhood cancers, effect sizes are relatively modest. One problem with previous studies of environmental exposures includes the limitations of using questionnaire data to estimate exposure or the use of proxies for exposure assessment (e.g., residential information). While residential information is arguably better than self-reported exposures, epidemiologic studies of childhood cancer must leverage novel approaches to better characterize the role of environment in etiology. For example, correlating information on environmental exposures to the landscape of somatic mutations could provide novel insights into the carcinogenic properties of these factors (41).

Table 2. Selected reviews for childhood cancer and associated risk factors.

Topic	Authors	Year	PMID
Childhood cancers			
ALL	Williams et al.	2019	30770347
AML	Puumala et al.	2013	23303597
Brain tumors	Johnson et al.	2014	25192704
Hepatoblastoma	Spector and Birch	2012	22692949
Rhabdomyosarcoma	Skapek et al.	2019	30617281
Wilms tumor	Chu et al.	2010	20670226
Risk factors			
Pesticides	Chen et al.	2015	26371195
Ionizing radiation	Kendall et al.	2018	30131551
Genetic predisposition	Plon and Lupo	2019	31082280

Genetic variation

Chromosomal abnormalities, subchromosomal structural variation, and pathogenic germline point mutations confer a sharply increased risk of cancer but underlie a minority of cases of childhood cancer (42–45). Next-generation sequencing studies have yielded precise estimates of the prevalence of germline pathogenic variation in most types of childhood cancer; for a few types such as adrenocortical carcinoma or hypodiploid ALL, half or more of cases have such variation, while in most cancers the prevalence is 5%–10% (46, 47). In fact, according to a large-scale effort by Zhang and colleagues, those childhood cancers where >10% can be attributed to highly penetrant pathogenic variants in known cancer predisposition genes include osteosarcoma, retinoblastoma, and adrenocortical carcinoma (47). Continued sequencing efforts have also yielded novel, rare, high-penetrance predisposition genes (48) and moderately rare, medium-penetrance variation (49–51). Importantly, there has been a recent systematic effort to outline the guidelines for pediatric cancer predisposition surveillance. While it is beyond the scope of this review to fully outline those recommendations, they can be found at https://clincancerres.aacrjournals.org/pediatricseries (52).

Against expectations, genome-wide association studies (GWAS) have succeeded in identifying common single nucleotide polymorphisms (SNP) associated with several childhood cancers despite sample sizes that, at least initially, fell far short of recommendations. This is likely due to the interesting and as yet unexplained fact that the magnitude of association of common SNPs with childhood cancer is

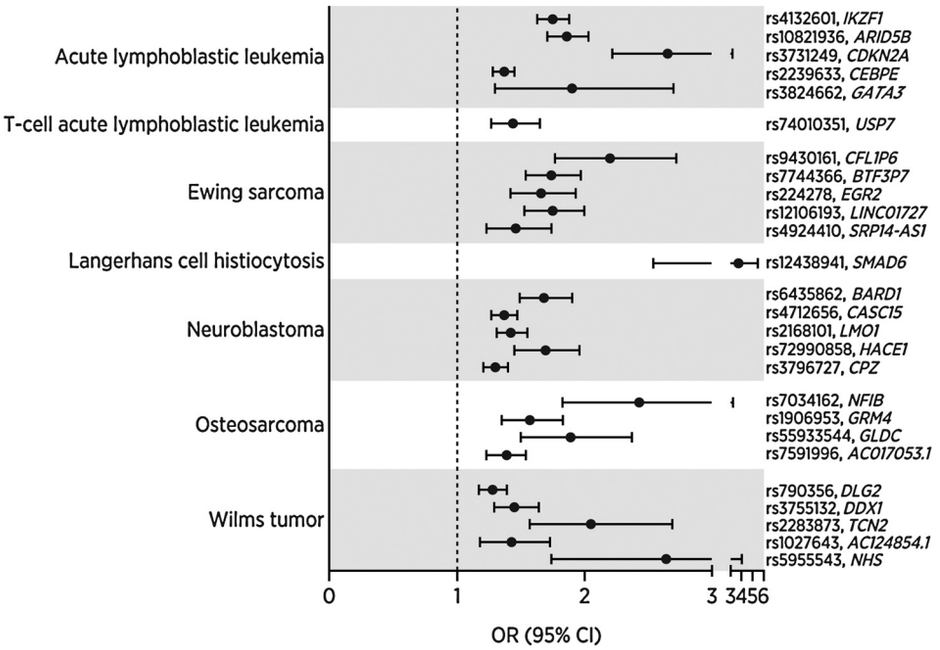

Figure 4.
Genes and variants identified in GWAS of childhood cancer; up to 5 of the top SNPs with $P < 10–8$ in the GWAS catalogue (https://www.ebi.ac.uk/gwas/home) are displayed, with information for recent GWAS of T-cell ALL and LCH added.

greater than in adults (23), which seems to be a general property of pediatric diseases (53). The genetic architectures of ALL and neuroblastoma are mature, with multiple validated loci, subtype-specific associations, transethnic replication, and ethnically-specific loci (49–51, 54–59). Two GWAS of Ewing sarcoma in European populations have also identified multiple loci (60, 61), but genetic risk in non-European populations has not been examined. Single GWAS of Wilms tumor (62) and osteosarcoma (63) have also identified a limited number of loci. More recently investigators have demonstrated associations of childhood cancers with trait-related variation, such as genetically-determined telomere length (64) and height (65). The most significant variants found to be associated with childhood cancers in GWAS are depicted in **Fig. 4**. While potential mechanisms for the genetic associations have been proposed (57–63), there have been few efforts to fully elucidate the functional consequences of variants identified in GWAS of childhood cancers. This is in part due to several variants being intronic or intergenic (63). However, there are some emerging efforts to elucidate the role of variants and genes identified in GWAS of childhood cancer, including Ewing sarcoma–related loci (66), *IKZF1* variants and ALL (67), and *BMI1* variants and ALL (68). Many SNPs do appear to be associated with lymphocyte development; however, additional work is needed to explore the biological underpinnings of these associations. Lastly, while small studies have examined transethnic replication of GWAS SNPs discovered in Europeans, genome-wide discovery has mostly not been performed in non-European populations despite many recent calls to diversify genomic research.

Etiologic Heterogeneity

There is emerging evidence that etiologic heterogeneity within childhood cancer subtypes may have limited previous epidemiologic assessments of these conditions. Furthermore, our understanding of subtypes continues to emerge. For example, ALL has traditionally been classified as B-cell or T-cell, based on the cell type affected. However, advances in cytogenetics has led to the latest version of the WHO classification of ALL to include several subtypes defined by their translocations and other cytogenetic features: *BCR-ABL1, MLL* rearranged, *TEL-AML1*, hyperdiploidy, hypodiploidy, *IL3-IGH*, and *E2A-PBX1* (69). Another example is rhabdomyosarcoma, which was originally classified by histologic type, for example, embryonal versus alveolar. However, through molecular advancements, further distinctions due to specific gene fusions between either *PAX3* or *PAX7* and *FOXO1* that typically occur among the previously named alveolar types, are preferred risk stratification strategies compared with histology alone (70). Recent advances in genomics, epigenomics, and transcriptomics have allowed for molecular subtyping for a number of childhood malignancies. For example, at least four molecular subgroups of childhood medulloblastoma now exist (WNT, SHH, Group 3, and Group 4), each exhibiting different molecular and clinical features (71); more recent tumor phenotyping suggests even further subtypes (72). Likewise, for other brain tumors, distinct molecular subgroups have now been established for ependymoma (73), high-grade gliomas (74), low-grade gliomas (75), and AT/RT (76). Recently, four molecular subtypes have been suggested for diffuse large B-cell lymphoma: MCD (harboring the cooccurrence of $MYD88^{L265P}$ and *CD79B* mutations), BN2 (harboring *BCL6* fusions and *NOTCH2* mutations), N1 (harboring *NOTCH1* mutations), and EZB (harboring *EZH2* mutations and *BCL2* translocations; ref. 77). Less often, molecular analyses have suggested "lumping" tumors previously thought to be dissimilar, as with Ewing sarcoma and primitive neuroectodermal tumors (PNET), which both frequently feature the *EWS-FLI1* translocation (78). Also, GWAS of childhood cancers (including ALL and neuroblastoma) have pointed to differences in association between SNPs and molecularly defined subtypes (79, 80). These are just a few examples of the emerging landscape of tumor subtypes based on molecular features. Future epidemiologic studies must account for this information as etiologic factors could differ based on these characteristics.

Screening and Prevention

The ultimate goal of etiologic research in childhood cancer is to enable risk prediction, early detection, and, eventually, prevention.

However, these goals remain distant for most children. Population-wide screening for pediatric cancer has, to our knowledge, only been attempted for neuroblastoma. The basis for screening was homovanillic acid, a catecholamine metabolite which serves as a biomarker for tumor burden in neuroblastoma and which is shed in urine. Thus, in the late 1980s and 1990s, screening for neuroblastoma in infants was attempted in three areas with the capacity for population-wide urine collection in infants: Quebec (81), Germany (82), and Japan (83). While these programs succeeded in identifying neuroblastoma earlier than clinical diagnosis, they did not improve mortality as they primarily detected favorable cases with a regressing phenotype, many of which would never have come to clinical attention. Hence, these programs were abandoned (84).

More recently, experts have issued recommendations in support of surveillance for tumor development in children with most genetic syndromes conferring high risk of cancer (85). Although there are few preventive measures to implement, there is consensus that surveillance can reduce morbidity and mortality through early detection. Screening for cancer predisposition, as opposed to screening for cancer in those with known predispositions, is more controversial. Newborn screening increasingly involves genetic in addition to metabolic testing (86), and thus could easily detect most types of pathogenic variation in cancer-associated genes. However, many screening programs prefer to include only conditions that are early-onset and for which there are interventions proven to improve outcome (87), which does not describe most pediatric cancers. Thus to our knowledge only one area in the world has instituted newborn screening for pediatric cancer predisposition, in the Brazilian state of Paraná where the R337H founder mutation in *TP53* has an especially high prevalence (88).

Prevention of pediatric cancer is not yet feasible for a number of reasons. The first is simply that for diseases as rare as these the number needed to "treat" with an intervention would be impractically large, possibly population-wide, and consequently would be economically unfavorable. A second reason is that, as discussed above, there are no modifiable risk factors for childhood cancer that are strong and prevalent enough to justify intervention. However, most of the modifiable risk factors for pediatric cancer (e.g., maternal smoking, obesity, air pollution) are also associated with far more common diseases, thus efforts to reduce exposure for other reasons may have the effect of reducing childhood cancer incidence.

Future Directions

Molecular epidemiology

Initial epidemiologic studies of childhood cancer gathered data mainly by parental interview and medical record abstraction. These assessments relied on the case–control study design. However, the focus of the past decade has largely been on the molecular epidemiology of childhood cancers. This has been facilitated in part through the case–parent trio study design. Case–parent trios allow the estimation of inherited genetic effects, maternal genetic effects (which can be used as a proxy or mediator of the intrauterine environment), and gene–environment interactions. In addition, the case–parent trio approach does not require the inclusion of a control group, which is a practical advantage, as control selection on the national scale has become increasingly difficult in recent years. This is, in part, due to the reliance on random digit dialing for control selection (89). Another option for control selection is utilizing birth certificate controls, which have been leveraged for two Children's Oncology Group (COG) studies (90, 91), as well as studies of other pediatric and perinatal outcomes (92). This could be a feasible approach for epidemiology studies of childhood cancer that require a comparison group. However, the scientific and practical appeal of the case–parent trio design for molecular epidemiology studies remains compelling. Because of this, several recent COG epidemiology studies have relied on this approach. This includes studies of osteosarcoma (93), neuroblastoma (94), Wilms tumor, Ewing sarcoma, germ cell tumors (95), and rhabdomyosarcoma. However, beyond genetic susceptibility to childhood cancer, few studies have explored using biological markers of exposure in studies of childhood cancer, which is in part due to the limited availability of samples collected prior to diagnosis. An emerging and important population-based resource for molecular epidemiology of childhood cancer is the use of dried blood spots (DBS) collected and archived as part of newborn screening efforts. DBS have been used in genetic epidemiology studies of childhood cancer (67), as well as using metabolomics to reveal novel ALL phenotypes (96). In addition, DBS can be used to estimate prenatal exposures, including cotinine from tobacco smoke (97) and benzene (98).

There are also methods for leveraging genetic data to address questions not necessarily related to inherited genetic susceptibility. Two primary examples are (i) evaluating maternal genetic effects (as described earlier), which can be done using parental genetic data from case–parent trios (99), and (ii) Mendelian randomization (100), which is a method of using genetic variation to examine the effect of an exposure (or another trait like birth weight) on disease in observational studies. These methods are more recently being leveraged in epidemiologic studies of childhood cancer. For instance, there has been an exome-wide association study of maternal genetic effects on ALL (101). In addition, Mendelian randomization has been used to characterize the role of height on osteosarcoma risk (65) and telomere length on neuroblastoma risk (64).

A final underexplored area in the molecular epidemiology of childhood cancer is leveraging epigenetics, especially as these modifications relate to germline DNA. Notably, environmental exposures can lead to epigenetic modifications that influence gene expression and can modulate disease risk associated with genetic variation (101). For example, there is emerging evidence that air pollution exposure (a suspected risk factor for several childhood cancers) is associated with changes in DNA methylation (102). Therefore, a novel approach in better ascertaining the association between air pollution and particular childhood cancers could be evaluating DNA methylation marks associated with this exposure. Epigenetics therefore holds substantial promise for identifying mechanisms through which genetic and environmental factors jointly contribute to childhood cancer risk and outcome. As the underlying etiologies of the vast majority of childhood cancers appear multifactorial, including both genetic and environmental risk factors, molecular epidemiology will continue to be an important component in the assessment of these conditions.

Tumor biology

As discussed, there is a growing awareness of the molecular heterogeneity within childhood cancer subtypes. As this molecular heterogeneity could point to etiologic heterogeneity, it will be vital to incorporate information on somatic mutations in future epidemiologic studies of childhood cancer. Furthermore, information on somatic mutations could be leveraged to better understand biological processes underlying etiology. For example, in an assessment by Alexandrov and colleagues of over 7,000 tumors yielded more than

20 distinct mutational signatures, which were associated with various features including age, mutagenic exposures, and defects in DNA maintenance (41). In addition, several of these mutational signatures are of "cryptic" origin. Epidemiologic assessments that characterize the exposures associated with these signatures could yield novel insights into the mutational processes underlying the development of cancer with potential implications for prevention and therapy.

Global epidemiology

It should be noted that the overwhelming majority of etiologic studies of ALL have been conducted in high-income countries, especially the United States and countries in Europe. It is critical that future studies include populations in middle- and low-income countries as exposures as well as genetic variation are likely to differ in these populations and etiologic features may differ.

Conclusions

While there have been tremendous strides in improving outcomes for children with cancer, there is still a great deal of work related to disentangling the etiologic origins of these conditions. Future studies should incorporate novel exposure methodologies, molecular features of tumors, and a more complete assessment of gene–environment interactions. Through these efforts, it is hoped that our understanding of the causes of childhood cancer can be better ascertained, leading to novel surveillance or prevention strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.J. Lupo, L.G. Spector
Development of methodology: P.J. Lupo, L.G. Spector
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.J. Lupo, L.G. Spector
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.J. Lupo, L.G. Spector
Writing, review, and/or revision of the manuscript: P.J. Lupo, L.G. Spector
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.J. Lupo, L.G. Spector
Study supervision: P.J. Lupo

Acknowledgments

This work was funded, in part, through the National Cancer Institute (U10CA180886), Cancer Prevention and Research Institute of Texas (CPRIT RP170071 and RP180755), and St. Baldrick's Foundation (522277). We would like to acknowledge the work of the Children's Oncology Group Epidemiology Committee in supporting this work.

Received August 7, 2019; revised December 18, 2019; accepted March 9, 2020; published first June 1, 2020.

References

1. Bhakta N, Force LM, Allemani C, Atun R, Bray F, Coleman MP, et al. Childhood cancer burden: a review of global estimates. Lancet Oncol 2019; 20:e42–e53.
2. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review, 1975–2015. Bethesda (MD): National Cancer Institute; 2017. Available from: http://seer.cancer.gov/csr/1975_2015/.
3. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. Lancet Oncol 2019;20: 483–93.
4. American Cancer Society. Cancer facts and figures, 2019. Atlanta (GA): American Cancer Society; 2019.
5. Spector LG, DeWan A, Pankratz N, Turcotte L, Yang J, Scheurer M. Race/ethnicty, socioeconomic position, and childhood acute lymphoblastic leukemia. Am J Epidemiol 2019;188:1192–3.
6. Lim JY-S, Bhatia S, Robison LL, Yang JJ. Genomics of racial and ethnic disparities in childhood acute lymphoblastic leukemia. Cancer 2014;120: 955–62.
7. Ferlay J. GLOBOCAN 2018. Lyon (France): World Health Organization, International Agency for Research on Cancer; 2018.
8. Bosetti C, Bertuccio P, Chatenoud L, Negri E, Levi F, La Vecchia C. Childhood cancer mortality in Europe, 1970–2007. Eur J Cancer 2010; 46:384–94.
9. Chatenoud L, Bertuccio P, Bosetti C, Levi F, Negri E, La Vecchia C. Childhood cancer mortality in America, Asia, and Oceania, 1970 through 2007. Cancer 2010;116:5063–74.
10. Jemal A. The cancer atlas. 2nd ed. Atlanta (GA): American Cancer Society; 2015.
11. Centers for Disease Control and Prevention; National Center for Health Statistics. Underlying Cause of Death 1999–2017 on CDC WONDER Online Database, released December, 2018. Data are from the Multiple Cause of Death Files, 1999–2017, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Available from: http://wonder.cdc.gov/ucd-icd10.html.
12. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al, editors. Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. Bethesda (MD): National Cancer Institute, SEER Program; 1999. NIH Pub. No. 99-4649.
13. Williams LA, Spector LG. Survival differences between males and females diagnosed with childhood cancer. JNCI Cancer Spectrum 2019;3: pkz032.
14. Amirian ES. The role of Hispanic ethnicity in pediatric Wilms' tumor survival. Pediatr Hematol Oncol 2013;30:317–27.
15. Holmes L, Chavan P, Blake T, Dabney K. Unequal cumulative incidence and mortality outcome in childhood brain and central nervous system malignancy in the USA. J Racial Ethn Health Disparities 2018;5:1131–41.
16. Jacobs AJ, Lindholm EB, Levy CF, Fish JD, Glick RD. Racial and ethnic disparities in treatment and survival of pediatric sarcoma. J Surg Res 2017; 219:43–9.
17. Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA 2003;290: 2008–14.
18. Kahn JM, Keegan TH, Tao L, Abrahão R, Bleyer A, Viny AD. Racial disparities in the survival of American children, adolescents, and young adults with acute lymphoblastic leukemia, acute myelogenous leukemia, and Hodgkin lymphoma. Cancer 2016;122:2723–30.
19. Panagopoulou P, Georgakis MK, Baka M, Moschovi M, Papadakis V, Polychronopoulou S, et al. Persisting inequalities in survival patterns of childhood neuroblastoma in Southern and Eastern Europe and the effect of socioeconomic development compared with those of the US. Eur J Cancer 2018; 96:44–53.
20. Bhatia S. Disparities in cancer outcomes: lessons learned from children with cancer. Pediatr Blood Cancer 2011;56:994–1002.
21. Valery PC, Holly EA, Sleigh AC, Williams G, Kreiger N, Bain C. Hernias and Ewing's sarcoma family of tumours: a pooled analysis and meta-analysis. Lancet Oncol 2005;6:485–90.
22. Williams LA, Richardson M, Marcotte EL, Poynter JN, Spector LG. Sex ratio among childhood cancers by single year of age. Pediatr Blood Cancer 2019;66: e27620.
23. Chow EJ, Puumala SE, Mueller BA, Carozza SE, Fox EE, Horel S, et al. Childhood cancer in relation to parental race and ethnicity: a 5-state pooled analysis. Cancer 2010;116:3045–53.
24. O'Neill KA, Murphy MF, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. Int J Epidemiol 2015;44:153–68.

25. Spector LG, Puumala SE, Carozza SE, Chow EJ, Fox EE, Horel S, et al. Cancer risk among children with very low birth weights. Pediatrics 2009;124:96–104.
26. Lupo P. Cancer risk among children and adolescents with birth defects: a population-based assessment in 10 million live births. JAMA Oncol 2019;5: 1232.
27. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: a Danish population-based registry study. Cancer Epidemiol 2017;49:202–15.
28. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001;30:1428–37.
29. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology 2009;20:475–83.
30. Marcotte EL, Druley TE, Johnson KJ, Richardson M, von Behren J, Mueller BA, et al. Parental age and risk of infant leukaemia: a pooled analysis. Paediatr Perinat Epidemiol 2017;31:563–72.
31. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. Int J Epidemiol 2006;35: 1495–503.
32. Contreras ZA, Ritz B, Virk J, Cockburn M, Heck JE. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California. Cancer Causes Control 2016;27:1273–85.
33. Deleskog A, den Hoed M, Tettamanti G, Carlsson S, Ljung R, Feychting M, et al. Maternal diabetes and incidence of childhood cancer - a nationwide cohort study and exploratory genetic analysis. Clin Epidemiol 2017;9:633–42.
34. Kessous R, Wainstock T, Walfisch A, Sheiner E. The risk for childhood malignancies in the offspring of mothers with previous gestational diabetes mellitus: a population-based cohort study. Eur J Cancer Prev 2018;28:377–81.
35. Søegaard SH, Rostgaard K, Kamper-Jørgensen M, Schmiegelow K, Hjalgrim H. Maternal diabetes and risk of childhood acute lymphoblastic leukaemia in the offspring. Br J Cancer 2018;118:117–20.
36. Stacy SL, Buchanich JM, Ma ZQ, Mair C, Robertson L, Sharma RK, et al. Maternal obesity, birth size, and risk of childhood cancer development. Am J Epidemiol 2019;188:1503–11.
37. Xu X, Ritz B, Cockburn M, Lombardi C, Heck JE. Maternal preeclampsia and odds of childhood cancers in offspring: a California statewide case-control study. Paediatr Perinat Epidemiol 2017;31:157–64.
38. Kendall GM, Bithell JF, Bunch KJ, Draper GJ, Kroll ME, Murphy MFG, et al. Childhood cancer research in oxford III: the work of CCRG on ionising radiation. Br J Cancer 2018;119:771–8.
39. Chen M, Chang C-H, Tao L, Lu C. Residential exposure to pesticide during childhood and childhood cancers: a meta-analysis. Pediatrics 2015;136:719–29.
40. Filippini T, Hatch EE, Rothman KJ, Heck JE, Park AS, Crippa A, et al. Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. Environ Health Perspect 2019; 127:46002.
41. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013; 500:415–21.
42. Plon SE, Lupo PJ. Genetic predisposition to childhood cancer in the genomic era. Annu Rev Genom Hum Genet 2019;20:241–63.
43. Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, et al. Childhood cancer predisposition syndromes-a concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A 2017;173:1017–37.
44. Ross JA, Spector LG, Robison LL, Olshan AF. Epidemiology of leukemia in children with Down syndrome. Pediatr Blood Cancer 2005;44:8–12.
45. Zimmerman R, Schimmenti L, Spector L. A catalog of genetic syndromes in childhood cancer. Pediatr Blood Cancer 2015;62:2071–5.
46. Parsons DW, Roy A, Yang Y, Wang T, Scollon S, Bergstrom K, et al. Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors. JAMA Oncol 2016;2:616–24.
47. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 2015;373:2336–46.
48. Mahamdallie S, Yost S, Poyastro-Pearson E, Holt E, Zachariou A, Seal S, et al. Identification of new Wilms tumour predisposition genes: an exome sequencing study. Lancet Child Adolesc Health 2019;3:322–31.
49. Churchman ML, Qian M, Te Kronnie G, Zhang R, Yang W, Zhang H, et al. Germline genetic IKZF1 variation and predisposition to childhood acute lymphoblastic leukemia. Cancer Cell 2018;33:937–48.
50. Moriyama T, Metzger ML, Wu G, Nishii R, Qian M, Devidas M, et al. Germline genetic variation in ETV6 and risk of childhood acute lymphoblastic leukaemia: a systematic genetic study. Lancet Oncol 2015;16:1659–66.
51. Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, et al. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. Nat Genet 2013;45:1226–31.
52. Brodeur GM, Nichols KE, Plon SE, Schiffman JD, Malkin D. Pediatric cancer predisposition and surveillance: an overview, and a tribute to Alfred G. Knudson Jr. Clin Cancer Res 2017;23:e1–e5.
53. Agopian AJ, Eastcott LM, Mitchell LE. Age of onset and effect size in genome-wide association studies. Birth Defects Res A Clin Mol Teratol 2012;94:908–11.
54. Diskin SJ, Capasso M, Schnepp RW, Cole KA, Attiyeh EF, Hou C, et al. Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma. Nat Genet 2012;44:1126–30.
55. Maris JM, Mosse YP, Bradfield JP, Hou C, Monni S, Scott RH, et al. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med 2008;358:2585–93.
56. Qian M, Xu H, Perez-Andreu V, Roberts KG, Zhang H, Yang W, et al. Novel susceptibility variants at the ERG locus for childhood acute lymphoblastic leukemia in Hispanics. Blood 2019;133:724–9.
57. Trevino LR, Yang W, French D, Hunger SP, Carroll WL, Devidas M, et al. Germline genomic variants associated with childhood acute lymphoblastic leukemia. Nat Genet 2009;41:1001–5.
58. Wang K, Diskin SJ, Zhang H, Attiyeh EF, Winter C, Hou C, et al. Integrative genomics identifies LMO1 as a neuroblastoma oncogene. Nature 2011;469: 216–20.
59. Wiemels JL, Walsh KM, de Smith AJ, Metayer C, Gonseth S, Hansen HM, et al. GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21. Nat Commun 2018;9:286.
60. Machiela MJ, Grunewald TGP, Surdez D, Reynaud S, Mirabeau O, Karlins E, et al. Genome-wide association study identifies multiple new loci associated with Ewing sarcoma susceptibility. Nat Commun 2018;9:3184.
61. Postel-Vinay S, Veron AS, Tirode F, Pierron G, Reynaud S, Kovar H, et al. Common variants near TARDBP and EGR2 are associated with susceptibility to Ewing sarcoma. Nat Genet 2012;44:323–7.
62. Turnbull C, Perdeaux ER, Pernet D, Naranjo A, Renwick A, Seal S, et al. A genome-wide association study identifies susceptibility loci for Wilms tumor. Nat Genet 2012;44:681–4.
63. Savage SA, Mirabello L, Wang Z, Gastier-Foster JM, Gorlick R, Khanna C, et al. Genome-wide association study identifies two susceptibility loci for osteosarcoma. Nat Genet 2013;45:799–803.
64. Walsh KM, Whitehead TP, de Smith AJ, Smirnov IV, Park M, Endicott AA, et al. Common genetic variants associated with telomere length confer risk for neuroblastoma and other childhood cancers. Carcinogenesis 2016;37: 576–82.
65. Zhang C, Morimoto LM, de Smith AJ, Hansen HM, Gonzalez-Maya J, Endicott AA, et al. Genetic determinants of childhood and adult height associated with osteosarcoma risk. Cancer 2018;124:3742–52.
66. Musa J, Cidre-Aranaz F, Aynaud MM, Orth MF, Knott MML, Mirabeau O, et al. Cooperation of cancer drivers with regulatory germline variants shapes clinical outcomes. Nat Commun 2019;10:4128.
67. Brown AL, de Smith AJ, Gant VU, Yang W, Scheurer ME, Walsh KM, et al. Inherited genetic susceptibility of acute lymphoblastic leukemia in Down syndrome. Blood 2019;134:1227–37.
68. de Smith AJ, Walsh KM, Francis SS, Zhang C, Hansen HM, Smirnov I, et al. BMI1 enhancer polymorphism underlies chromosome 10p12.31 association with childhood acute lymphoblastic leukemia. Int J Cancer 2018;143:2647–58.
69. Mrozek K, Harper DP, Aplan PD. Cytogenetics and molecular genetics of acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2009;23:991–1010.
70. Skapek SX, Ferrari A, Gupta AA, Lupo PJ, Butler E, Shipley J, et al. Rhabdomyosarcoma. Nat Rev Dis Primers 2019;5:1.
71. Northcott PA, Jones DT, Kool M, Robinson GW, Gilbertson RJ, Cho YJ, et al. Medulloblastomics: the end of the beginning. Nat Rev Cancer 2012;12:818–34.
72. Ma X, Liu Y, Liu Y, Alexandrov LB, Edmonson MN, Gawad C, et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. Nature 2018;555:371–6.

73. Johnson RA, Wright KD, Poppleton H, Mohankumar KM, Finkelstein D, Pounds SB, et al. Cross-species genomics matches driver mutations and cell compartments to model ependymoma. Nature 2010;466:632–6.
74. Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, Konermann C, et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell 2012;22:425–37.
75. Zhang J, Wu G, Miller CP, Tatevossian RG, Dalton JD, Tang B, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet 2013;45:602–12.
76. Torchia J, Picard D, Lafay-Cousin L, Hawkins CE, Kim SK, Letourneau L, et al. Molecular subgroups of atypical teratoid rhabdoid tumours in children: an integrated genomic and clinicopathological analysis. Lancet Oncol 2015;16:569–82.
77. Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, Wang JQ, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med 2018;378:1396–407.
78. Ladanyi M. EWS-FLI1 and Ewing's sarcoma: recent molecular data and new insights. Cancer Biol Ther 2002;1:330–6.
79. Tolbert VP, Coggins GE, Maris JM. Genetic susceptibility to neuroblastoma. Curr Opin Genet Dev 2017;42:81–90.
80. Williams LA, Yang JJ, Hirsch BA, Marcotte EL, Spector LG. Is there etiologic heterogeneity between subtypes of childhood acute lymphoblastic leukemia? A review of variation in risk by subtype. Cancer Epidemiol Biomarkers Prev 2019;28:846–56.
81. Woods WG, Gao R-N, Shuster JJ, Robison LL, Bernstein M, Weitzman S, et al. Screening of infants and mortality due to neuroblastoma. N Engl J Med 2002;346:1041–6.
82. Schilling FH, Spix C, Berthold F, Erttmann R, Fehse N, Hero B, et al. Neuroblastoma screening at one year of age. N Engl J Med 2002;346:1047–53.
83. Hiyama E. Neuroblastoma screening in Japan: population-based cohort study and future aspects of screening. Ann Acad Med 2008;37:88–4.
84. Maris JM, Woods WG. Screening for neuroblastoma: a resurrected idea? Lancet 2008;371:1142–3.
85. Malkin D, Nichols KE, Schiffman JD, Plon SE, Brodeur GM. The future of surveillance in the context of cancer predisposition: through the murky looking glass. Clin Cancer Res 2017;23:e133–e7.
86. Almannai M, Marom R, Sutton VR. Newborn screening: a review of history, recent advancements, and future perspectives in the era of next generation sequencing. Curr Opin Pediatr 2016;28:694–9.
87. Pitt JJ. Newborn screening. Clin Biochem Rev 2010;31:57–68.
88. Custódio G, Parise GA, Kiesel Filho N, Komechen H, Sabbaga CC, Rosati R, et al. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. J Clin Oncol 2013;31:2619–26.
89. Spector LG, Ross JA, Olshan AF. Children's Oncology Group's 2013 blueprint for research: epidemiology. Pediatr Blood Cancer 2013;60:1059–62.
90. Puumala SE, Spector LG, Robison LL, Bunin GR, Olshan AF, Linabery AM, et al. Comparability and representativeness of control groups in a case-control study of infant leukemia: a report from the Children's Oncology Group. Am J Epidemiol 2009;170:379–87.
91. Spector LG, Ross JA, Puumala SE, Roesler M, Olshan AF, Bunin GR. Feasibility of nationwide birth registry control selection in the United States. Am J Epidemiol 2007;166:852–6.
92. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The National Birth Defects Prevention Study. Public Health Rep 2001;116:32–40.
93. Yang Y, Basu S, Mirabello L, Spector L, Zhang L. A bayesian gene-based genome-wide association study analysis of osteosarcoma trio data using a hierarchically structured prior. Cancer Inform 2018;17:1176935118775103.
94. Mazul AL, Weinberg CR, Engel SM, Siega-Riz AM, Zou F, Carrier KS, et al. Neuroblastoma in relation to joint effects of vitamin A and maternal and offspring variants in vitamin A-related genes: a report of the Children's Oncology Group. Cancer Epidemiol 2019;61:165–71.
95. Marcotte EL, Pankratz N, Amatruda JF, Frazier AL, Krailo M, Davies S, et al. Variants in BAK1, SPRY4, and GAB2 are associated with pediatric germ cell tumors: a report from the children's oncology group. Genes Chromosomes Cancer 2017;56:548–58.
96. Petrick LM, Schiffman C, Edmands WMB, Yano Y, Perttula K, Whitehead T, et al. Metabolomics of neonatal blood spots reveal distinct phenotypes of pediatric acute lymphoblastic leukemia and potential effects of early-life nutrition. Cancer Lett 2019;452:71–8.
97. Spector LG, Murphy SE, Wickham KM, Lindgren B, Joseph AM. Prenatal tobacco exposure and cotinine in newborn dried blood spots. Pediatrics 2014;133:e1632–8.
98. Funk WE, Waidyanatha S, Chaing SH, Rappaport SM. Hemoglobin adducts of benzene oxide in neonatal and adult dried blood spots. Cancer Epidemiol Biomarkers Prev 2008;17:1896–901.
99. Wilcox AJ, Weinberg CR, Lie RT. Distinguishing the effects of maternal and offspring genes through studies of "case-parent triads". Am J Epidemiol 1998;148:893–901.
100. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. Stat Methods Med Res 2017;26:2333–55.
101. Archer NP, Perez-Andreu V, Stoltze U, Scheurer ME, Wilkinson AV, Lin T-N, et al. Family-based exome-wide association study of childhood acute lymphoblastic leukemia among Hispanics confirms role of ARID5B in susceptibility. PLoS One 2017;12:e0180488.
102. Gondalia R, Baldassari A, Holliday KM, Justice AE, Mendez-Giraldez R, Stewart JD, et al. Methylome-wide association study provides evidence of particulate matter air pollution-associated DNA methylation. Environ Int 2019;132:104723.
103. Abdolahi A, van Wijngaarden E, McClean M, Herrick R, Allen J, Ganguly A, et al. A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. Occup Environ Med 2013;70:372–9.
104. Ajrouche R, Rudant J, Orsi L, Petit A, Baruchel A, Nelken B, et al. Maternal reproductive history, fertility treatments and folic acid supplementation in the risk of childhood acute leukemia: the ESTELLE Study. Cancer Causes Control 2014;25:1283–93.
105. Amitay EL, Keinan-Boker L. Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review. JAMA Pediatr 2015;169:e151025.
106. Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, Eden TOB. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. Eur J Cancer 2005;41:741–8.
107. Axelson O, Fredrikson M, Akerblom G, Hardell L. Leukemia in childhood and adolescence and exposure to ionizing radiation in homes built from uranium-containing alum shale concrete. Epidemiology 2002;13:146–50.
108. Azary S, Ganguly A, Bunin GR, Lombardi C, Park AS, Ritz B, et al. Sporadic retinoblastoma and parental smoking and alcohol consumption before and after conception: a report from the children's oncology group. PLoS One 2016;11:e0151728.
109. Bailey HD, Armstrong BK, De Klerk NH, Fritschi L, Attia J, Lockwood L, et al. Exposure to diagnostic radiological procedures and the risk of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev 2010;19:2897–909.
110. Bailey HD, Fritschi L, Infante-Rivard C, Glass DC, Miligi L, Dockerty JD, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. Int J Cancer 2014;135:2157–72.
111. Bailey HD, Infante-Rivard C, Metayer C, Clavel J, Lightfoot T, Kaatsch P, et al. Home pesticide exposures and risk of childhood leukemia: findings from the childhood leukemia international consortium. Int J Cancer 2015;137:2644–63.
112. Bailey HD, Miller M, Langridge A, De Klerk NH, Van Bockxmeer FM, Attia J, et al. Maternal dietary intake of folate and vitamins B6 and B12 during pregnancy and the risk of childhood acute lymphoblastic leukemia. Nutr Cancer 2012;64:1122–30.
113. Bartley K, Metayer C, Selvin S, Ducore J, Buffler P. Diagnostic X-rays and risk of childhood leukaemia. Int J Epidemiol 2010;39:1628–37.
114. Bluhm E, McNeil DE, Cnattingius S, Gridley G, El Ghormli L, Fraumeni JF. Prenatal and perinatal risk factors for neuroblastoma. Int J Cancer 2008;123:2885–90.
115. Botto LD, Flood T, Little J, Fluchel MN, Krikov S, Feldkamp ML, et al. Cancer risk in children and adolescents with birth defects: a population-based cohort study. PLoS One 2013;8:e69077.
116. Brondum J, Shu X-O, Steinbuch M, Severson RK, Potter JD, Robison LL, et al. Parental cigarette smoking and the risk of acute leukemia in children. Cancer 1999;85:1380–8.

117. Brooks DR, Mucci LA, Hatch EE, Cnattingius S. Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. Cancer Causes Control 2004;15:997–1005.
118. Buck GM, Michalek AM, Chen C-J, Nasca PC, Baptiste MS. Perinatal factors and risk of neuroblastoma. Paediatr Perinat Epidemiol 2001;15:14–53.
119. Buckley JD, Sather H, Ruccione K, Rogers PCJ, Haas JE, Henderson BE, et al. A case-control study of risk factors for hepatoblastoma a report from the childrens cancer study group. Cancer 1989;64:1169–79.
120. Bunin G, Buckley J, Boesel C, Rorke L, Meadows A. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the children's cancer group. Cancer Epidemiol Biomarkers Prev 1994;3:197–204.
121. Bunin GR, Felice MA, Davidson W, Friedman D, Shields C, Maidment A, et al. Medical radiation exposure and risk of retinoblastoma resulting from new germline RB1 mutation. Int J Cancer 2011;128:2393–404.
122. Bunin GR, Meadows AT, Emanuel BS, Buckley JD, Hammond GD, Woods WG. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. Cancer Res 1989;49:5730–5.
123. Carozza SE, Li B, Wang Q, Horel S, Cooper S. Agricultural pesticides and risk of childhood cancers. Int J Hyg Environ Health 2009;212:186–95.
124. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. Int J Cancer 2009;124: 2658–70.
125. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am J Epidemiol 2006;163:1091–100.
126. Chang JS, Tsai YW, Tsai CR, Wiemels JL. Allergy and risk of childhood acute lymphoblastic leukemia: a population-based and record-based study. Am J Epidemiol 2012;176:970–8.
127. Cheng J, Su H, Zhu R, Wang X, Peng M, Song J, et al. Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: A metaanalysis. Am J Obstet Gynecol 2014;210:151.e1–e10.
128. Chow EJ, Friedman DL, Mueller BA. Maternal and perinatal characteristics in relation to neuroblastoma. Cancer 2007;109:983–92.
129. Chu A, Heck JE, Ribeiro KB, Brennan P, Boffetta P, Buffler P, et al. Wilms' tumour: a systematic review of risk factors and meta-analysis. Paediatr Perinat Epidemiol 2010;24:449–69.
130. Chu P, Wang H, Han S, Jin Y, Lu J, Han W, et al. Maternal smoking during pregnancy and risk of childhood neuroblastoma: systematic review and meta-analysis. J Cancer Res Ther 2016;12:999.
131. Cooney MA, Daniels JL, Ross JA, Breslow NE, Pollock BH, Olshan AF. Household pesticides and the risk of Wilms tumor. Environ Health Perspect 2007;115:134–7.
132. Cordier S, Lefeuvre B, Filippini G, Peris-Bonet R, Farinotti M, Lovicu G, et al. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). Cancer Causes Control 1997;8:688–97.
133. Dahlhaus A, Prengel P, Spector L, Pieper D. Birth weight and subsequent risk of childhood primary brain tumors: an updated meta-analysis. Pediatr Blood Cancer 2017;64.
134. Daniels JL, Olshan AF, Pollock BH, Shah NR, Stram DO. Breast-feeding and neuroblastoma, USA and Canada. Cancer Causes Control 2002;13:401–5.
135. Daniels JL, Olshan AF, Teschke K, Hertz-Picciotto I, Savitz DA, Blatt J, et al. Residential pesticide exposure and neuroblastoma. Epidemiology 2001;12: 20–7.
136. De Paula Silva N, De Souza Reis R, Cunha RG, Oliveira JFP, De Oliveira Santos M, Pombo-De-Oliveira MS, et al. Maternal and birth characteristics and childhood embryonal solid tumors: a population-based report from Brazil. PLoS One 2016;11:e0164398.
137. De Roos AJ, Olshan AF, Teschke K, Poole C, Savitz DA, Blatt J, et al. Parental occupational exposures to chemicals and incidence of neuroblastoma in offspring. Am J Epidemiol 2001;154:106–14.
138. Dessypris N, Karalexi MA, Ntouvelis E, Diamantaras AA, Papadakis V, Baka M, et al. Association of maternal and index child's diet with subsequent leukemia risk: a systematic review and meta analysis. Cancer Epidemiol 2017;47:64–75.
139. Dockerty JD, Herbison P, Skegg DCG, Elwood M. Vitamin and mineral supplements in pregnancy and the risk of childhood acute lymphoblastic leukaemia: a case-control study. BMC Public Health 2007;7:136.
140. Evrard AS, Hémon D, Billon S, Laurier D, Jougla E, Tirmarche M, et al. Childhood leukemia incidence and exposure to indoor radon, terrestrial and cosmic gamma radiation. Health Phys 2006;90:569–79.
141. Fisher PG, Reynolds P, Von Behren J, Carmichael SL, Rasmussen SA, Shaw GM. Cancer in children with nonchromosomal birth defects. J Pediatr 2012;160: 978–83.
142. García-Pérez J, Morales-Piga A, Gómez-Barroso D, Tamayo-Uria I, Pardo Romaguera E, López-Abente G, et al. Residential proximity to environmental pollution sources and risk of rare tumors in children. Environ Res 2016;151: 265–74.
143. Glass DC, Reid A, Bailey HD, Milne E, Fritschi L. Risk of childhood acute lymphoblastic leukaemia following parental occupational exposure to pesticides. Occup Environ Med 2012;69:846–9.
144. Goel R, Olshan AF, Ross JA, Breslow NE, Pollock BH. Maternal exposure to medical radiation and Wilms tumor in the offspring: a report from the Children's Oncology Group. Cancer Causes Control 2009;20:957–63.
145. Goh YI, Koren G. Prenatal supplementation with multivitamins and the incidence of pediatric cancers: clinical and methodological considerations. Pediatr Blood Cancer 1008;50:487–9.
146. Gold EB, Leviton A, Lopez R, Gilles FH, Tessa Hedley-Whyte E, Kolonel LN, et al. Parental smoking and risk of childhood brain tumors. Am J Epidemiol 1993;137:620–8.
147. Greenop KR, Bailey HD, Miller M, Scott RJ, Attia J, Ashton LJ, et al. Breastfeeding and nutrition to 2 years of age and risk of childhood acute lymphoblastic leukemia and brain tumors. Nutr Cancer 2015;67:431–41.
148. Greenop KR, Peters S, Bailey HD, Fritschi L, Attia J, Scott RJ, et al. Exposure to pesticides and the risk of childhood brain tumors. Cancer Causes Control 2013; 24:1269–78.
149. Groves FD, Watkins BT, Roberts DJ, Tucker TC, Shen T, Flood TJ. Birth weight and risk of childhood acute lymphoblastic leukemia in Arizona, Illinois, and Kentucky. South Med J 2018;111:579–84.
150. Gunier RB, Kang A, Hammond SK, Reinier K, Lea CS, Chang JS, et al. A task-based assessment of parental occupational exposure to pesticides and childhood acute lymphoblastic leukemia. Environ Res 2017;156:57–62.
151. Ha M, Im H, Lee M, Kim HJ, Kim BC, Gimm YM, et al. Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. Am J Epidemiol 2007;166:270–9.
152. Hardell L, Dreifaldt AC. Breast-feeding duration and the risk of malignant diseases in childhood in Sweden. Eur J Clin Nutr 2001;55:179–85.
153. Harder T, Plagemann A, Harder A. Birth weight and risk of neuroblastoma: a meta-analysis. Int J Epidemiol 2010;39:746–56.
154. Harding NJ, Birch JM, Hepworth SJ, McKinney PA. Breastfeeding and risk of childhood CNS tumours. Br J Cancer 2007;96:815–7.
155. Heck JE, Contreras ZA, Park AS, Davidson TB, Cockburn M, Ritz B. Smoking in pregnancy and risk of cancer among young children: a population-based study. Int J Cancer 2016;139:613–6.
156. Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, Ritz B. Perinatal characteristics and retinoblastoma. Cancer Causes Control 2012; 23:1567–75.
157. Heck JE, Meyers TJ, Lombardi C, Park AS, Cockburn M, Reynolds P, et al. Case-control study of birth characteristics and the risk of hepatoblastoma. Cancer Epidemiol 2013;37:390–5.
158. Heck JE, Omidakhsh N, Azary S, Ritz B, von Ehrenstein OS, Bunin GR, et al. A case-control study of sporadic retinoblastoma in relation to maternal health conditions and reproductive factors: a report from the Children's Oncology Group. BMC Cancer 2015;15:735.
159. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. Retinoblastoma and ambient exposure to air toxics in the perinatal period. J Expo Sci Environ Epidemiol 2015;25:182–6.
160. Heck JE, Wu J, Lombardi C, Qiu J, Meyers TJ, Wilhelm M, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect 2013;121:1385–91.
161. Heuch JM, Heuch I, Akslen LA, Kvåle G. Risk of primary childhood brain tumors related to birth characteristics: a Norwegian prospective study. Int J Cancer 1998;77:498–503.
162. Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, et al. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. J Natl Cancer Inst 2004;96:1549–56.
163. Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H, et al. Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. Am J Epidemiol 2003;158: 724–35.
164. Huang Y, Huang J, Lan H, Zhao G, Huang C. A meta-analysis of parental smoking and the risk of childhood brain tumors. PLoS One 2014;9:e102910.

165. Hug K, Grize L, Seidler A, Kaatsch P, Schüz J. Parental occupational exposure to extremely low frequency magnetic fields and childhood cancer: a German case-control study. Am J Epidemiol 2010;171:27–35.
166. Huoi C, Olsson A, Lightfoot T, Roman E, Clavel J, Lacour B, et al. Parental occupational exposure and risk of childhood central nervous system tumors: a pooled analysis of case–control studies from Germany, France, and the UK. Cancer Causes Control 2014;25:1603–13.
167. Hyland C, Gunier RB, Metayer C, Bates MN, Wesseling C, Mora AM. Maternal residential pesticide use and risk of childhood leukemia in Costa Rica. Int J Cancer 2018;143:1295–304.
168. Janitz AE, Neas BR, Campbell JE, Pate AE, Stoner JA, Magzamen SL, et al. Childhood cancer in children with congenital anomalies in Oklahoma, 1997 to 2009. Birth Defects Res A Clin Mol Teratol 2016;106:633–42.
169. Janitz AE, Ramachandran G, Tomlinson GE, Krailo M, Richardson M, Spector L. Maternal and paternal occupational exposures and hepatoblastoma: results from the HOPE study through the Children's Oncology Group. J Expo Sci Environ Epidemiol 2017;27:359–64.
170. Jepsen P, Olsen ML, Mellemkjær L, Olsen JH, Sørensen HT. A registry-based study of gender, fetal growth, and risk of Wilms tumor. Pediatr Hematol Oncol 2004;21:435–9.
171. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer. Epidemiology 2009;20:475–83.
172. Johnson KJ, Puumala SE, Soler JT, Spector LG. Perinatal characteristics and risk of neuroblastoma. Int J Cancer 2008;123:1166–72.
173. Johnson KJ, Williams KS, Ross JA, Krailo MD, Tomlinson GE, Malogolowkin MH, et al. Parental tobacco and alcohol use and risk of hepatoblastoma in offspring: a report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev 2013;22:1837–43.
174. Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer 1991;68:1351–5.
175. Kerr MA, Michalek AM, Baptiste MS, Mahoney MC, Nasca PC, Mundt KA. Parental occupational exposures and risk of neuroblastoma: a case-control study (United States). Cancer Causes Control 2000;11:635–43.
176. Kuijten RR, Bunin GR, Nass CC, Meadows AT. Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. Cancer Res 1990;50:2608–12.
177. Kwan ML, Buffler PA, Wiemels JL, Metayer C, Selvin S, Ducore JM, et al. Breastfeeding patterns and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2005;93:379–84.
178. Lariou MS, Dikalioti SK, Dessypris N, Baka M, Polychronopoulou S, Athanasiadou-Piperopoulou F, et al. Allergy and risk of acute lymphoblastic leukemia among children: a nationwide case control study in Greece. Cancer Epidemiol 2013;37:146–51.
179. Latino-Martel P, Chan DSM, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: Systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19:1238–60.
180. Li P, McLaughlin J, Infante-Rivard C. Maternal occupational exposure to extremely low frequency magnetic fields and the risk of brain cancer in the offspring. Cancer Causes Control 2009;20:945–55.
181. Linabery AM, Jurek AM, Duval S, Ross JA. The association between atopy and childhood/adolescent leukemia: a meta-analysis. Am J Epidemiol 2010;171:749–64.
182. Linabery AM, Puumala SE, Hilden JM, Davies SM, Heerema NA, Roesler MA, et al. Maternal vitamin and iron supplementation and risk of infant leukaemia: a report from the Children's Oncology Group. Br J Cancer 2010;103:1724–8.
183. Linet MS, Gridley G, Cnattingius S, Nicholson HS, Martinsson U, Glimelius B, et al. Maternal and perinatal risk factors for childhood brain tumors (Sweden). Cancer Causes Control 1996;7:437–48.
184. Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. J Oncol 2011;2011:854584.
185. Lupo PJ, Lee LJ, Okcu MF, Bondy ML, Scheurer ME. An exploratory case-only analysis of gene-hazardous air pollutant interactions and the risk of childhood medulloblastoma. Pediatr Blood Cancer 2012;59:605–10.
186. Lupo PJ, Schraw JM, Desrosiers TA, Nembhard WN, Langlois PH, Canfield MA, et al. Association between birth defects and cancer risk among children and adolescents in a population-based assessment of 10 million live births. JAMA Oncol 2019 Jun 20 [Epub ahead of print].
187. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 2002;110:955–60.
188. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault G. Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. Cancer Causes Control 2008;19:283–95.
189. MacCarthy A, Bunch KJ, Fear NT, King JC, Vincent TJ, Murphy MFG. Paternal occupation and retinoblastoma: a case - control study based on data for Great Britain 1962–1999. Occup Environ Med 2009;66:644–9.
190. MacLean J, Partap S, Reynolds P, Von Behren J, Fisher PG. Birth weight and order as risk factors for childhood central nervous system tumors. J Pediatr 2010;157:450–5.
191. Mallol-Mesnard N, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, et al. Birth characteristics and childhood malignant central nervous sytem tumors: the ESCALE study (French Society for Childhood Cancer). Cancer Detect Prev 2008;32:79–86.
192. Marcotte EL, Thomopoulos TP, Infante-Rivard C, Clavel J, Petridou ET, Schüz J, et al. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). Lancet Haematol 2016;3:e176–e85.
193. Martin RM, Gunnell D, Owen CG, Smith GD. Breast-feeding and childhood cancer: a systematic review with metaanalysis. Int J Cancer 2005;117:1020–31.
194. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Maternal and infant birth characteristics and hepatoblastoma. Am J Epidemiol 2006;163:818–28.
195. McLaughlin CC, Baptiste MS, Schymura MJ, Zdeb MS, Nasca PC. Perinatal risk factors for neuroblastoma. Cancer Causes Control 2009;20:289–301.
196. Menegaux F, Steffen C, Bellec S, Baruchel A, Lescoeur B, Leverger G, et al. Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. Cancer Detect Prev 2005;29:487–93.
197. Metayer C, Colt JS, Buffler PA, Reed HD, Selvin S, Crouse V, et al. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. J Expo Sci Environ Epidemiol 2013;23:363–70.
198. Metayer C, Milne E, Dockerty JD, Clavel J, Pombo-de-Oliveira MS, Wesseling C, et al. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring. Epidemiology 2014;25:811–22.
199. Metayer C, Scelo G, Kang AY, Gunier RB, Reinier K, Lea S, et al. A task-based assessment of parental occupational exposure to organic solvents and other compounds and the risk of childhood leukemia in California. Environ Res 2016;151:174–83.
200. Metayer C, Zhang L, Wiemels JL, Bartley K, Schiffman J, Ma X, et al. Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype. Cancer Epidemiol Biomarkers Prev 2013;22:1600–11.
201. Michalek AM, Freedman AN, Mahoney MC, Buck GM, Nasca PC, Baptiste MS. Gravid health status, medication use, and risk of neuroblastoma. Am J Epidemiol 1996;143:996–1001.
202. Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, et al. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol 2012;175:43–53.
203. Milne E, Royle JA, Bennett LC, De Klerk NH, Bailey HD, Bower C, et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study. Cancer Causes Control 2011;22:207–18.
204. Milne E, Royle JA, Miller M, Bower C, De Klerk NH, Bailey HD, et al. Maternal folate and other vitamin supplementation during pregnancy and risk of acute lymphoblastic leukemia in the offspring. Int J Cancer 2010;126:2690–9.
205. Moore A, Enquobahrie DA. Paternal occupational exposure to pesticides and risk of neuroblastoma among children: a meta-analysis. Cancer Causes Control 2011;22:1529–36.
206. Mortensen JHS, Øyen N, Fomina T, Melbye M, Tretli S, Vollset SE, et al. Supplemental folic acid in pregnancy and childhood cancer risk. Br J Cancer 2016;114:71–5.
207. Müller-Schulte E, Kurlemann G, Harder A. Tobacco, alcohol and illicit drugs during pregnancy and risk of neuroblastoma: Systematic review. Arch Dis Child Fetal Neonatal Ed 2018;103:F467–F73.
208. Musselman JRB, Georgieff MK, Ross JA, Tomlinson GE, Feusner J, Krailo M, et al. Maternal pregnancy events and exposures and risk of hepatoblastoma: a Children's Oncology Group (COG) study. Cancer Epidemiol 2013;37:318–20.

209. Nasca PC, Baptiste MS, Maccubbin PA, Metzger BB, Carlton K, Greenwald P, et al. An epidemiologic case-control study of central nervous system tumors in children and parental occupational exposures. Am J Epidemiol 1988;128:1256–65.
210. Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L. Birth weight and other perinatal characteristics and childhood leukemia in California. Cancer Epidemiol 2012;36.
211. Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L. Birth weight and other perinatal factors and childhood CNS tumors: a case-control study in California. Cancer Epidemiol 2013;37:402–9.
212. Olshan AF, Breslow NE, Falletta JM, Gruferman S, Pendergrass T, Robison LL, et al. Risk factors for wilms tumor report from the National Wilms Tumor Study. Cancer 1993;72.
213. Olshan AF, Patton T, Neglia JP, Castleberry RP, Smith J. Parental exposure to medical radiation and neuroblastoma in offspring. Paediatr Perinat Epidemiol 2004;18:178–85.
214. Olshan AF, Smith JC, Bondy ML, Neglia JP, Pollock BH. Maternal vitamin use and reduced risk of neuroblastoma. Epidemiology 2002;13:575–80.
215. Omidakhsh N, Bunin GR, Ganguly A, Ritz B, Kennedy N, Von Ehrenstein OS, et al. Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group. Occup Environ Med 2018;75:205–11.
216. Omidakhsh N, Ganguly A, Bunin GR, von Ehrenstein OS, Ritz B, Heck JE. Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group. Am J Ophthalmol 2017;176:166–73.
217. O'Neill KA, Murphy MFG, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, et al. Infant birthweight and risk of childhood cancer: International population-based case control studies of 40 000 cases. Int J Epidemiol 2015;44:153–68.
218. Orsi L, Rudant J, Ajrouche R, Leverger G, Baruchel A, Nelken B, et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. Cancer Causes Control 2015;26:1003–17.
219. Panagopoulou P, Skalkidou A, Marcotte E, Erdmann F, Ma X, Heck JE, et al. Parental age and the risk of childhood acute myeloid leukemia: results from the Childhood Leukemia International Consortium. Cancer Epidemiol 2019;59:158–65.
220. Pang D, McNally R, Birch JM. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. Br J Cancer 2003;88:373–81.
221. Parodi S, Merlo DF, Ranucci A, Miligi L, Benvenuti A, Rondelli R, et al. Risk of neuroblastoma, maternal characteristics and perinatal exposures: The SETIL study. Cancer Epidemiol 2014;38:686–94.
222. Patel DM, Jones RR, Booth BJ, Olsson AC, Kromhout H, Straif K, et al. Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: Findings from the International Childhood Cancer Cohort Consortium (I4C). Int J Cancer 2019. doi 10.1002/ijc.32388.
223. Petridou ET, Georgakis MK, Erdmann F, Ma X, Heck JE, Auvinen A, et al. Advanced parental age as risk factor for childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia International Consortium. Eur J Epidemiol 2018;33:965–76.
224. Plichart M, Menegaux F, Lacour B, Hartmann O, Frappaz D, Ois Doz F, et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE)*. Eur J Cancer Prev 2008;17:376–83.
225. Preston-Martin S, Pogoda JM, Mueller BA, Lubin F, Modan B, Holly EA, et al. Prenatal vitamin supplementation and pediatric brain tumors: huge international variation in use and possible reduction in risk. Child's Nerv Syst 1998;14:551–7.
226. Puumala SE, Ross JA, Feusner JH, Tomlinson GE, Malogolowkin MH, Krailo MD, et al. Parental infertility, infertility treatment and hepatoblastoma: a report from the Childrens Oncology Group. Hum Reprod 2012;27:1649–56.
227. Puumala SE, Soler JT, Johnson KJ, Spector LG. Birth characteristics and Wilms tumor in Minnesota. Int J Cancer 2008;122:1368–73.
228. Rajaraman P, Simpson J, Neta G, De Gonzalez AB, Ansell P, Linet MS, et al. Early life exposure to diagnostic radiation and ultrasound scans and risk of childhood cancer: Case-control study. BMJ 2011;342:424.
229. Rangel M, Cypriano M, De Martino Lee ML, Luisi FAV, Petrilli AS, Strufaldi MWL, et al. Leukemia, non-Hodgkin's lymphoma, and Wilms tumor in childhood: the role of birth weight. Eur J Pediatr 2010;169:875–81.
230. Reid A, Glass DC, Bailey HD, Milne E, Armstrong BK, Alvaro F, et al. Parental occupational exposure to exhausts, solvents, glues and paints, and risk of childhood leukemia. Cancer Causes Control 2011;22:1575–85.
231. Rios L, Vásquez L, Oscanoa M, Maza I, Gerónimo J. Advancing parental age and risk of solid tumors in children: a case-control study in Peru. J Oncol 2018;2018:3924635.
232. Rios P, Bailey HD, Lacour B, Valteau-Couanet D, Michon J, Bergeron C, et al. Maternal use of household pesticides during pregnancy and risk of neuroblastoma in offspring. A pooled analysis of the ESTELLE and ESCALE French studies (SFCE). Cancer Causes Control 2017;28:1125–32.
233. Rios P, Bailey HD, Orsi L, Lacour B, Valteau-Couanet D, Levy D, et al. Risk of neuroblastoma, birth-related characteristics, congenital malformations and perinatal exposures: a pooled analysis of the ESCALE and ESTELLE French studies (SFCE). Int J Cancer 2016;139:1936–48.
234. Rios P, Bailey HD, Poulalhon C, Valteau-Couanet D, Schleiermacher G, Bergeron C, et al. Parental smoking, maternal alcohol consumption during pregnancy and the risk of neuroblastoma in children. A pooled analysis of the ESCALE and ESTELLE French studies. Int J Cancer 2019. doi 10.1002/ijc.32161.
235. Rosso AL, Hovinga ME, Rorke-Adams LB, Spector LG, Bunin GR. A case-control study of childhood brain tumors and fathers' hobbies: a Children's Oncology Group study. Cancer Causes Control 2008;19:1201–7.
236. Rudant J, Orsi L, Menegaux F, Petit A, Baruchel A, Bertrand Y, et al. Childhood acute leukemia, early common infections, and allergy: The ESCALE study. Am J Epidemiol 2010;172:1015–27.
237. Saddlemire S, Olshan AF, Daniels JL, Breslow NE, Bunin GR, Ross JA. Breastfeeding and Wilms tumor: a report from the Children's Oncology Group. Cancer Causes Control 2006;17:687–93.
238. Scélo G, Metayer C, Zhang L, Wiemels JL, Aldrich MC, Selvin S, et al. Household Exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood Leukemia. Environ Health Perspect 2009;117:133–9.
239. Schü J, Kaletsch U, Kaatsch P, Meinert R, Rg Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. Med Pediatr Oncol 2001;36:274–82.
240. Schüz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Risk of childhood leukemia and parental self-reported occupational exposure to chemicals, dusts, and fumes: results from pooled analyses of German population-based case-control studies. Cancer Epidemiol Biomarkers Prev 2000;9:835–8.
241. Schüz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. High birth weight and other risk factors for Wilms tumour: results of a population-based case-control study. Eur J Pediatr 2001;160:333–8.
242. Schüz J, Weihkopf T, Kaatsch P. Medication use during pregnancy and the risk of childhood cancer in the offspring. Eur J Pediatr 2007;166:433–41.
243. Sergentanis TN, Thomopoulos TP, Gialamas SP, Karalexi MA, Biniaris-Georgallis SI, Kontogeorgi E, et al. Risk for childhood leukemia associated with maternal and paternal age. Eur J Epidemiol 2015;30:1229–61.
244. Shim YK, Miynarek SP, van Wijngaarden E. Parental exposure to pesticides and childhood brain cancer: U.S. Atlantic Coast Childhood Brain Cancer Study. Environ Health Perspect 2009;117:1002–6.
245. Shu XO, Han D, Kersey JH, Neglia JP, Robison LL, Potter JD, et al. Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. Cancer Epidemiol Biomarkers Prev 2002;11:177–85.
246. Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. J Natl Cancer Inst 1996;88:24–31.
247. Singer AW, Carmichael SL, Selvin S, Fu C, Block G, Metayer C. Maternal diet quality before pregnancy and risk of childhood leukaemia. Br J Nutr 2016;116:1469–78.
248. Slater ME, Linabery AM, Spector LG, Johnson KJ, Hilden JM, Heerema NA, et al. Maternal exposure to household chemicals and risk of infant leukemia: a report from the Children's Oncology Group. Cancer Causes Control 2011;22:1197–204.
249. Smith A, Lightfoot T, Simpson J, Roman E. Birth weight, sex and childhood cancer: a report from the United Kingdom Childhood Cancer Study. Cancer Epidemiol 2009;33:363–7.
250. Sorahan T, Lancashire RJ. Parental cigarette smoking and childhood risks of hepatoblastoma: OSCC data. Br J Cancer 2004;90:1016–8.
251. Spector LG, Johnson KJ, Soler JT, Puumala SE. Perinatal risk factors for hepatoblastoma. Br J Cancer 2008;98:1570–3.

252. Stålberg K, Haglund B, Axelsson O, Cnattingius S, Pfeifer S, Kieler H. Prenatal X-ray exposure and childhood brain tumours: a population-based case-control study on tumour subtypes. Br J Cancer 2007;97:1583–7.
253. Stavrou EP, Baker DF, Bishop JF. Maternal smoking during pregnancy and childhood cancer in New South Wales: a record linkage investigation. Cancer Causes Control 2009;20:1551–8.
254. Tettamanti G, Ljung R, Mathiesen T, Schwartzbaum J, Feychting M. Maternal smoking during pregnancy and the risk of childhood brain tumors: results from a Swedish cohort study. Cancer Epidemiol 2016;40:67–72.
255. Thomopoulos TP, Ntouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E, et al. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. Cancer Epidemiol 2015;39:1047–59.
256. Thomopoulos TP, Skalkidou A, Dessypris N, Chrousos G, Karalexi MA, Karavasilis TG, et al. Prelabor cesarean delivery and early-onset acute childhood leukemia risk. Eur J Cancer Prev 2016;25:155–61.
257. Tsai J, Kaye WE, Bove FJ. Wilms' tumor and exposures to residential and occupational hazardous chemicals. Int J Hyg Environ Health 2006; 209:57–64.
258. Turner M, Wigle D, Krewski D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. Environ Health Perspect 2010;118:33–41.
259. Van Maele-Fabry G, Gamet-Payrastre L, Lison D. Household exposure to pesticides and risk of leukemia in children and adolescents: updated systematic review and meta-analysis. Int J Hyg Environ Health 2019;222: 49–67.
260. Van Maele-Fabry G, Hoet P, Lison D. Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: a systematic review and meta-analysis. Environ Int 2013;56:19–31.
261. Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. Environ Int 2011;37:280–91.
262. Wang R, Wiemels JL, Metayer C, Morimoto L, Francis SS, Kadan-Lottick N, et al. Cesarean section and risk of childhood acute lymphoblastic leukemia in a population-based, record-linkage study in California. Am J Epidemiol 2017; 185:96–105.
263. Wang YF, Wu LQ, Liu YN, Bi YY, Wang H. Gestational age and childhood leukemia: a meta-analysis of epidemiologic studies. Hematology 2018;23: 253–62.
264. Ward MH, Colt JS, Metayer C, Gunier RB, Lubin J, Crouse V, et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. Environ Health Perspect 2009;117:1007–13.
265. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environ Health Perspect 2009;117:1505–13.
266. Yang Q, Olshan AF, Bondy ML, Shah NR, Pollock BH, Seeger RC, et al. Parental smoking and alcohol consumption and risk of neuroblastoma. Cancer Epidemiol Biomarkers Prev 2000;9:967–72.

Cancer Progress and Priorities: Childhood Cancer

Philip J. Lupo and Logan G. Spector

Cancer Epidemiol Biomarkers Prev 2020;29:1081-1094.