Overview of the etiology of childhood cancer and future directions

Thanh T. Hoang[a,b,c], *Michael E. Scheurer*[a,b,c] *and Philip J. Lupo*[a,b,c]

Purpose of review
We provide an overview of the etiology of childhood cancer, the state of the literature, and highlight some opportunities for future research, including technological advancements that could be applied to etiologic studies of childhood cancer to accelerate our understanding.

Recent findings
Risk factors of childhood cancer were summarized based on demographics and perinatal factors, environmental risk factors, and genetic risk factors. Overall, demographics and perinatal factors are the most well studied in relation to childhood cancer. While environmental risk factors have been implicated, more work is needed to pinpoint specific exposures, identify window(s) of susceptibility, and understand mechanisms. With genome-wide association studies (GWAS), genetic risk factors of eight childhood cancers have emerged, and opportunities remain to conduct GWAS for other cancer types and determine whether risk variants are inherited or *de novo*. Technological advancements that can shed light into the susceptibility of childhood cancer include metabolomics, using primary teeth as an exposure matrix, and long-read sequencing.

Summary
The development of childhood cancer remains largely not well understood. Collaboration to increase sample size to conduct analyses by histology and/or molecular subtype and application of novel technologies will accelerate our understanding of childhood cancer.

Keywords
deciduous teeth, long-read sequencing, metabolomics, pediatric cancer, risk factors

INTRODUCTION

The incidence of cancer in children and adolescents has increased since the 1970s [1–3] and is estimated to be 103 to 208 cases per million, which translates to 200 000–400 000 new diagnoses before age 15 years [4]. Despite the increasing incidence, the underlying etiologies of childhood cancers remain largely elusive. In contrast, an estimated one in 5 or 20 million adults will develop cancer each year [5]. Compared to adult cancers, childhood cancers have very few somatic mutations [6], suggesting that germline variation and/or disruption of epigenetic mechanisms from extrinsic or intrinsic factors contribute to susceptibility in children or adolescents who develop cancer. Despite this, large-scale sequencing studies suggest that only about 10% of children diagnosed with cancer have a pathogenic or likely pathogenic variant in a known cancer predisposition gene [7], suggesting that more research is needed to identify the etiologies of the majority of cases. In this review, we summarize what is known about our current understanding of the etiologies of childhood cancer diagnosed from ages 0–19 years and state of the literature, as well as discuss considerations for future research.

DEMOGRAPHICS AND PERINATAL FACTORS

The incidence of childhood cancer varies by age, race/ethnicity, and sex. Leukemia, central nervous system (CNS) tumors, retinoblastoma, renal tumors, and hepatic tumors are more commonly diagnosed before age 10 years, whereas lymphomas, germ cell

[a]Department of Pediatrics, Division of Hematology-Oncology, [b]Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine and [c]Texas Children's Cancer and Hematology Center, Texas Children's Hospital, Houston, Texas, USA

Correspondence to Philip J. Lupo, One Baylor Plaza, MS: BCM622, Houston, TX 77030, USA. Tel: +1 713 798 2960;
e-mail: Philip.Lupo@bcm.edu

Curr Opin Pediatr 2025, 37:59–66

DOI:10.1097/MOP.0000000000001419

KEY POINTS

- The biggest progress in understanding the etiology of childhood cancers is from genome-wide association studies (GWAS), which have identified novel germline susceptibility genes, but these studies have only been conducted in 8 different types of childhood cancers.
- Long-read sequencing will improve our ability to further molecularly characterize germline and somatic variations.
- Application of metabolomics in the field of childhood cancer may lead to the identification of specific environmental exposures, window(s) of susceptibility, and insights into mechanisms.
- Collaboration to increase sample size and power to conduct analyses by histology and/or molecular subtype will accelerate our understanding of the etiology of childhood cancer.

and gonadal tumors, and epithelial tumors and melanoma are more common in adolescents (Fig. 1). In general, childhood cancer is more common in males and non-Hispanic Whites (Fig. 2) [8]. The differences in the incidence of childhood cancer by various demographic characteristics can be exploited to better our understanding of the origins of these malignancies.

Partially due to linkages with birth certificate records, medical records, and parental-reported questionnaire data, perinatal factors have been the most well studied examined in relation to the risk of childhood cancer. In fact, one of the strongest perinatal risk factors of childhood cancer is structural birth defects [9]. Structural birth defects are more commonly observed in pediatric cancers that arise during childhood compared to ones more prevalent in adolescence, suggesting that there are shared developmental pathways that are disrupted during pregnancy that increase cancer susceptibility. Despite the strong association, structural birth defects are only observed in 9% of childhood cancer cases [9].

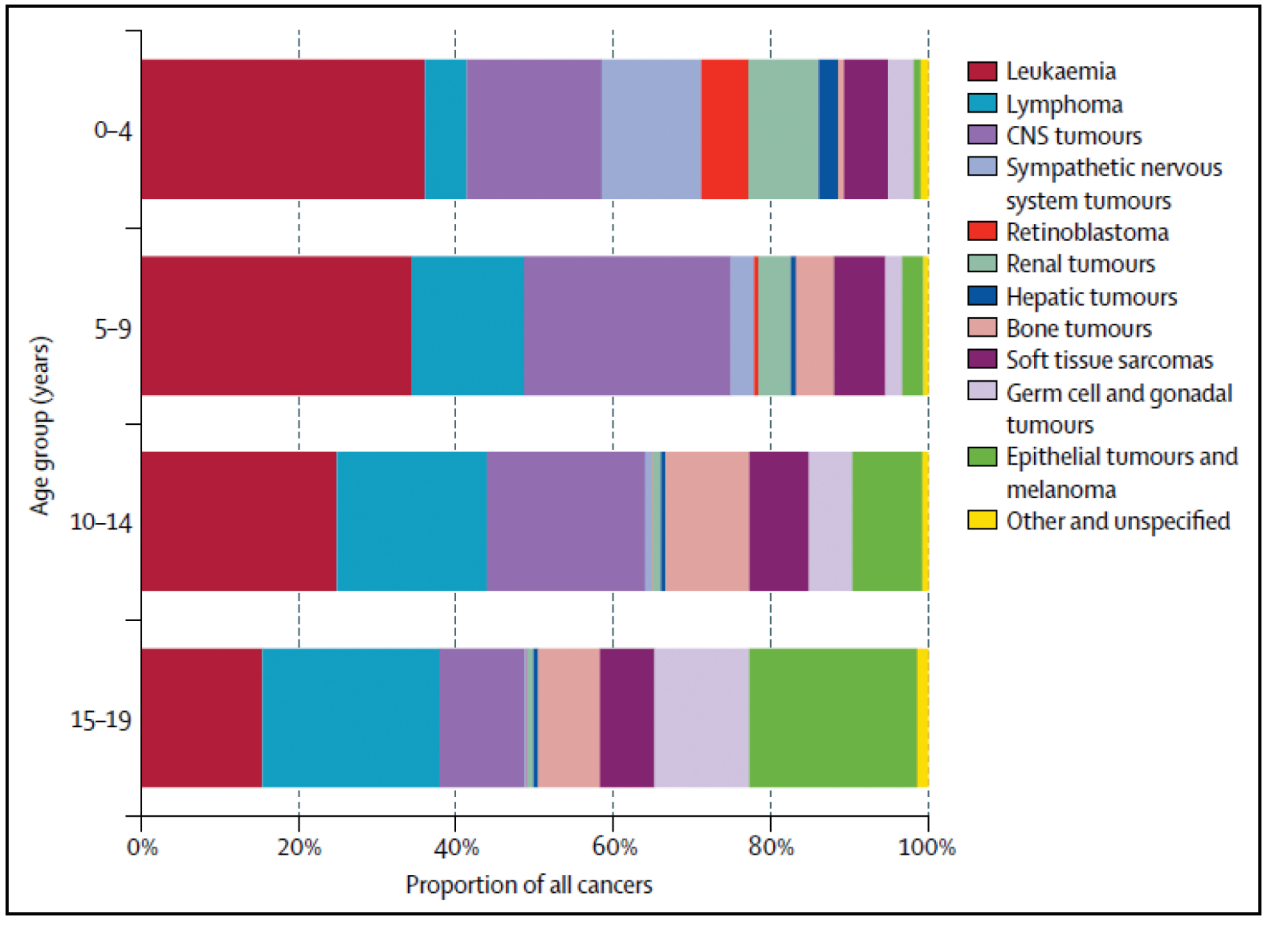

FIGURE 1. Proportional distribution of cancer type by age group, previously published in Steliarova-Foucher *et al.* [2].

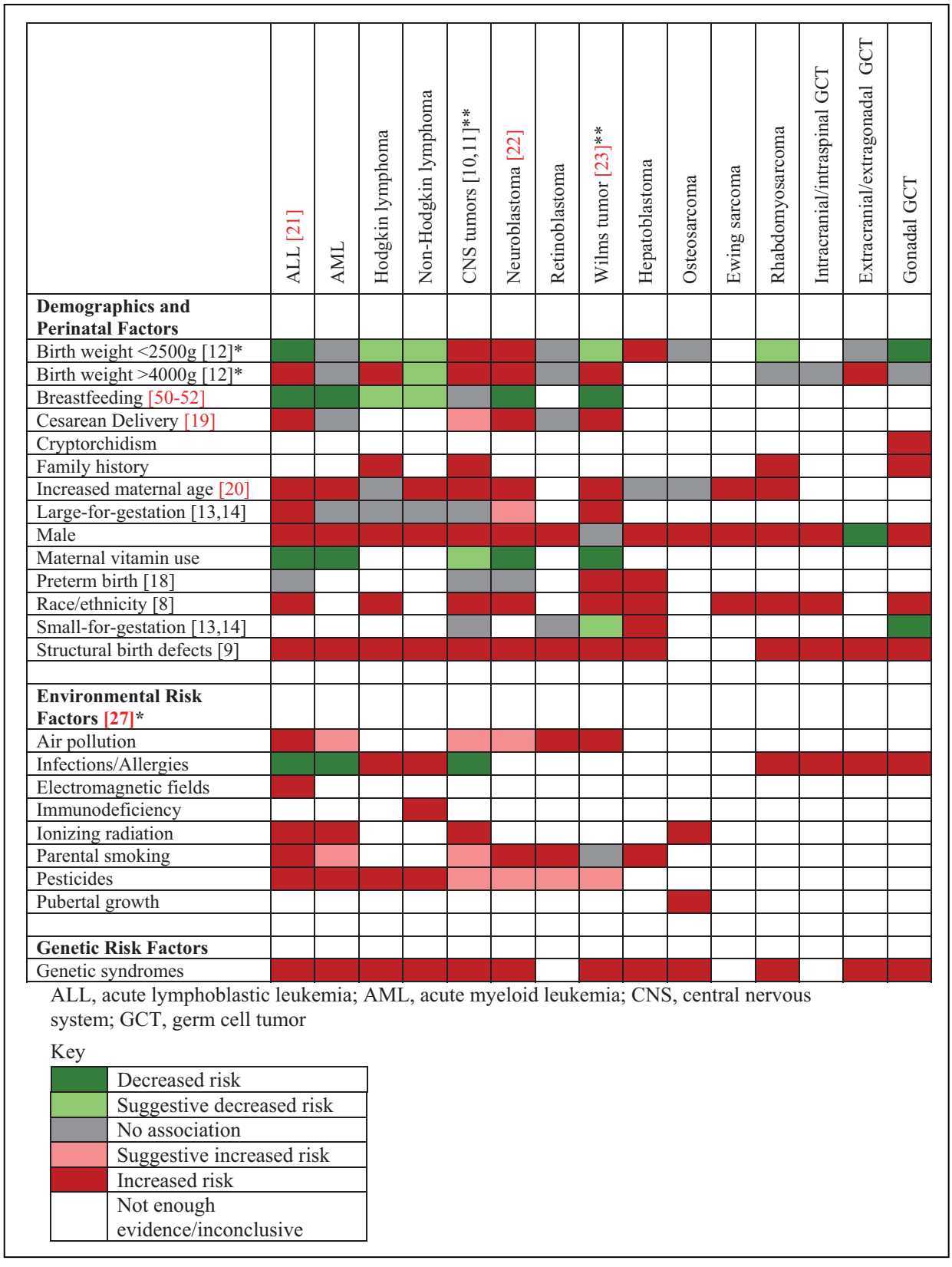

FIGURE 2. Confirmed and suggestive risk factors of childhood cancers.

Another well studied perinatal factors in relation to childhood cancer is birth weight or size for gestation with risk varying by cancer type. Notably, these two newborn measurements do not necessarily yield similar conclusions (Fig. 2). For example, low birth (<2500 g) and high birth weight (>4000 g) are associated with CNS tumors, but no association has been reported with small-for-gestation and large-for-gestation [10▪▪,11,12▪,13,14]. While size for gestation may be more informative than birth weight alone as it accounts for gestational age, the mechanisms underlying these associations are unclear and likely differ by characteristic and the malignancy in question. Having a higher birth weight or being large for gestational age may increase risk of childhood cancer because it may reflect pregnancies with altered maternal hormones, such as growth factors, or rapid fetal growth, which may increase risk of de novo mutations – both of which could contribute to carcinogenesis [15–17].

Other perinatal and parental factors explored in relation to the risk of childhood cancer include preterm birth [18], method of delivery [19], parental age [20], and vitamin intake [10▪▪,11,21,22,23▪▪]. Because there are many reasons for a preterm birth to occur [25], it is challenging to postulate mechanisms. More research is needed to parse this association by cause of the preterm birth. Infants born via cesarean delivery may have different hormonal exposures and are not exposed to the vaginal microbiome, which may increase susceptibility to certain childhood cancer (Fig. 2) [19,24]. Maternal age has also been reported to increase susceptibility [20], but because it is strongly correlated with paternal age, teasing the two apart can be challenging. In contrast, maternal vitamin intake during pregnancy and breastfeeding can reduce the risk of certain childhood cancer (Fig. 2) [10▪▪,11,21,22,23▪▪,50–52].

ENVIRONMENTAL RISK FACTORS

The potential effects of environmental exposures on childhood cancer development can occur through maternal exposures during pregnancy, paternal exposures that affect the sperm, and/or postnatal exposures. Maternal or postnatal ionizing radiation is the most well established environmental risk factor of childhood cancer, particularly for leukemia, central nervous system tumors, and osteosarcoma (Fig. 2). Despite the robust evidence, the absolute risk of early life exposure to ionizing radiation is small [26]. Several environmental exposures have been examined in relation to etiology of childhood cancer, including parental occupation, parental smoking, pesticide, air pollution, infections/allergies, and electromagnetic fields. While there is some suggestive evidence that certain exposures, such as pesticide, air pollution, infections/allergies, may increase susceptibility [27▪], additional studies are needed as the exposure assessments are not robust, specific environmental exposures have not been identified (e.g., there are over 800 different types of pesticides registered in the United States), and window(s) of susceptibility are not well established.

GENETIC RISK FACTORS

In terms of genetic susceptibility, both rare highly penetrant variants and common variants are established risk factors for childhood cancer [28]. Interestingly, there is emerging evidence that genetic variation associated with childhood cancer may be genetically constrained (i.e., genetic variations "associated with high risk of prereproductive fatal diseases…will be subject to natural selection due to a reproductive disadvantage" [29▪]). Before advancements in childhood cancer treatments, children with cancer would most likely die before reproduction, removing these pathogenetic variants from the human gene pool. It is well documented that children with known cancer predisposition genes or certain genetic syndromes (e.g., Down syndrome, neurofibromatosis, Beckwith-Wiedemann syndrome) are more likely to develop cancer. However, these predisposition genes or genetic syndromes have only been reported in approximately 10% of childhood cancers [7,30], suggesting there are additional molecular mechanisms that might contribute to risk.

Genome-wide association studies (GWAS) have been used to identify common variations that increase susceptibility to disease and have been utilized to study adult cancers. Due to multiple testing, GWAS requires large numbers of cases to identify robust single nucleotide variants (SNVs) and identified SNVs need to be confirmed in an independent study population. Given the rarity of pediatric cancers compared to adult cancers, GWAS of childhood cancers have lagged and have only been conducted for eight types: acute lymphoblastic leukemia, Langerhans cell histiocytosis (LCH), astrocytoma, medulloblastoma, neuroblastoma, Wilms tumor, osteosarcoma, and Ewing sarcoma. The sample size of these discovery cohorts has varied from 132 cases with LCH to 5321 children diagnosed with acute lymphoblastic leukemia (ALL). All these GWAS have identified at least one novel susceptibility loci (Table 1), but replication in an independent study population is still needed for some of the identified loci. Given the early age of onset compared to adult cancers, these GWAS have reported stronger magnitudes of association than those of adult cancers [31], suggesting that genetic variants may explain a

Table 1. Summary of genes or loci identified from genome-wide association studies of childhood cancers

Cancer	Mapped gene or locus	First author (year)	Number of cases in discovery cohort
ALL	*ARID5B, IKZF1, CEBPE, CDKN2A, GATA3, BMI1, PIP4K2A, ERG, USP7, 2p16.1, 2q22.3, 5q31.1, BAK1, 6q23, 8q24.21, 9q21.31, 10q21, LHPP, ELK3, IGF2BP1, IKZF3, SP4*	Papaemmanuil (2009)[53] Treviño (2009) [54] Orsi (2012) [55] Migliorini (2013) [56] Perez-Andreu (2013) [57] Xu (2013) [58] Xu (2015) [59] Archer (2017) [60] Wiemels (2018) [61] Qian (2019) [62] Qian (2019) [63] Vijayakrishnan (2019) [64] Lee (2021) [65] Jeon (2021) [66]	317–5321
Langerhans cell histiocytosis	*SMAD6*	Peckham-Gregory (2017) [67]	132
Astrocytoma	*CDKN2B-AS1 (9p21.3)*	Foss-Skiftesvik (2023) [68]	2348
Medulloblastoma	*18p11.23*	Dahlin (2020) [69]	244
Neuroblastoma	*CASC15/NBAT-1, BARD1, LMO1, HACE1, LIN28B, DUSP12, DDX4, IL31RA, HSD17B12, RPTN, MRPS18B, LRRC45, KANSL1L, ARHGEF40, IL15RA, L1TD1, ANO7, LAMA5, OR7G2, SALL4, NEUROG2, TMEM72-AS1, CRIM1, CPZ, RSRC1, MAGI3*	Maris (2008) [70] Capasso (2009) [71] Nguyen (2011) [72] Wang (2011) [73] Diskin (2012) [74] McDaniel (2017) [75] Avitabile (2020) [76] Bae (2020) [77] Testori (2022) [78]	254–2817
Wilms tumor	*DLG2, DDX1, TCN2, PCBP2P3,* 2p24, 11q14	Turnbull (2012) [79]	*757*
Osteosarcoma	*GRM4, SOX11-LINC00487, ADAMTS6, ADAMTS17, FAM208B,* 2p25.2	Savage (2013) [80]	941
Ewing sarcoma	*CFL1P6, EGR2, LOC100131089,* 1p36.22, 10q21.3, 15q15.1, 6p25.1, 20p11.22, 20p11.23	Postel-Vinay (2012) [81] Machiela (2018) [82] Lin (2020) [83]	401–733

greater proportion of the variation of childhood than adult cancers.

If childhood cancer predisposition variants are genetically constrained, it is possible that some alternations may occur *de novo*. While GWAS may identify novel loci that increases susceptibility, they do not provide information on whether the variant is *de novo* or inherited, which may inform our understanding of the biology of the cancer (e.g., penetrance of the variant) and inform genetic testing and surveillance of first-degree family members. In relation to childhood cancer, the conditions that allow *de novo* mutations to arise include increasing parental age [32,33], a suspected risk factor of childhood cancer, paternal exposures during spermatogenesis [34], or disrupted DNA repair processes [35]. Based on a paper published in 2022, four case-parent trio studies have been conducted – three on retinoblastoma and one on osteosarcoma, focusing on either *RB1* or *TP53*, established cancer predisposition genes [36]. *De novo* mutations were identified in all four studies, suggesting that *de novo* mutations may have a larger role in the etiology of childhood cancer that has not yet been fully explored.

LIMITATIONS OF PREVIOUS STUDIES

Because of the rarity of childhood cancer, case-control studies are commonly conducted to provide insights into etiology. While there is not robust evidence for the role of environmental risk factors on risk of childhood cancer, a major limitation of most prior studies was the assessment of the exposure, where parents were asked to recall and self-report their exposures or studies approximated exposure based on occupation. Quantifying exposure for different environmental risk factors via questionnaires is extremely challenging. Some studies have

tried to overcome those limitations by linking residential addresses (typically collected at birth or cancer diagnosis) to databases with area-based environmental data. While an objective exposure measurement can be assigned, we are limited to area-based environmental data that are available, may not have full residential address history, and the area-based environmental data may not accurately reflect individual-level exposures.

As noted, there are several different types of childhood cancer. For example, CNS tumors alone have over 100 histologies. With a limited sample size, studies may not have been able to conduct analyses by specific types of childhood cancer. The molecular characterization of childhood cancers has revealed additional heterogeneity within specific histologies. For instances, the World Health Organization classification of ALL acknowledged 10 subtypes, including *BCR::ABL1*, *ETV6::RUNX1*, hyperdiploidy, hypodiploidy, *BCR::ABL1*-like [37]. Based on RNA-sequencing or DNA methylation data, medulloblastoma has four molecular subtypes: Shh, Wnt, group 3, and group 4 – each with different proposed cell of origin [38]. These molecular characteristics have been described across various patient demographics and treatment outcomes, revealing heterogeneity based on the molecular type [39]. This suggests that etiology likely varies by molecular subtype. Most prior etiologic studies of childhood cancer did not have information on molecular characteristics to account for it in their analyses. As the field moves forward in collecting these molecular subtype information, epidemiologic studies can begin to investigate risk factors by subtype.

LEVERAGING NOVEL TECHNOLOGIES FOR ETIOLOGIC STUDIES OF CHILDHOOD CANCER

Metabolomics

The human metabolome reflects the interaction between the genome and environment and consists of low weight molecules from endogenous or exogenous sources [40,41]. Endogenous metabolites include are produced naturally in humans (e.g., essential nutrients, amino acids, and fatty acids), whereas exogenous metabolites are those that are not produced in the human body (e.g., environmental chemicals, drugs, food additives). Using targeted or untargeted approaches, metabolomics can measure both endogenous and exogenous chemicals simultaneously. An advantage of metabolomics is that it can capture biological response to transient exposures [40,42]. Because the etiology of childhood cancers is not well understood, untargeted metabolomics provide an opportunity to agnostically identify biological pathways that are dysregulated in children affected by cancer to generate hypothesis-driven research questions [42]. Metabolomics can be applied to different biological matrices relevant to childhood cancer, such as newborn dried blood spots [43,44], cord blood [45], and primary teeth [46].

Primary teeth as a novel exposure matrix

Primary teeth (also known as deciduous or baby teeth) are a novel exposure matrix that can accelerate our understanding of the role environmental exposures may have on the etiology of childhood cancer [42]. Most biological matrices such as blood, urine, and saliva, only capture metabolites at the time of collection, making retrospective measurements of exposures challenging for studying risk factors of childhood cancer. Primary teeth begin to form prenatally, mineralize in the second trimester, and grow daily through early childhood, akin to tree rings [47]. At birth, a neonatal line appears in the tooth, delineating between pre and postnatal uptake [47]. Thus, using primary teeth, exogenous and endogenous metabolites can be measured daily from the second trimester of pregnancy to early life, allowing for retrospective reconstruction of exposures, overcoming the limitations of questionnaire-based and area-based exposure assessment approaches [47].

Long-read sequencing

GWAS studies have been performed using next-generation sequencing (NGS). The era of third generation of sequencing or long read sequencing (LRS) has arrived. Compared to NGS which uses read lengths of 150–300 bp, LRS uses much longer read lengths – an average of 15 000–20 000 bp. LRS will revolutionize our understanding of childhood cancer as this new technology can better genotype regions of the genome that have been challenging to sequence with NGS (e.g., structural variants, tandem repeats, indels), identify rare variants, characterize novel fusion genes, assemble *de novo* cancer genomes, capture the DNA methylation landscape, quantify transcriptome variation, and detect isoforms [48]. Furthermore, for DNA sequences and methylation, phasing information will be known and can be leveraged in case-parent studies to determine whether the haplotype was maternal or paternal in origin.

CONCLUSION

In this review, we provide a brief overview of the etiology of childhood cancer. Due to multiple reasons, risk factors are not well understood. First,

power is challenging due to the rarity of disease. Collaborations across institutions and countries will increase sample size to make robust inferences, especially by histology and/or molecular subtype. A great example is the formation of the Childhood Cancer Data Initiative (CCDI), which will become a powerful resource for studying childhood cancer [49]. Second, environmental exposures are challenging to capture retrospectively. Leveraging metabolomics in early-life matrices can quantify differences to provide robust insights. Third, infrastructure and resources to support this area of research are necessary to adopt novel technologies to accelerate discoveries in the next several years. Lastly, as childhood cancer likely stems from gene-environment interactions, it will be of interest to conduct research combining molecular and environmental risk factors.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Siegel RL, Miller KD, Fuchs HE, *et al.* Cancer statistics, 2021. CA Cancer J Clin 2021; 71:7–33.
2. Steliarova-Foucher E, Colombet M, Ries LAG, *et al.* International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol 2017; 18:719–731.
3. Steliarova-Foucher E, Fidler MM, Colombet M, *et al.* Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991–2010 (Automated Childhood Cancer Information System): a population-based study. Lancet Oncol 2018; 19:1159–1169.
4. Johnston WT, Erdmann F, Newton R, *et al.* Childhood cancer: estimating regional and global incidence. Cancer Epidemiol 2021; 71(Pt B):101662.
5. Bray F, Laversanne M, Sung H, *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74:229–263.
6. Grobner SN, Worst BC, Weischenfeldt J, *et al.* The landscape of genomic alterations across childhood cancers. Nature 2018; 555:321–327.
7. Zhang J, Walsh MF, Wu G, *et al.* Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 2015; 373:2336–2346.
8. Marcotte EL, Domingues AM, Sample JM, *et al.* Racial and ethnic disparities in pediatric cancer incidence among children and young adults in the United States by single year of age. Cancer 2021; 127:3651–3663.
9. Lupo PJ, Schraw JM, Desrosiers TA, *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; 5:1150–1158.
10. ■■ Onyije FM, Dolatkhah R, Olsson A, *et al.* Risk factors for childhood brain tumours: a systematic review and meta-analysis of observational studies from 1976 to 2022. Cancer Epidemiol 2024; 88:102510.

The authors conducted a systematic review of the literature published from 1976 to 2022 on risk factors of childhood brain tumors, including birth and parental characteristics and environmental exposures. They summarized the literature across 181 publications and conducted meta-analyses when possible. Meta-analyses were conducted separately for case-control studies and cohort studies, as well as combined.

11. Hoang TT, Whitcomb E, Reardon EE, *et al.* Environmental risk factors for childhood central nervous system tumors: an umbrella review. Curr Epidemiol Rep 2022; 9:338–360.
12. ■ Rashti R, Ghasemi F, Poorolajal J. Association between birth weight and risk of nonneurological childhood cancers: a systematic review and meta-analysis. Eur J Cancer Prev 2024.

This is a systematic review on birth weight and risk of non-CNS tumors of the literature published up to May 2023. The authors identifed 56 publications and conducted metaanalyses for 8 cancer or tumor types.

13. Bjorge T, Sorensen HT, Grotmol T, *et al.* Fetal growth and childhood cancer: a population-based study. Pediatrics 2013; 132:e1265–e1275.
14. Hoang TT, Schraw JM, Peckham-Gregory EC, *et al.* Fetal growth and pediatric cancer: a pan-cancer analysis in 7000 cases and 37 000 controls. Int J Cancer 2024; 154:41–52.
15. Lagiou P, Samoli E, Hsieh CC, *et al.* Maternal and cord blood hormones in relation to birth size. Eur J Epidemiol 2014; 29:343–351.
16. Nagata C, Iwasa S, Shiraki M, *et al.* Estrogen and alpha-fetoprotein levels in maternal and umbilical cord blood samples in relation to birth weight. Cancer Epidemiol Biomarkers Prev 2006; 15:1469–1472.
17. Samuelsen SO, Bakketeig LS, Tretli S, *et al.* Birth weight and childhood cancer. Epidemiology 2009; 20:484–487.
18. Paquette K, Coltin H, Boivin A, *et al.* Cancer risk in children and young adults born preterm: a systematic review and meta-analysis. PLoS One 2019; 14: e0210366.
19. Jiang LL, Gao YY, He WB, *et al.* Cesarean section and risk of childhood leukemia: a systematic review and meta-analysis. World J Pediatr 2020; 16:471–479.
20. Johnson KJ, Carozza SE, Chow EJ, *et al.* Parental age and risk of childhood cancer: a pooled analysis. Epidemiology 2009; 20:475–483.
21. Onyije FM, Olsson A, Baaken D, *et al.* Environmental risk factors for childhood acute lymphoblastic leukemia: an umbrella review. Cancers (Basel) 2022; 14:382.
22. Rios P, Bailey HD, Orsi L, *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; 139:1936–1948.
23. ■■ Onyije FM, Dolatkhah R, Olsson A, *et al.* Environmental risk factors of Wilms tumour: a systematic review and meta-analysis. EJC Paediatr Oncol 2024; 4:.

The authors conducted a systematic review of etiological studies of Wilms tumor published from 1987 to 2022 and reported their synthesis of 58 publications. Risk factors that have been studied include birth and parental characteristics, as well as environmental exposures

24. Marcotte EL, Thomopoulos TP, Infante-Rivard C, *et al.* Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). Lancet Haematol 2016; 3:e176–e185.
25. Goldenberg RL, Culhane JF, Iams JD, *et al.* Epidemiology and causes of preterm birth. Lancet 2008; 371:75–84.
26. Abalo KD, Rage E, Leuraud K, *et al.* Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis. Pediatr Radiol 2021; 51:45–56.
27. ■ Navarrete-Meneses MDP, Salas-Labadia C, Gomez-Chavez F, *et al.* Environmental pollution and risk of childhood cancer: a scoping review of evidence from the last decade. Int J Mol Sci 2024; 25:3284.

The authors conducted a systematic review of the literature on environmental factors and risk of childhood cancers published from 2013 to 2023. They synthesized the literature on 174 articles based on environmental factors, including air pollution, pesticide, tobacco, alcohol, indoor exposures, and electromagnetic fields.

28. Plon SE, Lupo PJ. Genetic predisposition to childhood cancer in the genomic era. Annu Rev Genomics Hum Genet 2019; 20:241–263.
29. ■ Stoltze UK, Foss-Skiftesvik J, Hansen TVO, *et al.* The evolutionary impact of childhood cancer on the human gene pool. Nat Commun 2024; 15:1881.

This study provides evidence that genetic risk factors of pediatric cancers may be genetically constrained, providing a new perspective to better understand the molecular mechanism of pediatric cancer.

30. Bakhuizen JJ, Hopman SMJ, Bosscha MI, *et al.* Assessment of cancer predisposition syndromes in a national cohort of children with a neoplasm. JAMA Netw Open 2023; 6:e2254157.
31. Raynor LA, Pankratz N, Spector LG. An analysis of measures of effect size by age of onset in cancer genomewide association studies. Genes Chromosomes Cancer 2013; 52:855–859.
32. Belyeu JR, Brand H, Wang H, *et al.* De novo structural mutation rates and gamete-of-origin biases revealed through genome sequencing of 2396 families. Am J Hum Genet 2021; 108:597–607.
33. Jonsson H, Sulem P, Kehr B, *et al.* Parental influence on human germline de novo mutations in 1548 trios from Iceland. Nature 2017; 549:519–522.
34. Olsen AK, Andreassen A, Singh R, *et al.* Environmental exposure of the mouse germ line: DNA adducts in spermatozoa and formation of de novo mutations during spermatogenesis. PLoS One 2010; 5:e11349.
35. Acuna-Hidalgo R, Veltman JA, Hoischen A. New insights into the generation and role of de novo mutations in health and disease. Genome Biol 2016; 17:241.
36. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am 2015; 62:11–25.

37. Arber DA, Orazi A, Hasserjian R, *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391–2405.
38. Juraschka K, Taylor MD. Medulloblastoma in the age of molecular subgroups: a review. J Neurosurg Pediatr 2019; 24:353–363.
39. Kool M, Korshunov A, Remke M, *et al.* Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol 2012; 123:473–484.
40. Niedzwiecki MM, Walker DI, Vermeulen R, *et al.* The exposome: molecules to populations. Annu Rev Pharmacol Toxicol 2019; 59:107–127.
41. Uppal K, Walker DI, Liu K, *et al.* Computational metabolomics: a framework for the million metabolome. Chem Res Toxicol 2016; 29:1956–1975.
42. Lupo PJ, Petrick LM, Hoang TT, *et al.* Using primary teeth and archived dried spots for exposomic studies in children: exploring new paths in the environmental epidemiology of pediatric cancer. Bioessays 2021; 43:e2100030.
43. Petrick LM, Schiffman C, Edmands WMB, *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; 452:71–78.
44. Petrick LM, Uppal K, Funk WE. Metabolomics and adductomics of newborn bloodspots to retrospectively assess the early-life exposome. Curr Opin Pediatr 2020; 32:300–307.
45. Kadakia R, Talbot O, Kuang A, *et al.* Cord blood metabolomics: association with newborn anthropometrics and C-peptide across ancestries. J Clin Endocrinol Metab 2019; 104:4459–4472.
46. Yu M, Tu P, Dolios G, *et al.* Tooth biomarkers to characterize the temporal dynamics of the fetal and early-life exposome. Environ Int 2021; 157:106849.
47. Arora M, Austin C. Teeth as a biomarker of past chemical exposure. Curr Opin Pediatr 2013; 25:261–267.
48. Ermini L, Driguez P. The application of long-read sequencing to cancer. Cancers (Basel) 2024; 16:1275.
49. Flores-Toro JA, Jagu S, Armstrong GT, *et al.* The childhood cancer data initiative: using the power of data to learn from and improve outcomes for every child and young adult with pediatric cancer. J Clin Oncol 2023; 41:4045–4053.
50. Schraw JM, Bailey HD, Bonaventure A, *et al.* Infant feeding practices and childhood acute leukemia: findings from the Childhood Cancer & Leukemia International Consortium. Int J Cancer 2022; 151:1013–1023.
51. Schraw JM, Petridou ET, Bonaventure A, *et al.* Breastfeeding and risk of childhood brain tumors: a report from the Childhood Cancer and Leukemia International Consortium. Cancer Causes Control 2023; 34:1005–1015.
52. Su Q, Sun X, Zhu L, *et al.* Breastfeeding and the risk of childhood cancer: a systematic review and dose–response meta-analysis. BMC Med 2021; 19:90.
53. Papaemmanuil E, Hosking FJ, Vijayakrishnan J, *et al.* Loci on 7p12.2, 10q212 and 14q11 2 are associated with risk of childhood acute lymphoblastic leukemia. Nat Genet 2009; 41:1006–1010.
54. Trevino LR, Yang W, French D, *et al.* Germline genomic variants associated with childhood acute lymphoblastic leukemia. Nat Genet 2009; 41:1001–1005.
55. Orsi L, Rudant J, Bonaventure A, *et al.* Genetic polymorphisms and childhood acute lymphoblastic leukemia: GWAS of the ESCALE study (SFCE). Leukemia 2012; 26:2561–2564.
56. Migliorini G, Fiege B, Hosking FJ, *et al.* Variation at 10p12.2 and 10p14 influences risk of childhood B-cell acute lymphoblastic leukemia and phenotype. Blood 2013; 122:3298–3307.
57. Perez-Andreu V, Roberts KG, Harvey RC, *et al.* Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. Nat Genet 2013; 45:1494–1498.
58. Xu H, Yang W, Perez-Andreu V, *et al.* Novel susceptibility variants at 10p12.31-12.2 for childhood acute lymphoblastic leukemia in ethnically diverse populations. J Natl Cancer Inst 2013; 105:733–742.
59. Xu H, Zhang H, Yang W, *et al.* Inherited coding variants at the CDKN2A locus influence susceptibility to acute lymphoblastic leukaemia in children. Nat Commun 2015; 6:7553.
60. Archer NP, Perez-Andreu V, Stoltze U, *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.
61. Wiemels JL, Walsh KM, de Smith AJ, *et al.* GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21. Nat Commun 2018; 9:286.
62. Qian M, Xu H, Perez-Andreu V, *et al.* Novel susceptibility variants at the ERG locus for childhood acute lymphoblastic leukemia in Hispanics. Blood 2019; 133:724–729.
63. Qian M, Zhao X, Devidas M, *et al.* Genome-wide association study of susceptibility loci for T-cell acute lymphoblastic leukemia in children. J Natl Cancer Inst 2019; 111:1350–1357.
64. Vijayakrishnan J, Qian M, Studd JB, *et al.* Identification of four novel associations for B-cell acute lymphoblastic leukaemia risk. Nat Commun 2019; 10:5348.
65. Lee SHR, Qian M, Yang W, *et al.* Genome-wide association study of susceptibility loci for TCF3-PBX1 acute lymphoblastic leukemia in children. J Natl Cancer Inst 2021; 113:933–937.
66. Jeon S, de Smith AJ, Li S, *et al.* Genome-wide trans-ethnic meta-analysis identifies novel susceptibility loci for childhood acute lymphoblastic leukemia. Leukemia 2022; 36:865–868.
67. Peckham-Gregory EC, Chakraborty R, Scheurer ME, *et al.* A genome-wide association study of LCH identifies a variant in SMAD6 associated with susceptibility. Blood 2017; 130:2229–2232.
68. Foss-Skiftesvik J, Li S, Rosenbaum A, *et al.* Multiancestry genome-wide association study of 4069 children with glioma identifies 9p21.3 risk locus. Neuro Oncol 2023; 25:1709–1720.
69. Dahlin AM, Wibom C, Andersson U, *et al.* A genome-wide association study on medulloblastoma. J Neurooncol 2020; 147:309–315.
70. Maris JM, Mosse YP, Bradfield JP, *et al.* Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med 2008; 358:2585–2593.
71. Capasso M, Devoto M, Hou C, *et al.* Common variations in BARD1 influence susceptibility to high-risk neuroblastoma. Nat Genet 2009; 41:718–723.
72. Nguyen le B, Diskin SJ, Capasso M, *et al.* Phenotype restricted genome-wide association study using a gene-centric approach identifies three low-risk neuroblastoma susceptibility Loci. PLoS Genet 2011; 7:e1002026.
73. Wang K, Diskin SJ, Zhang H, *et al.* Integrative genomics identifies LMO1 as a neuroblastoma oncogene. Nature 2011; 469:216–220.
74. Diskin SJ, Capasso M, Schnepp RW, *et al.* Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma. Nat Genet 2012; 44:1126–1130.
75. McDaniel LD, Conkrite KL, Chang X, *et al.* Common variants upstream of MLF1 at 3q25 and within CPZ at 4p16 associated with neuroblastoma. PLoS Genet 2017; 13:e1006787.
76. Avitabile M, Succoio M, Testori A, *et al.* Neural crest-derived tumor neuroblastoma and melanoma share 1p13.2 as susceptibility locus that shows a long-range interaction with the SLC16A1 gene. Carcinogenesis 2020; 41: 284–295.
77. Bae JS, Lee JW, Yoo JE, *et al.* Genome-wide association study for the identification of novel genetic variants associated with the risk of neuroblastoma in Korean children. Cancer Res Treat 2020; 52:1251–1261.
78. Testori A, Vaksman Z, Diskin SJ, *et al.* Genetic analysis in African American children supports ancestry-specific neuroblastoma susceptibility. Cancer Epidemiol Biomarkers Prev 2022; 31:870–875.
79. Turnbull C, Perdeaux ER, Pernet D, *et al.* A genome-wide association study identifies susceptibility loci for Wilms tumor. Nat Genet 2012; 44:681–684.
80. Savage SA, Mirabello L, Wang Z, *et al.* Genome-wide association study identifies two susceptibility loci for osteosarcoma. Nat Genet 2013; 45:799–803.
81. Postel-Vinay S, Veron AS, Tirode F, *et al.* Common variants near TARDBP and EGR2 are associated with susceptibility to Ewing sarcoma. Nat Genet 2012; 44:323–327.
82. Machiela MJ, Grunewald TGP, Surdez D, *et al.* Genome-wide association study identifies multiple new loci associated with Ewing sarcoma susceptibility. Nat Commun 2018; 9:3184.
83. Lin SH, Sampson JN, Grunewald TGP, *et al.* Low-frequency variation near common germline susceptibility loci are associated with risk of Ewing sarcoma. PLoS One 2020; 15:e0237792.