References for Environmental Causes of Childhood Cancer Meeting
Wingspread
April 14-16
May 15-17

Abalo, K. D., et al. "Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis."
Ionizing radiation use for medical diagnostic purposes has substantially increased over the last three decades. Moderate to high doses of radiation are well established causes of cancer, especially for exposure at young ages. However, cancer risk from low-dose medical imaging is debated.

Ahern, T. P., et al. (2022). "Medication-Associated Phthalate Exposure and Childhood Cancer Incidence." J Natl Cancer Inst **114**(6): 885-894.
BACKGROUND: Human phthalate exposure is widespread through contact with myriad consumer products. Exposure is particularly high through medications formulated with phthalates. Phthalates disrupt normal endocrine signaling and are associated with reproductive outcomes and incidence of some cancers. We measured associations between gestational and childhood medication-associated phthalate exposures and the incidence of childhood cancers. METHODS: We identified all live births in Denmark between 1997 and 2017, including both children and birth mothers. Using drug ingredient data merged with the Danish National Prescription Registry, we measured phthalate exposure through filled prescriptions for mothers during pregnancy (gestational exposure) and for children from birth until age 19 years (childhood exposure). Incident childhood cancers were ascertained from the Danish Cancer Registry, and associations were estimated with Cox regression models. RESULTS: Among 1278685 children, there were 2027 childhood cancer cases diagnosed over 13.1 million person-years of follow-up. Childhood phthalate exposure was strongly associated with incidence of osteosarcoma (hazard ratio [HR] = 2.78, 95% confidence interval [CI] = 1.63 to 4.75). We also observed a positive association with incidence of lymphoma (HR = 2.07, 95% CI = 1.36 to 3.14), driven by associations with Hodgkin and non-Hodgkin lymphoma but not Burkitt lymphoma. Associations were apparent only for exposure to low-molecular phthalates, which have purportedly greater biological activity. CONCLUSIONS: Childhood phthalate exposure was associated with incidence of osteosarcoma and lymphoma before age 19 years. Lingering questions include which specific phthalate(s) are responsible for these associations, by what mechanisms they occur, and to what extent childhood cancer cases could be avoided by reducing or eliminating the phthalate content of medications and other consumer products.

Alsen, M., et al. (2021). "Endocrine Disrupting Chemicals and Thyroid Cancer: An Overview." Toxics **9**(1).
Endocrine disruptive chemicals (EDC) are known to alter thyroid function and have been associated with increased risk of certain cancers. The present study aims to provide a comprehensive overview of available studies on the association between EDC exposure and thyroid cancer. Relevant studies were identified via a literature search in the National Library of Medicine and National Institutes of Health PubMed as well as a review of reference lists of all retrieved articles and of previously published relevant reviews. Overall, the current literature suggests that exposure to certain congeners of flame retardants, polychlorinated biphenyls (PCBs), and phthalates as well as certain pesticides may potentially be associated with an increased risk of thyroid cancer. However, future research is urgently needed to evaluate the different EDCs and their potential carcinogenic effect on the thyroid gland in humans as most EDCs have been studied sporadically and results are not consistent.

Barrington-Trimis, J. L., et al. (2017). "Trends in childhood leukemia incidence over two decades from 1992 to 2013." Int J Cancer **140**(5): 1000-1008.
Incidence rates of childhood leukemia in the United States have steadily increased over the last several decades, but only recently have disparities in the increase in incidence been recognized. In the current analysis, Surveillance, Epidemiology and End Results (SEER) data were used to evaluate recent trends in the incidence of childhood leukemia diagnosed at age 0-19 years from 1992 to 2013, overall and by age, race/ethnicity, gender and histologic subtype. Hispanic White children were more likely than non-Hispanic White, non-Hispanic Black or non-Hispanic Asian children to be diagnosed with acute lymphocytic leukemia (ALL) from 2009 to 2013. From 1992 to 2013, a significant increase in ALL incidence was observed for Hispanic White children [annual percent change (APC)(Hispanic) = 1.08, 95% CI: 0.59, 1.58]; no significant increase was observed for non-Hispanic White, Black or Asian children. ALL incidence increased by about

3% per year from 1992 to 2013 for Hispanic White children diagnosed from 15 to 19 years (APC = 2.67; 95% CI: 0.88, 4.49) and by 2% for those 10-14 years (APC = 2.09; 95% CI: 0.57, 3.63), while no significant increases in incidence were observed in non-Hispanic White, Black, or Asian children of the same age. Acute myeloid leukemia (AML) incidence increased among non-Hispanic White children under 1 year at diagnosis, and among Hispanic White children diagnosed at age 1-4. The increase in incidence rates of childhood ALL appears to be driven by rising rates in older Hispanic children (10-14, and 15-19 years). Future studies are needed to evaluate reasons for the increase in ALL among older Hispanic children.

Filippini, T., et al. (2019). "Association between Outdoor Air Pollution and Childhood Leukemia: A Systematic Review and Dose-Response Meta-Analysis." Environ Health Perspect **127**(4): 46002.

BACKGROUND: A causal link between outdoor air pollution and childhood leukemia has been proposed, but some older studies suffer from methodological drawbacks. To the best of our knowledge, no systematic reviews have summarized the most recently published evidence and no analyses have examined the dose-response relation. OBJECTIVE: We investigated the extent to which outdoor air pollution, especially as resulting from traffic-related contaminants, affects the risk of childhood leukemia. METHODS: We searched all case-control and cohort studies that have investigated the risk of childhood leukemia in relation to exposure either to motorized traffic and related contaminants, based on various traffic-related metrics (number of vehicles in the closest roads, road density, and distance from major roads), or to measured or modeled levels of air contaminants such as benzene, nitrogen dioxide, 1,3-butadiene, and particulate matter. We carried out a meta-analysis of all eligible studies, including nine studies published since the last systematic review and, when possible, we fit a dose-response curve using a restricted cubic spline regression model. RESULTS: We found 29 studies eligible to be included in our review. In the dose-response analysis, we found little association between disease risk and traffic indicators near the child's residence for most of the exposure range, with an indication of a possible excess risk only at the highest levels. In contrast, benzene exposure was positively and approximately linearly associated with risk of childhood leukemia, particularly for acute myeloid leukemia, among children under 6 y of age, and when exposure assessment at the time of diagnosis was used. Exposure to nitrogen dioxide showed little association with leukemia risk except at the highest levels. DISCUSSION: Overall, the epidemiologic literature appears to support an association between benzene and childhood leukemia risk, with no indication of any threshold effect. A role for other measured and unmeasured pollutants from motorized traffic is also possible. https://doi.org/10.1289/EHP4381.

Giddings, B. M., et al. (2016). "Childhood leukemia incidence in California: High and rising in the Hispanic population." Cancer.

BACKGROUND: High rates of childhood leukemia incidence have been reported in Latin America and among Hispanic children in the United States. California's large Hispanic population affords an important opportunity to perform a detailed analysis of the leukemia burden among Hispanic children. METHODS: Leukemias diagnosed among non-Hispanic white (NHW), Hispanic, African American (AA), and Asian/Pacific Islander (API) children aged birth to 19 years between January 1, 1990 and December 31, 2012 were obtained from the California Cancer Registry (11,084 cases). Age-adjusted incidence rates, standardized rate ratios (SRRs), and secular trends in incidence (annual percent change [APC]) were analyzed by subtype, race/ethnicity, sex, and age. RESULTS: Compared with NHW children, the incidence of acute lymphoblastic leukemia (ALL) was higher among Hispanic (SRR, 1.32) and lower among AA (SRR, 0.55) and API (SRR, 0.91) children. From 1990 to 2012, the incidence of ALL increased overall (APC, 1.1%) and among males (APC, 1.0%), females (APC, 1.3%), Hispanics (APC, 1.1%), AAs (APC, 1.9%), AA males (APC, 2.8%), API males (APC, 1.9%), and Hispanic females (APC, 1.5%). The incidence of ALL increased among Hispanic males aged 15 to 19 years (APC, 2.5%) and Hispanic females aged birth to 4 years and 15 to 19 years (APCs of 2.2% and 1.9%, respectively). The incidence of acute myeloid leukemia did not appear to differ among racial/ethnic groups. From 1990 to 2012, the overall incidence of acute myeloid leukemia remained stable but increased among Hispanics (APC, 1.2%), females (APC, 1.0%), Hispanic females (APC, 2.3%), and Hispanic females aged 15 to 19 years (APC, 3.4%). CONCLUSIONS: Notable differences in the incidence of childhood leukemia were observed among 4 racial/ethnic groups in California. Factors that may contribute to these differences include differential exposure to carcinogens and/or genetic susceptibility. Cancer 2016. (c) 2016 American Cancer Society.

Greaves, M. (2018). "A causal mechanism for childhood acute lymphoblastic leukaemia." Nat Rev Cancer **18**(8): 471-484.

In this Review, I present evidence supporting a multifactorial causation of childhood acute lymphoblastic

leukaemia (ALL), a major subtype of paediatric cancer. ALL evolves in two discrete steps. First, in utero initiation by fusion gene formation or hyperdiploidy generates a covert, pre-leukaemic clone. Second, in a small fraction of these cases, the postnatal acquisition of secondary genetic changes (primarily V(D)J recombination-activating protein (RAG) and activation-induced cytidine deaminase (AID)-driven copy number alterations in the case of ETS translocation variant 6 (ETV6)-runt-related transcription factor 1 (RUNX1)(+) ALL) drives conversion to overt leukaemia. Epidemiological and modelling studies endorse a dual role for common infections. Microbial exposures earlier in life are protective but, in their absence, later infections trigger the critical secondary mutations. Risk is further modified by inherited genetics, chance and, probably, diet. Childhood ALL can be viewed as a paradoxical consequence of progress in modern societies, where behavioural changes have restrained early microbial exposure. This engenders an evolutionary mismatch between historical adaptations of the immune system and contemporary lifestyles. Childhood ALL may be a preventable cancer.

Heijmans, B. T., et al. (2008). "Persistent epigenetic differences associated with prenatal exposure to famine in humans." Proc Natl Acad Sci U S A **105**(44): 17046-17049.

Extensive epidemiologic studies have suggested that adult disease risk is associated with adverse environmental conditions early in development. Although the mechanisms behind these relationships are unclear, an involvement of epigenetic dysregulation has been hypothesized. Here we show that individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944-45 had, 6 decades later, less DNA methylation of the imprinted IGF2 gene compared with their unexposed, same-sex siblings. The association was specific for periconceptional exposure, reinforcing that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks. These data are the first to contribute empirical support for the hypothesis that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life.

Hein, D., et al. (2020). "Insights into the prenatal origin of childhood acute lymphoblastic leukemia." Cancer Metastasis Rev **39**(1): 161-171.

Pediatric acute lymphoblastic leukemia (ALL) is defined by recurrent chromosomal aberrations including hyperdiploidy and chromosomal translocations. Many of these aberrations originate in utero and the cells transform in early childhood through acquired secondary mutations. In this review, we will discuss the most common prenatal lesions that can lead to childhood ALL, with a special emphasis on the most common translocation in childhood ALL, t(12;21), which results in the ETV6-RUNX1 gene fusion. The ETV6-RUNX1 fusion arises prenatally and at a 500-fold higher frequency than the corresponding ALL. Even though the findings regarding the frequency of ETV6-RUNX1 were originally challenged, newer studies have confirmed the higher frequency. The prenatal origin has also been proven for other gene fusions, including KMT2A, the translocations t(1;19) and t(9;22) leading to TCF3-PBX1 and BCR-ABL1, respectively, as well as high hyperdiploidy. For most of these aberrations, there is evidence for more frequent occurrence than the corresponding leukemia incidences. We will briefly discuss what is known about the cells of origin, the mechanisms of leukemic transformation through lack of immunosurveillance, and why only a part of the carriers develops ALL.

Kratz, C. P., et al. (2021). "Predisposition to cancer in children and adolescents." Lancet Child Adolesc Health **5**(2): 142-154.

Childhood malignancies are rarely related to known environmental exposures, and it has become increasingly evident that inherited genetic factors play a substantial causal role. Large-scale sequencing studies have shown that approximately 10% of children with cancer have an underlying cancer predisposition syndrome. The number of recognised cancer predisposition syndromes and cancer predisposition genes are constantly growing. Imaging and laboratory technologies are improving, and knowledge of the range of tumours and risk of malignancy associated with cancer predisposition syndromes is increasing over time. Consequently, surveillance measures need to be constantly adjusted to address these new findings. Management recommendations for individuals with pathogenic germline variants in cancer predisposition genes need to be established through international collaborative studies, addressing issues such as genetic counselling, cancer prevention, cancer surveillance, cancer therapy, psychological support, and social-ethical issues. This Review represents the work by a group of experts from the European Society for Paediatric Oncology (SIOPE) and aims to summarise the current knowledge and define future research needs in this evolving field.

Landrigan, P. J. and L. R. Goldman (2011). "Children's vulnerability to toxic chemicals: a challenge and opportunity to

strengthen health and environmental policy." Health Aff (Millwood) **30**(5): 842-850.

A key policy breakthrough occurred nearly twenty years ago with the discovery that children are far more sensitive than adults to toxic chemicals in the environment. This finding led to the recognition that chemical exposures early in life are significant and preventable causes of disease in children and adults. We review this knowledge and recommend a new policy to regulate industrial and consumer chemicals that will protect the health of children and all Americans, prevent disease, and reduce health care costs. The linchpins of a new US chemical policy will be: first, a legally mandated requirement to test the toxicity of chemicals already in commerce, prioritizing chemicals in the widest use, and incorporating new assessment technologies; second, a tiered approach to premarket evaluation of new chemicals; and third, epidemiologic monitoring and focused health studies of exposed populations.

Lu, Y., et al. (2020). "Domestic radon exposure and risk of childhood leukemia: A meta-analysis." J buon **25**(2): 1035-1041.

PURPOSE: This meta-analysis evaluated the potential influence of environmental radon exposure on childhood leukemia. METHODS: We searched comprehensive electronic databases from PubMed, EMBASE, and Cochrane Library to identify studies evaluating the association between radon and leukemia. RESULTS: Ten eligible studies published from 1995 to 2014 were enrolled. Of these 10 studies, 8 were case-control studies (involving 10803 cases and 16202 controls) and 2 were cohort studies (involving 1,428 cases). Overall results as odds ratio (OR) with the corresponding 95% confidence intervals (95%CI) for case-control studies and fully adjusted hazard ratio (HR) with corresponding 95%CI for cohort studies were identified. A positive but weak association was found between radon exposure and childhood leukemia in case-control studies (summary OR 1.22, 95%CI 1.01-1.42) rather than cohort studies (summary HR 0.97, 95%CI 0.81-1.15). Heterogeneity or publication bias was not observed. Moreover, overall ORs were not changed by removing any single study, suggesting the stability and reliability of conclusions. CONCLUSIONS: Future prospective studies with well-controlled confounders are needed to verify the conclusion.

Pembrey, M., et al. (2014). "Human transgenerational responses to early-life experience: potential impact on development, health and biomedical research." J Med Genet **51**(9): 563-572.

Mammalian experiments provide clear evidence of male line transgenerational effects on health and development from paternal or ancestral early-life exposures such as diet or stress. The few human observational studies to date suggest (male line) transgenerational effects exist that cannot easily be attributed to cultural and/or genetic inheritance. Here we summarise relevant studies, drawing attention to exposure sensitive periods in early life and sex differences in transmission and offspring outcomes. Thus, variation, or changes, in the parental/ancestral environment may influence phenotypic variation for better or worse in the next generation(s), and so contribute to common, non-communicable disease risk including sex differences. We argue that life-course epidemiology should be reframed to include exposures from previous generations, keeping an open mind as to the mechanisms that transmit this information to offspring. Finally, we discuss animal experiments, including the role of epigenetic inheritance and non-coding RNAs, in terms of what lessons can be learnt for designing and interpreting human studies. This review was developed initially as a position paper by the multidisciplinary Network in Epigenetic Epidemiology to encourage transgenerational research in human cohorts.

Rios, P., et al. (2020). "Environmental exposures related to parental habits in the perinatal period and the risk of Wilms' tumor in children." Cancer Epidemiol **66**: 101706.

INTRODUCTION: Wilms' tumor is the most frequently diagnosed renal tumor in children. Little is known about its etiology. The aim of this study was to investigate the potential role of specific exposures related to parental habits such as parental smoking, maternal alcohol consumption and the use of household pesticides during pregnancy. METHODS: The ESTELLE study was a nationwide case-control study that included 117 Wilms' tumor cases and 1100 control children from the general French population, frequency-matched by age and gender. Unconditional logistic regression was used to estimate odds ratios and 95 % confidence intervals. RESULTS: After controlling for matching variables and potential confounders, the maternal use of any type of pesticide during pregnancy was associated with the risk of Wilms' tumor in children (OR 1.6 [95 % CI 1.1-2.3]). Insecticides were the most commonly reported type of pesticide and there was a positive association with their use (OR 1.7 [95 % CI 1.1-2.6]. The association was stronger when they were used more often than once a month (OR 1.9 [95 % CI 1.2-3.0]. Neither maternal smoking

during pregnancy nor paternal smoking during preconception/pregnancy was associated with a risk of Wilms' tumor (ORs 1.1[95 % CI 0.7-1.8] and 1.1 [95 % CI 0.7-1.7], respectively). No association was observed with maternal alcohol intake during pregnancy (OR 1.2 [95 % CI 0.8-2.0]). CONCLUSION: Our findings suggest an association between the maternal use of household pesticides during pregnancy and the risk of Wilms' tumor.

Schraw, J. M., et al. (2022). "Infant feeding practices and childhood acute leukemia: Findings from the Childhood Cancer & Leukemia International Consortium." Int J Cancer **151**(7): 1013-1023.

Increasing evidence suggests that breastfeeding may protect from childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). However, most studies have limited their analyses to any breastfeeding, and only a few data have examined exclusive breastfeeding, or other exposures such as formula milk. We performed pooled analyses and individual participant data metaanalyses of data from 16 studies (N = 17 189 controls; N = 10 782 ALL and N = 1690 AML cases) from the Childhood Leukemia International Consortium (CLIC) to characterize the associations of breastfeeding duration with ALL and AML, as well as exclusive breastfeeding duration and age at introduction to formula with ALL. In unconditional multivariable logistic regression analyses of pooled data, we observed decreased odds of ALL among children breastfed 4 to 6 months (0.88, 95% CI 0.81-0.96) or 7 to 12 months (OR 0.85, 0.79-0.92). We observed a similar inverse association between breastfeeding ≥4 months and AML (0.82, 95% CI 0.71-0.95). Odds of ALL were reduced among children exclusively breastfed 4 to 6 months (OR 0.73, 95% CI 0.63-0.85) or 7 to 12 months (OR 0.70, 95% CI 0.53-0.92). Random effects metaanalyses produced similar estimates, and findings were unchanged in sensitivity analyses adjusted for race/ethnicity or mode of delivery, restricted to children diagnosed ≥1 year of age or diagnosed with B-ALL. Our pooled analyses indicate that longer breastfeeding is associated with decreased odds of ALL and AML. Few risk factors for ALL and AML have been described, therefore our findings highlight the need to promote breastfeeding for leukemia prevention.

Steliarova-Foucher, E., et al. (2017). "International incidence of childhood cancer, 2001-10: a population-based registry study." Lancet Oncol **18**(6): 719-731.

BACKGROUND: Cancer is a major cause of death in children worldwide, and the recorded incidence tends to increase with time. Internationally comparable data on childhood cancer incidence in the past two decades are scarce. This study aimed to provide internationally comparable local data on the incidence of childhood cancer to promote research of causes and implementation of childhood cancer control. METHODS: This population-based registry study, devised by the International Agency for Research on Cancer in collaboration with the International Association of Cancer Registries, collected data on all malignancies and non-malignant neoplasms of the CNS diagnosed before age 20 years in populations covered by high-quality cancer registries with complete data for 2001-10. Incidence rates per million person-years for the 0-14 years and 0-19 years age groups were age-adjusted using the world standard population to provide age-standardised incidence rates (WSRs), using the age-specific incidence rates (ASR) for individual age groups (0-4 years, 5-9 years, 10-14 years, and 15-19 years). All rates were reported for 19 geographical areas or ethnicities by sex, age group, and cancer type. The regional WSRs for children aged 0-14 years were compared with comparable data obtained in the 1980s. FINDINGS: Of 532 invited cancer registries, 153 registries from 62 countries, departments, and territories met quality standards, and contributed data for the entire decade of 2001-10. 385 509 incident cases in children aged 0-19 years occurring in 2·64 billion person-years were included. The overall WSR was 140·6 per million person-years in children aged 0-14 years (based on 284 649 cases), and the most common cancers were leukaemia (WSR 46·4), followed by CNS tumours (WSR 28·2), and lymphomas (WSR 15·2). In children aged 15-19 years (based on 100 860 cases), the ASR was 185·3 per million person-years, the most common being lymphomas (ASR 41·8) and the group of epithelial tumours and melanoma (ASR 39·5). Incidence varied considerably between and within the described regions, and by cancer type, sex, age, and racial and ethnic group. Since the 1980s, the global WSR of registered cancers in children aged 0-14 years has increased from 124·0 (95% CI 123·3-124·7) to 140·6 (140·1-141·1) per million person-years. INTERPRETATION: This unique global source of childhood cancer incidence will be used for aetiological research and to inform public health policy, potentially contributing towards attaining several targets of the Sustainable Development Goals. The observed geographical, racial and ethnic, age, sex, and temporal variations require constant monitoring and research. FUNDING: International Agency for Research on Cancer and the Union for International Cancer Control.

Steliarova-Foucher, E., et al. (2018). "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 **19**(9): 1159-1169.

BACKGROUND: A deceleration in the increase in cancer incidence in children and adolescents has been reported in several national and regional studies in Europe. Based on a large database representing 1·3 billion person-years over the period 1991-2010, we provide a consolidated report on cancer incidence trends at ages 0-19 years. METHODS: We invited all population-based cancer registries operating in European countries to participate in this population-based registry study. We requested a listing of individual records of cancer cases, including sex, age, date of birth, date of cancer diagnosis, tumour sequence number, primary site, morphology, behaviour, and the most valid basis of diagnosis. We also requested population counts in each calendar year by sex and age for the registration area, from official national sources, and specific information about the covered area and registration practices. An eligible registry could become a contributor if it provided quality data for all complete calendar years in the period 1991-2010. Incidence rates and the average annual percentage change with 95% CIs were reported for all cancers and major diagnostic groups, by region and overall, separately for children (age 0-14 years) and adolescents (age 15-19 years). We examined and quantified the stability of the trends with joinpoint analyses. FINDINGS: For the years 1991-2010, 53 registries in 19 countries contributed a total of 180 335 unique cases. We excluded 15 162 (8·4%) of 180 335 cases due to differing practices of registration, and considered the quality indicators for the 165 173 cases included to be satisfactory. The average annual age-standardised incidence was 137·5 (95% CI 136·7-138·3) per million person-years and incidence increased significantly by 0·54% (0·44-0·65) per year in children (age 0-14 years) with no change in trend. In adolescents, the combined European incidence was 176·2 (174·4-178·0) per million person-years based on all 35 138 eligible cases and increased significantly by 0·96% (0·73-1·19) per year, although recent changes in rates among adolescents suggest a deceleration in this increasing trend. We observed temporal variations in trends by age group, geographical region, and diagnostic group. The combined age-standardised incidence of leukaemia based on 48 458 cases in children was 46·9 (46·5-47·3) per million person-years and increased significantly by 0·66% (0·48-0·84) per year. The average overall incidence of leukaemia in adolescents was 23·6 (22·9-24·3) per million person-years, based on 4702 cases, and the average annual change was 0·93% (0·49-1·37). We also observed increasing incidence of lymphoma in adolescents (average annual change 1·04% [0·65-1·44], malignant CNS tumours in children (average annual change 0·49% [0·20-0·77]), and other tumours in both children (average annual change 0·56 [0·40-0·72]) and adolescents (average annual change 1·17 [0·82-1·53]). INTERPRETATION: Improvements in the diagnosis and registration of cancers over time could partly explain the observed increase in incidence, although some changes in underlying putative risk factors cannot be excluded. Cancer incidence trends in this young population require continued monitoring at an international level. FUNDING: Federal Ministry of Health of the Federal German Government, the European Union's Seventh Framework Programme, and International Agency for Research on Cancer.

Stephanie L. Foster, et al. Guidelines for Examining Unusual Patterns of Cancer and Environmental Concerns.

Timms, J. A., et al. (2019). "Exploring a potential mechanistic role of DNA methylation in the relationship between in utero and post-natal environmental exposures and risk of childhood acute lymphoblastic leukaemia." Int J Cancer **145**(11): 2933-2943.

The aetiology of childhood acute lymphoblastic leukaemia (ALL) is unclear. Genetic abnormalities have been identified in a number of ALL cases, although these alone are not sufficient for leukaemic transformation. Various in utero and post-natal environmental exposures have been suggested to alter risk of childhood ALL. DNA methylation patterns can be influenced by environmental exposures, and are reported to be altered in ALL, suggesting a potential mediating mechanism between environment and ALL disease risk. To investigate this, we used a 'meet in the middle' approach, investigating the overlap between exposure-associated and disease-associated methylation change. Genome-wide DNA methylation changes in response to possible ALL-risk exposures (i.e. breast feeding, infection history, day care attendance, maternal smoking, alcohol, caffeine, folic acid, iron and radiation exposure) were investigated in a sub-population of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort using an epigenome-wide association study (EWAS) approach (n = 861-927), and compared to a list of ALL disease-associated methylation changes compiled from published data. Hypergeometric probability tests suggested that the number of directionally concordant gene methylation changes observed in ALL disease and in response to the following exposures; maternal radiation exposure ($p = 0.001$), alcohol intake ($p = 0.006$); sugary caffeinated drink intake during pregnancy ($p = 0.045$); and infant day care attendance ($p = 0.003$), were not due to chance. Data presented suggests that DNA methylation may be one mediating mechanism in the multiple hit pathway needed for ALL disease manifestation.

Whitehead, T. P., et al. (2016). "Childhood Leukemia and Primary Prevention." Curr Probl Pediatr Adolesc Health Care **46**(10): 317-352.

Leukemia is the most common pediatric cancer, affecting 3800 children per year in the United States. Its annual incidence has increased over the last decades, especially among Latinos. Although most children diagnosed with leukemia are now cured, many suffer long-term complications, and primary prevention efforts are urgently needed. The early onset of leukemia-usually before 5 years of age-and the presence at birth of "pre-leukemic" genetic signatures indicate that pre- and postnatal events are critical to the development of the disease. In contrast to most pediatric cancers, there is a growing body of literature-in the United States and internationally-that has implicated several environmental, infectious, and dietary risk factors in the etiology of childhood leukemia, mainly for acute lymphoblastic leukemia, the most common subtype. For example, exposures to pesticides, tobacco smoke, solvents, and traffic emissions have consistently demonstrated positive associations with the risk of developing childhood leukemia. In contrast, intake of vitamins and folate supplementation during the preconception period or pregnancy, breastfeeding, and exposure to routine childhood infections have been shown to reduce the risk of childhood leukemia. Some children may be especially vulnerable to these risk factors, as demonstrated by a disproportionate burden of childhood leukemia in the Latino population of California. The evidence supporting the associations between childhood leukemia and its risk factors-including pooled analyses from around the world and systematic reviews-is strong; however, the dissemination of this knowledge to clinicians has been limited. To protect children's health, it is prudent to initiate programs designed to alter exposure to well-established leukemia risk factors rather than to suspend judgment until no uncertainty remains. Primary prevention programs for childhood leukemia would also result in the significant co-benefits of reductions in other adverse health outcomes that are common in children, such as detriments to neurocognitive development.

Wiemels, J. L., et al. (2018). "GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21." Nat Commun **9**(1): 286.

Childhood acute lymphoblastic leukemia (ALL) (age 0-14 years) is 20% more common in Latino Americans than non-Latino whites. We conduct a genome-wide association study in a large sample of 3263 Californian children with ALL (including 1949 of Latino heritage) and 3506 controls matched on month and year of birth, sex, and ethnicity, and an additional 12,471 controls from the Kaiser Resource for Genetic Epidemiology Research on Aging Cohort. Replication of the strongest genetic associations is performed in two independent datasets from the Children's Oncology Group and the California Childhood Leukemia Study. Here we identify new risk loci on 17q12 near IKZF3/ZPBP2/GSDMB/ORMDL3, a locus encompassing a transcription factor important for lymphocyte development (IKZF3), and at an 8q24 region known for structural contacts with the MYC oncogene. These new risk loci may impact gene expression via local (four 17q12 genes) or long-range (8q24) interactions, affecting function of well-characterized hematopoietic and growth-regulation pathways.

Xu, K., et al. (2021). "Epigenetic Biomarkers of Prenatal Tobacco Smoke Exposure Are Associated with Gene Deletions in Childhood Acute Lymphoblastic Leukemia." Cancer Epidemiol Biomarkers Prev **30**(8): 1517-1525.

BACKGROUND: Parental smoking is implicated in the etiology of acute lymphoblastic leukemia (ALL), the most common childhood cancer. We recently reported an association between an epigenetic biomarker of early-life tobacco smoke exposure at the AHRR gene and increased frequency of somatic gene deletions among ALL cases. METHODS: Here, we further assess this association using two epigenetic biomarkers for maternal smoking during pregnancy-DNA methylation at AHRR CpG cg05575921 and a recently established polyepigenetic smoking score-in an expanded set of 482 B-cell ALL (B-ALL) cases in the California Childhood Leukemia Study with available Illumina 450K or MethylationEPIC array data. Multivariable Poisson regression models were used to test the associations between the epigenetic biomarkers and gene deletion numbers. RESULTS: We found an association between DNA methylation at AHRR CpG cg05575921 and deletion number among 284 childhood B-ALL cases with MethylationEPIC array data, with a ratio of means (RM) of 1.31 [95% confidence interval (CI), 1.02-1.69] for each 0.1 β value reduction in DNA methylation, an effect size similar to our previous report in an independent set of 198 B-ALL cases with 450K array data [meta-analysis summary RM (sRM) = 1.32; 95% CI, 1.10-1.57]. The polyepigenetic smoking score was positively associated with gene deletion frequency among all 482 B-ALL cases (sRM = 1.31 for each 4-unit increase in score; 95% CI, 1.09-1.57). CONCLUSIONS: We provide further evidence that prenatal tobacco-smoke exposure may influence the generation of somatic copy-number deletions in childhood B-ALL. IMPACT: Analyses of deletion breakpoint sequences are required to further understand the mutagenic effects of tobacco smoke in childhood ALL.