

TECHNICAL APPENDIX
35th COLLEGIUM RAMAZZINI STATEMENT
NEED TO ENHANCE RESEARCH AND STRENGTHEN POLICY FOR
PREVENTION OF CHILDHOOD CANCER

This appendix is a summary of evidence on selected risk and protective factors for cancer in children and adolescents and not a systematic review of the evidence.

Environmental Risk and Protective Factors

Chemical Exposures

Pesticides

Many epidemiologic studies in recent decades have identified increased risk of pediatric cancers among children exposed to pesticides. A scoping review found that 80% of 49 studies conducted between 2013 and 2023 that examined the association between pesticide exposures and pediatric cancers found associations,⁹ linking pesticide exposure in early life to increased risks of childhood leukemias,^{10,11} Wilms tumors,^{12,13} neuroblastomas,¹⁴ and childhood brain tumors.¹⁴⁻¹⁶ Smaller numbers of studies have found evidence of associations between pesticide exposures and risks of retinoblastomas and lymphomas.⁹

Benzene

Benzene and other solvents have been associated with pediatric leukemia. Exposures to benzene, a Group 1 carcinogen, may occur through use of household products containing benzene, or the fetus may be exposed through prenatal parental occupational exposures. A 2016 meta-analysis evaluated 20 studies that looked at associations between

prenatal parental occupational exposures and household products containing benzene and found a summary relative risk for leukemia of 1.96 (95% CI 1.53-2.52), with a higher summary relative risk for **AML** 2.34 (95% CI 1.72-3.18) than for **ALL** 1.57 (95% CI 1.21-2.05).¹⁷ Significant associations were noted with maternal occupational benzene exposure.

Several studies have looked at the association between childhood cancer and solvents. A case control study found an increased risk of childhood brain tumors for certain types of paternal and maternal occupational exposures in certain timeframes before birth.¹⁸ An international pooled analysis from 8 case control studies found an increased risk for pediatric **ALL** when painting occurred in the home during the immediate preconception, prenatal, or after birth. Risks were accentuated if painting was done by professionals or oil-based paints were used.¹⁹

Parental Smoking

In 2009 IARC assessed that there was sufficient evidence of a causal link between prenatal smoking and hepatoblastoma and limited evidence of a causal link with childhood leukemia (particularly ALL).²⁰⁻²² A scoping review showed that 50% of 28 studies conducted between 2013 and 2023 found positive associations between tobacco exposure and childhood cancers,⁹ (particularly after prenatal exposure to tobacco) with leukemia, CNS cancer, retinoblastoma, neuroblastoma, and Wilms tumor. A number of studies found a positive association between parental smoking (especially paternal smoking) and leukemia.^{23,24} A meta-analysis of 11 studies reported a meta-RR for paternal smoking of 1.12 (95% CI 1.04-1.21).²⁵ Another meta-analysis points to an increase in the

risk for childhood **NHL**, but not **HL**, among children born by mothers smoking during pregnancy.²⁶

Outdoor Air Pollution

An increasing number of studies have demonstrated an association between exposure to traffic and pediatric leukemia; these studies have not separately measured exposures to air pollutants from indoor sources.^{9,27-33} Several studies have identified increased pediatric cancer rates among those living near petrol stations, which can increase the surrounding air concentrations of benzene.^{14,30,31}

Many studies and meta-analyses have found an increased risk of childhood leukemia related to traffic-related air pollution.^{17,28,30} Although traffic-related air pollution contains various carcinogens including diesel exhaust and 1,3-butadiene, benzene stood out as the main contributor to leukemia risk, particularly for **AML** in a meta-analysis with no evidence of a threshold dose.²⁸ Traffic-related air pollution and ambient air toxics also have been associated with increased risk for Wilms tumor,³⁵ brain tumors,³⁶ and other cancers. A meta-analysis that included 7 studies examining leukemia in relation to residential proximity to repair garages or petrol stations found a summary relative risk of 1.66 (95% CI 1.14-2.41).³⁴

Physical Risk Factors

Radiation

IARC has classified radiation as a Group 1 carcinogen.³⁷ Recent systematic review and meta-analyses of ionizing radiation from diagnostic imaging (especially CT scans) found associations with exposure during childhood and leukemia and brain tumors.^{38,39} Exposure to the Chernobyl plant meltdown was associated with thyroid cancer.⁴⁰ Studies examining

radon and childhood leukemia have had mixed results.^{9,41} IARC has classified solar radiation and UV-emitting tanning devices as Group 1 carcinogens.³⁷ Melanoma is associated with high sun exposure⁴² and indoor UV tanning.⁴³

Environmental Protective Factors

Breastfeeding

There is substantial evidence that alterations in immune regulation are a factor in development of childhood leukemia and possibly other childhood cancers.⁴⁴ Breastfeeding benefits multiple elements of the infant and child immune system and is a potentially modifiable protective factor. In a meta-analysis of literature up until 2020, ever breastfeeding was found to reduce the risk of childhood leukemia by 23% (0.77) (95% CI 0.65-0.91) versus non/occasional breastfeeding and longest breastfeeding duration was found to reduce the risk of childhood leukemia by 23% (0.77) (95% CI 0.63-0.94) versus shortest breastfeeding duration group.⁴⁵ A pooled analysis of exclusive breastfeeding duration included 16 case control studies from around the world.⁴⁶ Fifteen studies examined acute lymphoblastic leukemia (**ALL**) (10,782 cases) and 12 examined acute myeloid leukemia (**AML**) (1690 cases). A decrease in odds of developing **ALL** was found among children breastfed 4 to 6 months [odds ratio (OR) 0.88, 95% CI 0.81-0.96] and those breastfed 7 to 12 months (OR 0.85, 95% CI 0.79-0.92). A similar decrease was noted for breastfeeding \geq 4 months and **AML** (0.82, 95% CI 0.71-0.95). Among children exclusively breastfed for 7-12 months, the risk of **ALL** was reduced by 30% (OR 0.70, 95% CI 0.53-0.92). In a unique population-based cohort study of over 300,000 children in Denmark, a decreased risk of any cancer, especially hematologic cancers in children breastfed for 3

months or longer [primarily **ALL**; adjusted hazard ratio (AHR), 0.62; 95% CI 0.39-0.99] was identified.⁴⁷ Solid tumors also showed decrease in risk, though statistically imprecise, while no similar reductions were seen in CNS tumors. A pooled analysis of pediatric **brain** tumors (cases=2610), found no association with breastfeeding, including with breastfeeding \geq 6 months.⁴⁸

Folate

In multiple studies and meta-analyses, maternal prenatal folic acid intake has been found to protect children against multiple cancers. Conversely, reductions in folic acid intake during peri-conception and pregnancy have been associated with increased risk for childhood **leukemia**, **Wilms** tumor, and childhood **brain** tumors.⁴⁹ The largest pooled analysis from the Childhood Leukemia International Consortium contained 12 international case control studies that found that folic acid supplementation resulted in a 20% reduction in risk for **ALL** (95% CI 0.71-0.89) and a more than 30% reduction in risk of AML (95% CI 0.48-0.96).⁵⁰ Similar reductions in risk for pediatric leukemia were found in a study of diet quality during pregnancy and were greater in women who did not take vitamins prior to pregnancy.⁵¹ A meta-analysis of 10 studies identified a 23% reduction in risk for **brain** and spinal cord tumors (95% CI 0.67-0.88) with maternal folate consumption before and during pregnancy.⁵¹ In one study not included in the meta-analysis, increased folate in children's diets in the year before diagnosis was associated with reduced childhood **brain** tumor risk OR 0.63 (95% CI 0.41-0.97).⁵³

Folic acid fortification of grain in the US and Canada was instituted in the mid-1990s to reduce neural tube defects. In a natural experiment, a study using Surveillance,

Epidemiology, and End Results (SEER) data comparing 10 years prior to 10 years after fortification found a significant reduction in incidence of **Wilms** tumor and primitive neuroectodermal tumors in the US.⁵⁴