International Agency for Research on Cancer

World Health Organization

PRESS RELEASE No. 357

24 October 2024

Tracing cancer back to birth uncovers promising biomarkers for prevention, early detection, and targeted treatment of childhood leukaemia

Lyon, France, 24 October 2024 – A groundbreaking study published in the journal *Molecular Cancer*[1] has uncovered molecular markers in blood at birth that are linked to later development of acute lymphoblastic leukaemia (ALL), the most common cancer type that affects children. These markers were also present in cancerous tissues from children with leukaemia, and they served as indicators of patient survival. This research offers new hope for early diagnosis and potential therapeutic interventions in childhood cancer, which is the leading cause of death among diseases in children.

The new study, which was led by scientists from the International Agency for Research on Cancer (IARC) in collaboration with 17 partner institutions worldwide, used an innovative approach to trace the molecular origins of cancer back to birth. The researchers profiled molecular maps in patients at various stages: birth, diagnosis, remission, and recurrence. At the core of these maps is the epigenome, which intricately weaves DNA strands into a molecular imprint of nature and nurture: what our genes provide, and how the environment influences them. This allows the epigenome to capture a molecular snapshot – a kind of diary – of early-life factors that the baby was exposed to during pregnancy.

“This study is the result of a large-scale multidisciplinary effort, substantial investment, and extensive international collaboration,” says Dr Zdenko Herceg, Head of the Epigenomics and Mechanisms Branch at IARC and co-senior author of the study. “By combining epidemiology, clinical oncology, and advanced laboratory science, we have gained unique insights into the causes of cancer and identified biomarkers that could lead to early detection and personalized risk stratification and therapy.”

To generate epigenetic imprints, biological samples are required. However, most paediatric cancer research has relied on clinical samples collected after disease onset. This raises concerns of reverse causality, where biological processes identified in this way may result from the cancer rather than being its cause.

To address this, the scientists searched for epigenetic (DNA methylation) markers in both surrogate (blood) and cancerous tissues across the course of leukaemia development, starting at the time of birth by using archived Guthrie cards (or cord blood, when available) from the children. Guthrie cards harbour blood spots, often

[1] Ghantous A, Nusslé SG, Nassar FJ, Spitz N, Novoloaca A, Krali O, et al. (2024). Epigenome-wide analysis across the development span of pediatric acute lymphoblastic leukemia: backtracking to birth. *Mol Cancer*. Published online 23 October 2024; https://doi.org/10.1186/s12943-024-02118-4

originating from baby heel pricks, and are commonly collected as part of routine neonatal screenings. This uncovered potential epigenetic precursors of leukaemia detectable at birth, before the disease manifests.

After the patients were followed up for more than 10 years, the findings revealed that specific DNA methylation alterations at birth can serve as significant biomarkers for ALL development, prognosis, and survival. In the absence of changes in the DNA code, methylation levels are potentially reversible, and this is what was observed in patients who responded positively to therapy. The findings of this research were reproducible with different technologies, in three continents, and in two ethnicities, including the often-underrepresented Hispanic ethnicity; Hispanic children have the highest rates of childhood leukaemia worldwide.

“Because childhood cancer may have origins in utero, we have essentially travelled back in time to collect blood samples at birth from children who later developed cancer,” says IARC scientist Dr Akram Ghantous, the lead author of the study. “We are mapping the molecular ‘diaries’ of nature and nurture in patients with cancer while tracing these diaries back to birth – in a way, reversing the arrow of time to uncover early origins of the disease.”

With further validation, these findings could revolutionize early detection and treatment of childhood leukaemia. Future research will expand to larger, more diverse populations to uncover additional molecular precursors of paediatric ALL and enhance clinical applications.

Note to Editors:

This research is supported by the French National Cancer Institute (PEDIAHRG-2020 INCa_15817, PEDIAC INCa_15670), INCa/Plan Cancer-EVA-INSERM (France), the IARC Postdoctoral Fellowship and Marie Curie Actions-People-COFUND, Children with Cancer UK, the Swiss National Foundation and the SICPA Foundation, the Swedish Research Council, the Swedish Childhood Cancer Foundation, the Göran Gustafsson Foundation, the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, the Norwegian Research Council’s Centre of Excellence funding scheme, through “Centre for Fertility and Health”, the United States National Institutes of Health and Environmental Protection Agency, the JGW Patterson Foundation, and Children’s Cancer North.

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