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Appendices

1. BACKGROUND

Although childhood cancers are rare, research on childhood cancer could have major impact on public health particularly on the potential gain of years or quality of life. However, there is a lack of large-scale etiological studies in all types of childhood cancers and there are very limited data on causes and mechanisms. Previous studies of childhood cancers other than leukaemia and brain tumours, have been small and lacking in power. In addition, a number of important gaps can be identified in the current literature, including (i) the role of exposure to suspected risk factors at different key periods (preconceptional, prenatal or postnatal) are not elucidated, thus reducing the scope for intervention; (ii) limited studies have been conducted on genetic susceptibility factors and gene-environmental interactions; (iii) novel molecular markers (e.g., methylation and DNA repair capacity) have not been integrated in studies aimed to elucidate aetiology and eventually prevent and control these neoplasms.

To address these gaps in knowledge and provide new tools for their prevention and control, IARC has initiated a multicenter study, which aims to include large sample sizes to address the problems of lack of power and chance findings, to incorporate biomarkers of exposure and mechanism (e.g. DNA methylation and repair capacity), and to conduct comprehensive investigations on gene-environment interactions. To achieve these research goals, the study will be conducted in collaboration with clinical networks such as SIOP and COG.

The study will be focused on non-CNS embryonal tumors which have been severely under-studied due to their rarity. Non-CNS embryonal tumors are a group of specialized tumors seen in very young children, with microscopic appearance resembling the structures seen in developing tissues of the embryo and fetus. The study will include; retinoblastoma, Wilms tumor, rhabdomyosarcoma, neuroblastoma and hepatoblastoma. The pilot study will be focused on Wilms tumor and neuroblastoma.

2. OBJECTIVES OF THE STUDY

The objectives of the full-scale study are to understand the etiology of embryonal tumors focusing on genetic susceptibility, prenatal factors and neonatal exposures as well as aspects of molecular epidemiology including epigenetic profiles, DNA repair capacity and mutation patterns. The following hypothesis will be addressed:

1) Factors associated with prenatal growth and development are important in determining risk
2) There are particularly vulnerable periods during histogenesis and organ development which may vary for different tumors
3) Maternal factors during the periconceptional period and pregnancy, including exogenous agents (e.g. viruses, diet, tobacco smoke) may influence risk
4) Paternal lifestyle and occupational exposures during the periconceptional period and the mother's pregnancy may influence risk
5) Exposure of the child during the neonatal period and infancy to potentially mutagenic agents may play a role. Premature and other infants experiencing neonatal intensive care may be particularly at risk.
6) Risk may be modified by the genotype of the child (or the parents) with respect to polymorphic variants of genes involved in metabolism, growth and development, as well as DNA repair and cell cycle.
7) DNA repair capacity and epigenetic profiles of the parents and / or the index child may influence risk.
8) A proportion of cases will occur in children with predisposing congenital anomalies/syndromes and/or mutations to high penetrance cancer-associated genes. These may be due to new germline mutations (see iii and iv above)

<u>The main objectives of the pilot study are</u>:

1) To test the various methods of case and control recruitment (the primary objective)
2) To assess the clarity and effectiveness of the questionnaire
3) To estimate the proportion of cases recruited, compared to the cancer registries
4) To estimate the exposure frequencies in our study population for power calculation of the full-scale study
5) To test the feasibility and mechanism of biological sample collection
6) To harmonise the study across participating countries

Participating centers will aim to achieve following items during the pilot phase

1) Obtain agreement to case recruitment in major treating hospitals in their region
2) Identify the best mechanisms of recruiting unrelated controls, and establish collaboration with the clinics or institutes accordingly.
3) Clarify the feasibility of obtaining biological samples, including tumor tissues in collaboration with the clinical trial group

Participating centers will start the subject recruitment, interview and biological sample collection with the most desirable mechanisms specified in each section. When the most desirable mechanism is proven not feasible, the center may proceed with the second option. A summary matrix will be prepared at the end of the pilot study to illustrate the feasible mechanisms in each center. This will help the protocol WG to come up with a set of criteria and a harmonized protocol for the full study.

The data collected prospectively in the pilot study will be included in the full-scale study. The biological samples collected in the pilot study will be analyzed for quality assessment, and the laboratory results obtained from the pilot samples will also be included in the full scale study when the quality is proven to be adequate.

3. SUMMARY OF THE STUDY DESIGN

Summary points

1. Multicenter study
2. Recruit cases of Wilms tumor and neuroblastoma
3. Trio design. Every center will recruit parents of the index cases
4. Unrelated controls are optional. Centers will test the feasibility of recruiting population-based controls in the pilot phase.
5. Structured lifestyle questionnaire and interview for parental and index child exposures
6. Obtain DNA sources from all subjects (trios and unrelated controls)
7. Obtain tumour tissue samples when possible