Cohort-based association study of germline genetic variants with acute and chronic health complications of childhood cancer and its treatment: Genetic risks for childhood cancer complications Switzerland (GECCOS) study protocol

Supplemental Tables

Supplemental Table 1: Description of data sources used in the GECCOS study.

Data source	Data type	Data collection
Germline DNA biobank Switzerland for childhood cancer and blood disorders (BISKIDS) within the Paediatric Biobank for Research in Haematology and Oncology (BaHOP)	- Collection and storage of samples (saliva, buccal swabs, blood) - Extracted DNA - Raw sequencing data - Variant calls - Information of quality measures at the different stages of sample collection, DNA extraction, and analysis	Recruitment from the Swiss Childhood Cancer Registry (SCCR) database for childhood cancer survivors and Swiss childhood cancer hospitals for newly diagnosed patients
Swiss Childhood Cancer Registry (SCCR)	- Patient identification data (identification number, month and year of birth, diagnosis month and year, gender) - Diagnosis information (exact diagnosis, localisation, morphology, behaviour, staging and metastases) - Treatment information - Information on health and survival status (including relapses, late-effects, second tumours, and reason of death)	Data extraction from Swiss childhood cancer hospitals, regular updates with the Swiss mortality statistics
Swiss Childhood Cancer Survivor Study (SCCSS)	- Self-reported health status (various somatic and psychosocial outcomes including cause-specific long-term mortality, second primary malignancies and somatic health effects, medication use, mental health status, educational achievements, and health-related quality of life) - Socio-demographic characteristics - Functional outcome assessment from medical records (audiograms, echocardiographs, pulmonary function tests and others)	Baseline medical information, abstracted data from medical records, and questionnaire data collected among patients registered in the SCCR who survived at least 5 years, follow-up data collection at regular intervals (+/- every 5 years, for 40 years)

Supplemental Table 2: In- and exclusion criteria for the conceptualized sub-projects on pulmonary dysfunction, hearing loss and second primary neoplasms.

Outcome of interest	Inclusion criteria	Exclusion criteria
Pulmonary dysfunction	1) **Irradiation** of any dose potentially including the lungs: a. Total body irradiation; b. Total lung irradiation; c. Radiation to the chest including the lungs; d. Spinal irradiation; e. Radiation to the upper abdomen or the neck. 2) **Chemotherapies** with known and suspected lung-toxic agents: a. Bleomycin; b. Busulfan; c. Nitrosoureas (Carmustine, Lomustine); d. High-dose Methotrexate.	**Surgery** to the lungs (except biopsies)
Hearing loss	1) **Irradiation** to the head of 30 Gy or more 2) **Chemotherapies** with known hearing-toxic agents: a. Cisplatin; b. Carboplatin; c. Oxaliplatin 3) Survivors of leukaemia, CNS tumours, neuroblastoma, soft tissue sarcomas, and germ cell tumours who were not exposed to established ototoxic treatments (as defined above) but who are suspected to be at risk for hearing loss due to potential additional risk such as other drugs like aminoglycosides or loop diuretics.	1) **Pre-existing hearing loss** before start of the cancer treatment 2) **Surgery** involving the ear which were associated with hearing loss.
Second primary neoplasms	**1) Cases with second primary neoplasms** **2) Matched control design:** matched by demographic, primary cancer diagnosis, and treatment factors, age at primary diagnosis, follow-up time, year of primary neoplasm treatment, and exposure to relevant treatments (e.g. chest radiation, or alkylating agents), where appropriate. **3) Case-cohort design:** Random selection of a subcohort from all childhood cancer survivors and retrieval of the same information as needed for the cases.	Identified from medical records, follow-up reports to the SCCR, linkage with cantonal cancer registries, death records, and questionnaire information (as defined by IARC)[1]

Supplemental Table 3: Clinical information collected for the three conceptualized sub-projects on pulmonary dysfunction, hearing loss and second primary neoplasms.

Pulmonary dysfunction	**Spirometry**	Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), Peak expiratory flow (PEF), Max. expiratory flow (MEF 25-75)
	Body plethysmography	Total lung capacity (TLC), Vital Capacity (VC), Functional residual capacity (FRC), Residual volume (RV)
	Carbon monoxide diffusion capacity corrected for haemoglobin (DLCO)	mmol/min/kPa corrected for haemoglobin if available
	Multiple breath washout	Lung clearance index (LCI), Ventilation distribution inhomogeneity (SIII, S_{acin}, S_{cond})
	Self-reported symptoms and environmental exposure	Self-reported questionnaire information on pneumonias, chronic cough, and risk factors for lung problems (smoking, etc.)
Hearing loss	**Audiometry**	Bilateral pure tone audiometry with air and bone conduction spanning 125 Hz to 8,000 Hz (where available up to 16,000 Hz)
	Video otoscopy	Assessment of the tympanic membrane (where available)
	Self-reported symptoms and environmental exposure	Self-reported questionnaire information on hearing loss, tinnitus, hearing aid use, exposure to noise
Second primary neoplasms	**Age at diagnosis**	Years
	Date of diagnosis	Month/ year
	Type of diagnosis	ICCC3 code; ICDO3 morphology, topography, behaviour code
	Laterality	Left/ right/ bilateral/ medial/ not applicable
	Relapse date	Month/ year
	Relapse type	Local/ distant/ systemic/ other
	Relapse location	Organ and morphology
	Treatment information	Cumulative doses of individual antineoplastic agents and radiotherapy
	Self-reported symptoms and environmental exposure	Self-reported questionnaire information on risk factors for second primary neoplasms (smoking, etc.)

Legend: CNS, central nervous system; Gy, gray; Hz, Hertz; IARC, International Agency for Research on Cancer; ICCC3, international classification of childhood cancer, third edition; ICDO3, international classification of diseases for oncology, third edition SCCR, Swiss Childhood Cancer Registry.