

Proposal No: 01-01  
Topic: Second Malignant Neoplasms in Wilms Tumor

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## CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS PROPOSAL

**TITLE:** Second Malignant Neoplasms in Survivors of Wilms Tumor:  
An International Collaborative Study

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### **SPECIFIC AIMS/OBJECTIVES:**

- To combine the resources of the Childhood Cancer Survivor Study (CCSS), the US National Wilms Tumor Study Group (NWTSG), the British Childhood Cancer Survivor Study (BCCSS) and the Nordic cancer registries
- To estimate the rates of second malignant neoplasms in survivors of Wilms Tumor (WT) and other childhood kidney tumors by gender; age at diagnosis and time since diagnosis.
- To determine risk factors for second tumors by studying their association with:
  1. sites and doses of radiation therapy;
  2. type and doses of chemotherapy;
  3. specific subtypes of Wilms tumor identified by bilaterality, histology, associated congenital anomalies and syndromes (aniridia, Denys-Drash, hemihypertrophy, etc.) and precursor lesions (perilobar and intralobar nephrogenic rests);
  4. family history of Wilms tumor and other cancer.

### **PROPOSED ANALYSIS PLAN:**

#### **Combined cohort study:**

Data from the collaborating programs will be merged into analysis files using standard data items and codes. These will enable estimation of cumulative incidence rates of SMNs by site/type, gender, age at diagnosis and either time since diagnosis or current age. Comparison rates for the U.S. will be obtained from the SEER program, for the UK from the UK Office of National Statistics and for the Nordic countries from the national cancer registries in those countries.

Patients from the NWTSG diagnosed during 1969-1995 (NWTS1-4), UKCCG during 1962-1990 and the Nordic registries (dates to be specified for each registry) will be entered into follow-up as of the time of the Wilms tumor diagnosis. CCSS patients, diagnosed at member institutions during 1970-1986, will be considered at risk of SMN from the point five years post WT diagnosis at which they were entered into the CCSS cohort. The NWTSG and CCSS cohorts will be compared to identify and eliminate patients common to both. Patients will be followed until death, loss to follow-up or an exit date determined appropriately for each registry: 31 Dec 1999 for NWTSG; date of questionnaire for CCSS; 31 Dec 1990 for BCCSS (soon to be extended); and dates to be determined for each Nordic registry.

To the extent possible, separate analyses will be conducted for children with clear cell sarcoma of kidney (CCSK) and rhabdoid tumor of kidney (RTK) due to the known tendency of the former to metastasize to bone and of the latter to occur in conjunction with PNET tumors.

The master file for the cohort study will ideally contain the following data items:

1. Date of diagnosis of WT or other childhood renal tumor
2. Birthdate and gender
3. Country (DK, UK, US, etc.)
4. Cell type of childhood renal tumor (WT, CCSK or RTK)
- 5. Stage (NWTS) and laterality of disease (unilateral vs. bilateral)
6. Dates of diagnosis and ICD-O-2 site/morphology codes of all subsequent malignant neoplasms
7. Date and cause (ICD-9) of death
8. Date of last contact and/or exit date appropriate to each registry

The consolidated data will be analyzed using standard methods for cohort studies including

1. Cumulative incidence rates (tables and graphs), both overall and by various combinations of registry, age at diagnosis, gender, time since diagnosis, current age and, to the extent possible, histologic type and stage of childhood renal tumor
2. Standardized incidence ratios (SIR) based on comparisons with the population rates appropriate to each registry, with possible breakdowns as indicated
3. Poisson and/or Cox regression analysis to evaluate the significance of the differences observed according to the mentioned factors

Third and subsequent malignant neoplasms that may occur in the same patient will be included using appropriate methods for the analysis of recurrent events.

Preliminary data from each registry indicate that the numbers of patients, person-years of observation and SMNs that will be available for analysis in the near future are as follows:

Registry	No. of patients	Person-years	No. of SMNs
CCSS	1174		14*
NWTSG	6484	69,179	70*
BCCSS			
Nordic registries			

\* Overlap of one case (retinoblastoma)

### **Nested case-control studies**

A series of nested case-control studies will be planned and conducted according to the resources available to each participating registry to estimate relative risks of SMNs according to treatment, tumor and host factors. Data items for this series of studies will ideally include

1. Dates of administration, sites (particularly operative bed, whole abdomen and chest) and doses of radiation therapy used for initial treatment of WT or for any subsequent relapse
2. Dates of administration, routes of administration, type and doses of all chemotherapeutic agents used for the initial treatment of WT or for any subsequent relapse
3. Characteristic congenital anomalies and syndromes
4. Family history of Wilms tumor, other cancers and congenital anomalies
5. Detailed histologic subtype of Wilms tumors
6. Precursor lesions occurring in conjunction with WT

Matched sets of cases and controls will be constructed from the risk sets formed during Cox regression analysis of the cohort data. They will be specific for registry, age and calendar period of Wilms tumor diagnosis, gender (for some analyses) and time since WT diagnosis. The data will be analyzed using standard methods for analysis of case-control studies including conditional logistic regression. Since the sampling fractions (ratios of sampled cases and controls to those available in each risk set) are known, absolute risks of SMNs can be estimated as well as relative risks.

### **Pilot study**

In order to demonstrate the feasibility of this study, and to generate pilot data to include in a grant submission to secure funding for the main study, a pilot study of breast cancer occurrence in the NWTSG and CCSS cohorts will be carried out immediately. (The BCCSS and Nordic registries may participate in this if they are able.) To date the NWTSG and CCSS have identified a total of nine patients with

secondary breast cancers, 6 in the NWTSG and 3 in CCSS. All are female and the possibility of duplication has been ruled out. Preliminary analysis of the NWTSG data showed that five of the breast cancers occurred among 272 female patients who received chest irradiation for pulmonary metastases, contributed 3883 person-years of observation and had an expectation of 0.052 cases based on SEER rates (SIR=96, 95% CI=31-224). The risk of breast cancer in female patients who received chest irradiation of 1200 cGy is tentatively estimated to be 10% or higher by 30 years from Wilms tumor diagnosis.