Twenty-Five Year Follow-Up Among Survivors of Childhood Wilms' Tumor. A Report from the Childhood Cancer Survivor Study.

Working Group: Chronic Diseases

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Wilms' tumor is the most common primary renal cancer of childhood. With current multi-modal therapies including chemotherapy, radiation therapy, and surgery, the majority of patients are long term survivors. Long term complications of Wilms' tumor and therapy for Wilms' tumor have been reviewed in the literature (Green 1995; Shearer 1993). Specific late effects include cardiovascular (Finklestein 1993; Sorenson 1995; Green 2001; Iarussi 2003), musculoskeletal (Rate 1991) and renal sequelae (Ritchey 1996, Breslow 2005). Second malignant neoplasms (Breslow 1995; Shearer 2001) and late effects of radiation therapy (Paulino 1999) have also been described. Reproductive outcomes in the CCSS cohort have been previously reported.

The Childhood Cancer Survivor Study (CCSS) provides a valuable resource to understand the late effects of Wilms' tumor therapy. The current study proposes to utilize the CCSS cohort to examine the late mortality of Wilms' tumor survivors, the incidence of late recurrences and second malignant neoplasms; the incidence of chronic health conditions specifically looking at congestive heart failure, hypertension, musculoskeletal problems, and renal failure; health status; health care utilization, marriage, employment, income, insurance coverage, and educational attainment.

Specific Aims/Hypotheses:

The specific aim of this proposed project is to provide a comprehensive description of the outcomes of 5 year survivors of childhood Wilms' tumor from both a medical, psychosocial, and health care practices perspective.

Hypotheses:

1. Mortality
    a. The overall survival of 5 year survivors of Wilms' tumor 25 years from diagnosis will be lower than the general US population.

    b. The standardized mortality ratio (SMR) will be greater in 5 year Wilms' tumor survivors exposed to treatments including: doxorubicin, chest irradiation, abdominal irradiation >/=1500 cGy examined in a non-overlapping manner. Subjects who are 5-year survivors of relapsed Wilms' tumor will also have a higher SMR.

2. Second malignant neoplasms
    a. The standard incidence ration (SIR) of SMNs will be greater in 5 year survivors of Wilms' tumor exposed to treatments including: doxorubicin, chest irradiation, and abdominal irradiation >/= 1500 cGy examined in a non-overlapping manner. Subjects who are 5-year survivors of relapsed Wilms' tumor will also have a higher SIR for SMN.

3. Chronic medical conditions
    a. Overall chronic medical conditions
        i. Survivors of Wilms' tumor have an increased likelihood of chronic medical conditions (grade 1-4) and severe chronic medical conditions (grade 3 or 4) than the sibling control group.
        ii. Survivors of Wilms' tumor have an increased likelihood of specific medical conditions (congestive heart failure, hypertension, renal failure, musculoskeletal problems) than the sibling control group.
        iii. Treatment with irradiation to the left ventricle >1200cGy and/or left flank >/=1500 cGy increases the likelihood of congestive heart failure in Wilms' tumor survivors receiving DOX. The likelihood will be examined by DOX exposure (DOX < 100 mg/m^2, 101-250 mg/m^2, and >250 mg/m^2).

4. Health status
    a. Survivors of Wilms' tumor have an increased likelihood of adverse general health status, mental health status, activity limitation, and functional impairment compared to the sibling comparison group.

5. Social
    a. Survivors of Wilms' tumor who are over 25 years old at time of response are less likely to report ever being married, ever being employed, and having health insurance coverage than the sibling comparison group; they have a lower educational attainment and income than the sibling comparison group; they have a higher likelihood of being unemployed due to illness or disability.

6. Health care utilization
    a. Survivors of Wilms' tumor are more likely to report medical follow-up within 2 years and undergo more cancer screening (self and medical) than the sibling comparison group.

Analysis Framework:

A Outcomes of interest

1. Mortality
    a. Overall survival at 25 years compared to US population
    b. Cumulative mortality at 25 years
    c. SMR if a 5-year survivor of relapsed vs. non-relapsed Wilms' tumor
    d. SMR by non-overlapping treatment exposure:*
    e. Number of deaths and cause of death
        i. Recurrence
        ii. Second malignant neoplasm
        iii. Cardiac
        iv. Renal failure
        v. Infection
        ~~v.~~vi. Other

*Categories of non-overlapping treatment exposure for mortality and SMN analysis:

DOX (Any)	XRT Chest (Any)	XRT Abdomen >/=1500cGy
No	No	No
No	No	Yes
No	Yes	No
No	Yes	Yes
Yes	No	No
Yes	No	Yes
Yes	Yes	No
Yes	Yes	Yes

2. Second malignant neoplasms
    a. Cumulative incidence at 25 years: overall, secondary leukemia and solid tumors (excluding skin cancers)
    b. SIR of SMN overall and of specific types of second malignant neoplasms and number of each
    c. SIR of SMN if a 5-year survivor of relapsed vs. non-relapsed Wilms' tumor
    d. SIR of SMN by non-overlapping treatment exposure (see table * above)

3. Chronic medical conditions: Wilms' tumor survivors compared to sibling control group
    a. Overall – severity 1-4 (Coding from Oeffinger/Hudson manuscript)
       Frequency (N and %) and Hazard Ratio (HR) compared to sibling group
    b. Severe – ranked 3-4
       Frequency (N and %) and HR compared to sibling group
    c. Multiple chronic medical conditions
       2 or more (N and %) and HR compared to sibling group
       3 or more (N and %) and HR compared to sibling group
    d. HR compared to sibs of specific chronic medical conditions:
        i. Congestive heart failure
            Baseline F4 (**yes**)
            FU 2000 10d (**yes**)
        ii. Hypertension
            Baseline F 8 (**yes**-medication for BP)
            FU 2000 6 L (**yes**-medication for BP)
            FU 2003 Q 6 (**yes**-medication for BP)
        iii. Renal failure
            Baseline D 4 (**yes**-dialysis)
            Baseline I 25 (**yes**-kidney transplant)
        iv. Musculoskeletal
            Baseline I 2 (**yes**-scoliosis surgery)

4. Health status compared to sibling control group (OR) (per ALL paper)
    i. General health
    ii. Mental health
    iii. Activity limitations
    iv. Functional impairment

5. Social outcomes (>25 years old at survey)(frequency compared to siblings)
    a. Married (Ever married or living as married)
        Baseline L1 (**yes**-been married/lived as married)
        FU 2000 2b (**yes**-marital status change and indicate **married or living as married**)

    b. Employed (Ever)
        Baseline O5 (**yes**-ever had job)
        FU 2000 3b (**yes**-worked since 5/1995)
        FU 2003 4 (**working full-time, working part-time, unemployed looking for work, retired**)

       Cannot be employed (FU 2003 respondents only)
        FU 2003 4 (**unable to work due to illness/disability**)

c. Health insurance (Ever – use status at most recently completed questionnaire)
   Baseline Q2 (**yes**-current health insurance or **Canadian**)
   Baseline Q3 (collect all options)
   FU 2000 16 (**yes**-current health insurance or **Canadian**)
   FU 2000 16a (collect all options)
   FU 2003 M1 (**yes**-current health insurance or **Canadian**)
   FU 2003 M1a (collection all options)
   Health insurance (2003 respondents only)
   FU 2003 M1 (**yes**-current health insurance or **Canadian**)
   FU 2003 M1a (**collect all options**)

d. Educational attainment at most recently completed questionnaire]
   Baseline O1 (highest grade-**collect all options**)
   FU 2000 highest grade 1b (highest grade – **collect all options**)
   FU 2003 highest grade 1 (highest grade – **collect all options**)

e. Personal income at most recently completed questionnaire
   Baseline Q9
   FU 2003 S.3(**collect all options**)

6. Health care utilization/screening: OR compared to sibling group (stratified by age equal or greater than 40 years vs. less than 40 years)
   All subjects:
      Baseline N 16 (gen PE-not sick **yes less than 1 yr ago or 1-2 years**)
   Male subjects:
      Baseline N18 (testicular exam – **regular**)
   Female subjects:
      Baseline N19 (self breast exam – **regular**)
      Baseline N20 (PAP – **less than 1 yr ago or 1-2 yrs**)
      Baseline N21 (breast–med prof; **less than 1 yr ago or 1-2 yrs**)
      Baseline N22 (**yes** – mammogram)

   No mammogram ever
      FU 2003 B4 (**never**)
   No PAP ever
      FU 2003 B5 (**never**)

b. **Study population**: Subjects enrolled in the CCSS with confirmed histological diagnosis of Wilms' tumor and who responded to at least one questionnaire. Subjects will be compared to all siblings (comparison group) unless otherwise noted.

c. **Risk factors of interest**:

1. Mortality and SMN analyses
    a. Patients who relapsed and are 5-year survivors will be analyzed separately

    b. Treatment exposure for mortality analysis and for SMN analysis will be broken into non-overlapping exposures consisting of the following groups:

DOX	XRT Chest	XRT Abdomen >/=1500cGy
No	No	No
No	No	Yes
No	Yes	No
No	Yes	Yes
Yes	No	No
Yes	No	Yes
Yes	Yes	No
Yes	Yes	Yes

2. Treatment exposure for congestive heart failure will be broken into non-overlapping exposures consisting of the following groups:

DOX mg/m^2	Left ventricle >/=1200cGy	Left Flank XRT >/=1500cGy
None	None	None
</= 100	None	None
</= 100	None	Yes
</= 100	Yes	No
</= 100	Yes	Yes
101 -249	No	No
101 -249	No	Yes
101 -249	Yes	No
101 -249	Yes	Yes
250+	No	No
250+	No	Yes
250+	Yes	No
250+	Yes	Yes

3. Treatment exposure for hypertension and renal failure:
    Dose to contralateral kidney: none, < 1499cGy, 1500 to 2500cGy,> 2501cGy

d. **Confounding variables**: age at diagnosis, duration of follow-up, age at survey, gender, and race

e. **Statistical analysis**

*Mortality***:** We will compare mortality rates for CCSS survivors to age, gender and calendar year matched rates from the US population, depicting with Kaplan-Meier survival curves and Standardized Mortality Ratios (SMRs).

Second malignant neoplasms: Cumulative incidence of SMN with death as a competing risk event will be summarized. Standardized Incidence Ratios (SIR) will be calculated using SEER data to determine expected rates in age, gender and calendar year matched US population.

Chronic medical conditions: Among subjects free of a chronic medical condition at study entry, cumulative incidence of grade 1-4 and grades 3-4 will be evaluated, treating death as a competing risk. Cox proportional hazards models will be used to compare survivors to sibling after 5 years post diagnosis. Prevalence of subjects who experienced an event prior to study entry will be summarized and compared with age standardized rates among the siblings.

In addition to the above summary measures of chronic conditions, the specific conditions below will be examined in the same fashion:

CHF, HTN, renal failure, musculoskeletal problems

Health status, social outcomes, health care utilization: These measures will be summarized using frequencies and compared to siblings using odds ratios (ORs), evaluated using logistic regression models adjusted for demographic factors such as age, gender and socio-economic measures listed above.

All analyses comparing survivors to siblings will appropriately account for intra-family correlation using sandwich robust variance estimator within the context of the regression model being used.

f. **Specific tables and figures:**

Table 1. Characteristics of CCSS Wilms' Tumor Survivors.

	WT Survivors (N=)	Siblings (N=)
Gender		
Male		
Female		
Median age at diagnosis (range)		
Canadian		
Age at Last Questionnaire (yrs)		
0-9		
10-19		
20-29		
30-39		
40-49		
>50		
Follow-up from diagnosis (yrs)		
5-14		
15-24		
25-33		
Treatment Exposure		
-Surgery alone		
-Surgery + chemotherapy		
-Surgery + chemotherapy/XRT		
Anthracycline exposure		
-none		
-1-100 mg/m^2		
-101 to 250 mg/m^2		
>250 mg/m^2		
Abdominal XRT		
None		
Whole abdomen		
<1500 cGy		
1500 – 2500 cGy		
>2500 cGy		
Left flank		
<1500 cGy		
1500 – 2500 cGy		
>2500 cGy		
Right flank		
<1500 cGy		
1500 – 2500 cGy		
>2500 cGy		
Chest		
</=1200 cGy		
>1200 cGy		

Figure 1. Overall survival of Wilms' tumor survivors in comparison to the US population

Figure 2. Cumulative incidence of second malignant neoplasms (overall, secondary leukemia and secondary solid tumor) (excluding skin cancers)

Table 2. SMR of 5-year Wilms' tumor survivors by treatment exposure and relapsed status.

	Wilms' Survivors Without DOX N= SMR (95%CI)	Wilms' Survivors With DOX N= SMR (95%CI)
No Chest XRT No Abd XRT	1.00	
No Chest XRT Abd XRT >/=1500cGy		
Chest XRT No Abd XRT		
Chest XRT Abd XRT >/=1500cGy		
Relapsed Wilms' Tumor		

Table 3. SIR of second malignant neoplasms (excluding skin cancer) by treatment exposure and relapsed status in 5-year survivors.

	Wilms' Survivors Without DOX N= SIR (95%CI)	Wilms' Survivors With DOX N= SIR (95%CI)
No Chest XRT No Abd XRT	1.00	
No Chest XRT Abd XRT >/=1500cGy		
Chest XRT No Abd XRT		
Chest XRT Abd XRT >/=1500cGy		
Relapsed Wilms' Tumor		

Figure 4. Cumulative incidence of chronic medical conditions grade 1-4 and grade 3-4

Table 4. Hazard ratios of congestive heart failure, hypertension, renal failure, and musculoskeletal problems in Wilms' tumor survivors compared to siblings.

	Wilms' Tumor Survivor Number (N=)	Sibling Number (N=)	HR (95%CI)
Congestive heart failure			
Hypertension			
Renal failure			
Musculoskeletal problems			

Table 5. Hazard Ratio of congestive heart failure in Wilms' tumor survivors by treatment with doxorubicin and site-specific irradiation.

	Without DOX N= HR (95%CI)	With DOX < 100 mg/m^2 N= HR (95%CI)	With DOX 101-250 mg/m^2 N= HR (95%CI)	With DOX >250 mg/m^2 N= HR (95%CI)
No XRT	1.00			
No LV XRT L flank XRT>/=1500cGy				
LV XRT >1200cGy No L flank				
LV XRT >1200cGy L flank XRT>/=1500cGy				

Table 6. Hazard ratios of developing hypertension and renal failure in Wilms' Tumor survivors by radiation exposure.

	No abd Irradiation HR (95%CI)	Contralateral kidney XRT <1500cGy HR (95%CI)	Contralateral kidney XRT 1500-2500cGy HR (95%CI)	Contralateral kidney XRT >2500cGy HR (95%CI)
HTN requiring treatment	1.00			
Renal failure	1.00			

Table 7. Frequencies and odds ratios of adverse health status in Wilms' tumor survivors compared to siblings.

	Wilms' Tumor Survivors N= %	Siblings N= %	OR (95% CI)
Adverse general health status			
Adverse mental health status			
Activity limitations			
Functional impairment			

Table 8. Frequencies of social and economic outcomes in survivors of Wilms' tumor and siblings over 25 years of age at response.

	Wilms' Tumor Survivors N=	Siblings N=	P for survivors vs. siblings
Marital status, no.			
Ever married %			
Education, no.			
Not high school graduate %			
High school graduate/GED %			
College graduate %			
Employment, no.			
Ever Employed %			
Full time, % (FU2003)			
Part time, % (FU 2003)			
Unable to be employed % (FU 2003)			
Income, no.			
< $ 20K, %			
$ 20 to 60 K, %			
> $ 60 K, %			
Health Insurance, no.			
Ever covered or Canadian %			
Public health Insurance %			
Private health Insurance %			
Uninsured %			

Table 9. Frequencies of health care practices in survivors of Wilms' tumor compared to siblings stratified by age above and below 40 years at response.

	Wilms' Survivors <40 yrs old	Wilms' Survivors >/=40 yrs old	Siblings <40 yrs old	Siblings >/=40 yrs old	OR (95% CI) <40 yrs old	OR (95% CI) >/=40 yrs old
General medical exam within 2 years, no. (%)						
Testicular self-exam (males), no. (%)						
Breast self-exam (females), no. (%)						
Breast exam by health professional within 2 yrs						
PAP test within 2 years, no. (%)						
Mammogram ever, no. (%)						
Never had PAP at FU 2003, no. (%)						
Never had mammogram at FU 2003, no. (%)						

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