CCSS Analysis Concept Proposal
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STUDY TITLE: Renal carcinoma following therapy for cancer in childhood.

Working groups: Second malignancy, Epidemiology/Biostatistics

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BACKGROUND AND RATIONALE:
Although substantial increases in survival rates have been observed for many childhood cancers over the past several decades, survivors of childhood cancer are at risk of developing second cancers as a consequence of the anti-cancer therapies received in childhood. The overall cumulative incidence of second malignancies following treatment for childhood cancer has been reported to range between 3% and 10% at 25 to 30 years post diagnosis; 3- to 6-fold higher than that observed in the general population[1-4]. Rates are even higher for some diagnostic subgroups such as Hodgkins lymphoma[5,6]. The most commonly reported second cancers among survivors are cancers of the thyroid, breast, bone and brain. Studies investigating the incidence of renal cancer among survivors of childhood cancer are limited[7].

The most common form of renal neoplasm observed in adults is renal cell carcinoma, which occurs in the cortex of the kidney and account for 80% to 85% of all renal neoplasms[8]. The majority of renal cell carcinomas are of the clear cell subtype, followed by the papillary and chromophobe subtypes. Transitional cell carcinomas, which arise in the transitional epithelial cells and occur primarily in the renal pelvis and calyces, are the second most common form of kidney tumor, accounting for 8% of all renal neoplasms[8]. Factors that that have been associated with an increased risk of renal carcinoma include smoking[9,10], obesity[11-13], hypertension[14,15], end-stage renal disease and kidney transplantation[16,17], as well as increased parity among females[18,19]. Some evidence exists to that suggest that long-term use of diuretics or a history of diabetes mellitus may increase risk of renal carcinoma, although neither factor has been shown to be associated with renal carcinomas independently of obesity[15,20-22].

In the general population, renal cancer occurs predominantly in the sixth to eight decade of life with a median age at diagnosis of 64 years. Despite the rarity of renal cancer in individuals less than 45 years of age, several cases of renal carcinoma have been reported among survivors of childhood cancer[23,24], particularly among those treated for neuroblastoma[25-29]. For instance, in a previous report from the Childhood Cancer Survivor Study (CCSS), a 329-fold increase risk of renal cell carcinoma was noted among survivors of neuroblastoma when compared to the general population[7]. The strong link between neuroblastoma and subsequent renal cancer has lead to renal cell carcinomas associated with neuroblastoma to be recognized as a distinct entity in the 2004 WHO renal tumor classification[30]. While renal carcinomas occurring after neuroblastoma are morphologically heterogeneous, a large proportion of these tumors are characterized by oncocytoid cytoplasm, solid to papillary architecture and the

presence of psammoma bodies. Renal cell carcinoma after neuroblastoma may develop as a consequence of anti-cancer therapies given in childhood. However, the occurrence of second renal cancers outside the field of prior radiotherapy or in patients who have not receive irradiation, have lead some researchers to postulate underlying genetic predisposition as a possible cause of these cancers[26].

A second form of renal cell carcinoma, characterized by translocations in chromosome Xp11.2, has also been noted among survivors of childhood cancer[31]. This type of renal cell carcinoma is characterized by Xp11.2 translocations which result in gene fusions with the TFE3 transcription factor gene. In contrast to renal cell carcinoma associated with neuroblastoma, translocation renal carcinomas bearing TFE3 mutations resemble clear cell renal cell carcinomas upon gross examination[32]. This type of renal cell carcinoma predominantly affects children and young adults and often presents at an advanced stage with lymph node metastases[30]. Renal cancers associated with Xp11.2 translocations/TFE3 gene transfusions have been suggested to result as a consequence of exposure to chemotherapeutic agents in childhood[32]. This theory is supported by reports of the occurrence of Xp11.2 translocation tumors in individuals treated with chemotherapeutic agents for non-malignant conditions[33,34].

To date, the incidence of renal cell carcinoma among survivors of childhood cancer has not been well characterized. Most studies of subsequent renal carcinomas in survivors of childhood cancer have consisted of case reports or small series (n= 5, 4, 1, 4, 1, 2 and 1)[25,26,28,29,31,35,36]. Alternatively, in cohort studies of cancer survivors, such as the CCSS, renal cancers have generally been grouped with rare or unusual cancers without specifying the morphologies or sites of these cancers[37,38]. Therefore, the aim of this study is to describe 22 cases of pathologically confirmed renal carcinoma, identified by the 2007 follow-up questionnaire, in the CCSS cohort. This report will be among the largest to characterize the incidence of second renal carcinomas among survivors of childhood cancer, and among the first to examine factors that may increase the risk of second renal carcinomas. By evaluating potential associations between demographic and treatment-related characteristics with subsequent renal cancer, we hope to identify information that will improve surveillance guidelines and screening practices for survivors of childhood cancer at high risk of this disease.

AIMS:

1. Calculate the standardized incidence ratio (SIR), excess absolute risk (AER) and cumulative incidence of subsequent renal carcinomas among survivors of childhood cancer
2. Describe the occurrence of subsequent renal carcinomas among survivors of childhood cancer by demographic, lifestyle and treatment-related characteristics

ANALYSIS FRAMEWORK

Population:

All CCSS study participants who completed the baseline questionnaire and had information abstracted from medical records will be eligible for these analyses.

Outcome of interest:

Renal carcinomas ascertained through self report questionnaires and pathologically confirmed by the CCSS Pathology Center will be considered in these analyses. Cancers eligible for inclusion in these analyses will have International Classification of Diseases of Oncology (ICD-O-2) site codes of C64-C65.

Variables:

1. Date of birth
2. Date of questionnaire completion (FU2007)

3. Vital status
4. Date of death
5. Sex
6. Childhood cancer diagnosis
7. Date of childhood cancer diagnosis
8. Morphology of renal carcinoma (ICD-O-2 morphology code)
9. Date of diagnosis of renal carcinoma
10. Race/ethnicity (Race 5 code)
11. Radiation therapy (left kidney/right kidney/other/none)
12. Chemotherapy (all agents listed individually, each agent with cumulative dose)*
13. Nephrectomy (as treatment for childhood cancer, yes/no, partial/complete)
14. History of hypertension (G5 FU2007) †
15. BMI at follow-up (calculated from A1-2 FU2007)
16. Smoking status (current/ever/never - N7-N14 FU2007)
17. Diagnosis of a familial cancer syndrome (P1 BL)
18. History of a kidney transplant (I25 BL and J27 FU2007 - This variable is requested to ensure that the subsequent renal carcinoma occurs in the participant's own kidney and not in a donor organ).
19. Exposure to immunosuppressive agents (C8 FU2007)

*These variables will be used to describe the cytotoxic treatments received by participants who developed a subsequent renal carcinoma (data presented in Table 2). Chemotherapeutic agents will not be considered individually in analyses described below.

† Only cases of hypertension reported to occur prior to diagnosis of a renal carcinoma will be considered in analyses.

Statistics:

1. The cumulative incidence estimate of subsequent renal carcinoma will be calculated from the date five years post childhood cancer diagnosis to the first occurrence of renal carcinoma, treating death as a competing risk event and censoring at the date of last contact. Renal carcinomas occurring within five years of diagnosis will be excluded from analyses.
2. The SIRs and AERs of subsequent renal carcinomas in the CCSS cohort, overall and stratified by patient and treatment characteristics, will be calculated using age-, gender-, and calendar-specific incidence data from Surveillance, Epidemiology and End Results (SEER).
3. Descriptive statistics will be used to evaluate the contribution of diagnosis, treatment and lifestyle characteristics on the risk of developing a subsequent renal carcinoma
4. Associations between survivor characteristics (diagnosis and treatment) and subsequent renal carcinoma will be evaluated using Poisson univariate regression analyses. Because of the limited number of patients expected to develop a renal carcinoma in the study cohort, it is not anticipated that it will be feasible to perform adjusted analyses.

Table 1: Characteristics of CCSS participants

	Patients with subsequent renal carcinoma		CCSS cohort	
	Number	**%**	**Number**	**%**
Sex				
Male				
Female				
Age at diagnosis				
0-4 yrs				
5-9 yrs				
10-14 yrs				
15-19 yrs				
Race				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Other				
Diagnosis				
Leukemia				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
CNS				
Wilms Tumor				
Neuroblastoma				
Soft tissue sarcoma				
Bone				
Treatment era				
1970-1977				
1978-1986				
Therapy received for primary cancer				
Chemotherapy†				
Alkylating agent				
Epipodophyllotoxin				
Platinum agents				
Anthracyclines				
Anti-metabolites				
Radiotherapy				
Kidney				
Other				
None				
Nephrectomy (partial or complete)*				
Age at subsequent carcinoma				
10-19				
20-29				
30-39				
>40				
Vital status				
Alive				
Deceased				

† Chemotherapy agents are considered as yes/no variables

*Nephrectomy as treatment for initial childhood cancer

Table 2: Characteristics of childhood cancer survivors who developed a subsequent renal carcinoma

Patient	Childhood cancer diagnosis	Age at diagnosis	Chemotherapy (agents listed individually eg. DOX, VP16)	Radiotherapy involving kidney (yes/no)	Second cancer morphology	Age renal cancer	latency	Vital status	Genetic Condition	Smoking status (ever/never)	BMI (<25, ≥25)	Hypertension (yes/no)
1												
2												
3												
4												
5												
6												
7												
And so on												

Table 3: Unadjusted SIRs and 95% CIs of subsequent carcinomas stratified by patient characteristics

Characteristics	Observed events	Expected events	SIR (95%CI)	AER (95%CI)
Overall risk				
Sex				
Male				
Female				
Age at diagnosis				
<10 yrs				
≥10 yrs				
Diagnosis				
Leukemia				
Hodgkin's lymphoma				
Non-Hodgkin's lymphoma				
CNS				
Wilms Tumor				
Neuroblastoma				
Soft tissue sarcoma				
Bone				
Elapsed time between malignancies				
0-9 yrs				
10-19 yrs				
≥ 20 yrs				

Table 4: Unadjusted SIRs and 95% CIs of subsequent renal carcinomas stratified by treatment characteristics

Characteristics	Observed events	Expected events	SIR (95%CI)	AER (95%CI)
Treatment era				
1970-1977				
1978-1986				
Alkylating agent				
Yes				
No				
Epipodophyllotoxin				
Yes				
No				
Platinum agent				
Yes				
No				
Anthracycline				
Yes				
No				
Methotrexate				
Yes				
No				
Nephrectomy				
Yes				
No				
Radiation involving kidney				
Yes				
No				

Table 5: Univariate analyses of subsequent renal cancers

Characteristics	RR (95%CI)	p-value
Sex		
Male	1.0	
Female		
Age at diagnosis		
<10 yrs	1.0	
≥10 yrs		
Platinum agent		
No	1.0	
Yes		
Alkylating agent		
No	1.0	
Yes		
Epipodophyllotoxin		
No	1.0	
Yes		
Platinum agent		
No	1.0	
Yes		
Anthracycline		
No	1.0	
Yes		
Methotrexate		
No	1.0	
Yes		
Nephrectomy		
No	1.0	
Yes		
Radiation involving kidney	1.0	
No		
Yes		
Smoking	1.0	
Never		
Ever		
BMI	1.0	
<25		
≥25		
Hypertension	1.0	
No		
Yes		

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