

## Risk of a second kidney carcinoma following childhood cancer

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# Author's Accepted Manuscript

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Chemotherapy and of Radiation Dose to Kidneys

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**RISK OF A SECOND KIDNEY CARCINOMA FOLLOWING CHILDHOOD CANCER: ROLE OF  
CHEMOTHERAPY AND OF RADIATION DOSE TO KIDNEYS**

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**Running title:**

KIDNEY CARCINOMA AFTER CHEMOTHERAPY AND RADIOTHERAPY

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**Conflict of interest:**

We declare no conflicts of interest.

**Key words:**

Childhood cancer, radiotherapy, chemotherapy, kidney carcinoma (KC), radiation doses.

## ABSTRACT

**BACKGROUND:** Kidney carcinoma (KC) is a rare second malignant carcinoma following childhood cancer.

**METHODS:** In order to quantify the risk of KC following childhood cancer treatment, and to assess its risk factors, we followed over 27 years on average, a cohort of 4,350 5-year childhood cancer survivors treated between 1943 and 1985, in France and UK. Radiation dose received to the two kidneys during radiotherapy was estimated with dedicated software whatever the site of the childhood cancer.

**RESULTS:** Thirteen patients had developed a KC. The cumulative incidence of KC was 0.62% (95%CI: 0.27% - 1.45%), 40 years after diagnosis, i.e. 13.3-fold higher (95%CI: 7.1-22.3) than that expected in the general population. The absolute excess risk strongly increased ( $p < 0.0001$ ) with longer duration of follow-up. Compared to the general population, the incidence of KC was 5.7-fold higher (95%CI: 1.4-14.7) if no radiation therapy or less than 1 Gy had been absorbed by the kidney, but 66.3-fold higher (95%CI: 23.8-142.5) if the radiation dose to the kidneys was between 10 and 19 Gy, and 14.5-fold greater (95%CI: 0.8-63.9) for higher radiation doses to the kidney. Treatment with chemotherapy increased the risk of KC (RR=5.1, 95%CI: 1.1-22.7), but we were not able to identify a specific drug or drug category responsive for this increase.

**CONCLUSIONS:** Moderate radiation dose to the kidneys during childhood cancer treatment increased the risk of a second KC whose incidence will be on the increase when childhood cancer survivors reach old ages.

## INTRODUCTION

Survival after childhood cancer has strongly increased since the 1970s with 5-year survival rates now approaching 80%. Second primary cancers are among the most serious late effects of chemotherapy and radiation therapy and are an increasing concern regarding childhood cancer survivors [1,2,3,4].

Although genito-urinary cancers as a whole have been addressed in some large cohort studies [1,2,3,4], to date very few studies have investigated kidney carcinoma (KC) as a specific issue after childhood cancer [5,6,7]. The main explanation is that KC as a second malignancy following childhood cancer is still very rare, because most of the childhood cancer survivors are still quite young, below 50 years, age at which KC is very rare in the general population—[8].

Recently a publication of the large Childhood Cancer Survivor Study (CCSS) [5] concluded that a radiation dose to kidney of 5 Gy or higher increases the risk of KC by 3.8 (95%CI: 1.6-9.3), and that administration of platinum based chemotherapy increased this risk by 3.5 (95%CI: 1.0-11.2). Because this is, at this time, the only study focused on KC as a second malignancy following childhood cancer, these results had to be confirmed.

We studied the role of the first cancer type, type of treatment, and radiation dose absorbed by the kidney during radiation therapy on the risk of a second KC following childhood cancer treatment.

**MATERIAL AND METHODS****PATIENTS**

A retrospective cohort of children treated in 8 centers in France and the UK was constituted from 1985 to 1995, comprising patients who were alive 2 (France) or 3 (UK) years after a first solid cancer that was diagnosed before 16 years of age and before 1986. The method of constitution of the cohort has been firstly described in 1995 [9]. In this first publication, the cohort included 4,567 patients. From 1995 to 2009, some French patients have been excluded because of diagnostic errors and duplicate entries, and some others have been added, who were initially missed because some medical records were not available at time of initial cohort constitution, but were discovered during a systematic investigation in Gustave Roussy Institute archives performed afterward. The final database includes 4,649 patients, of whom 4,389 were five -year survivors.

Of these 4,389 patients, 39 patients who had undergone a bilateral nephrectomy ( $n=39$ ) were excluded from the analysis. The 4,350 (3,133 treated in France) remaining patients were included in the present study (Table 1).

The follow-up of the 3,133 French patients was initially assessed using the medical records from treatment centers, and later via a self-completed questionnaire sent from September 2005. This questionnaire based on that of the Childhood Cancer Survivor Study (CCSS) [10], provided information on the health outcomes. A total of 2,455 patients were still alive and therefore considered eligible for the questionnaire. This was sent by regular mail to the 2,105 patients for whom the most recent address was obtained and who had returned a signed consent agreement. A total of 1,920 (74% of 2,455) patients returned the completed questionnaire by December 31, 2012.

The 1,217 UK patients were monitored for the occurrence of KC and death using the National Health Service Central Registers [11, 12].

**RADIATION DOSIMETRY**

The radiation dose was estimated in the center for each of the two kidneys for each patient who had received radiation therapy. The doses to most of the other anatomical sites including the spleen, and gonads were also estimated. The Dos\_EG software was developed for these calculations [13,14]. The mean dose of radiation absorbed by the kidney was 8.6 Gy, the median value being 1.5 Gy (range: 0 to 66.2) (Figure 1).

## CHEMOTHERAPY

Drugs were pooled into 6 classes according to their known mechanisms of action within the cell: Anthracyclines, alkylating agents, epipodophyllotoxins, antimetabolites, Vinca alkaloids and other drugs. The cumulative dose of each cytotoxic drug was recorded. For alkylating agents, we computed the cyclophosphamide dose equivalent score for toxicity proposed by Green et al [15].

## STATISTICAL METHODS

We used estimates of the French national cancer incidence rates as reference rates for patients treated in French centers [16] and the UK-national cancer incidence rates for those treated in the UK [11]. The standardized incidence ratio (SIR), calculated as the ratio of the observed number of KCs to the expected number, was assessed statistically by considering that the observed number follows a Poisson distribution [16]. The absolute excess risk (AER) was calculated as the difference between the observed and expected number of KCs divided by the number of person-years of follow-up.

As the two kidneys of a given child may have received very different radiation doses during radiation therapy, we performed analyses of the relationship between the radiation dose absorbed by the kidney and the risk of KC using the kidney as the statistical unit. So, in these analyses, each patient counts for two kidneys, except the 877 patients who had a unilateral nephrectomy who only count for their remaining kidney.

An internal analysis was conducted using clustered Cox's proportional hazard regression model for aggregated data, in order to take into account the lack of independence between the two kidneys of the same subject [17].

In order to evaluate the dose-effect relationship between the kidney radiation dose and the risk of KC, we tested linear (1) and linear exponential (2) models by comparing nested models [18].

1. Linear = Relative Risk = Cst.  $[1 + \alpha \text{ dose}]$

2. Linear exponential Relative Risk = Cst.  $[1 + \alpha \text{ dose} \times \exp(\beta \text{ dose})]$

Cst = constant;  $\alpha, \beta$  = coefficients ; dose = kidney radiation dose

The DATAB and AMFIT modules of the EPICURE statistical software package were used for the analyses [19].



## RESULTS

From 12 to 52 years after the first cancer, 13 patients had developed a KC, six of which were on the left side and seven on the right side. Ten were renal cell carcinoma, two were papillary renal cell carcinoma and one was a chromophobe renal cell carcinoma. Of these 13 patients, 11 had returned the self-questionnaire, the other KC having been identified from clinical medical records.

The cumulative incidence of KC was 0.05% (95CI: 0.01%-0.21%) 20 years after the 1st cancer diagnosis, 0.20% (95CI: 0.09%-0.45%) 30 years after, and 0.60% (95CI: 0.27%-1.38%) 40 years after the diagnosis. This incidence was 13.4-fold higher (95%CI: 7.5-22.2) than expected in the general population (Table II), this ratio remained similar (SIR=15.2, 95%CI: 7.6-26.7) when the analysis was restricted to patients who returned the questionnaire, remained stable during the time since the childhood cancer; whereas the Absolute Excess Risk (AER) strongly increased ( $p<0.0001$ ) with increased duration of follow-up (Table II). Adjusting or not on other risk factors, KC risk increased with kidney radiation dose up to 10-19.9 Gy, and decreased or plateaued for higher doses (Table II). Figure 2 shows the cumulative incidence of KC by time since childhood cancer according to the kidney radiation dose.

When modeling these variations, a model including a linear term plus a negative exponential term, fitted the data significantly more adequately ( $p=0.03$ ) than a purely linear model. In this linear-exponential model, the linear dose coefficient was 1.1 (95%CI: 0.1- 9.8) (Figure 3).

Age at childhood cancer diagnosis did not significantly modify risk of KC nor radiation dose response ( $p=0.2$ ). No significant difference in radiation sensitivity, as measured by the linear term, was observed according to gender ( $p>0.5$ ), nor to the length of follow-up ( $p>0.5$ ).

Chemotherapy was significant risk factor ( $p=0.01$ ) for KC (RR=5.1, 95%CI: 1.1-22.7), but we were not able to identify any chemotherapeutic drug or drug category specifically

associated with an increased risk of KC. Due to the small number of KC cases, it was not possible to study the role of chemotherapy as a dose-response modifier for radiation. We failed to evidence an increased risk associated to cisplatin (282 survivors, 1 KC) or to cyclophosphamide administration (1579 survivors, 6 KCs).

Of the 13 KCs, four had occurred after nephroblastoma as a first cancer (RR=3.3, 95%CI: 1.0-18.3), but this over risk disappeared when adjusting for chemotherapy, radiation dose to the kidney, year of treatment, sex and age at first cancer (table IIII).

Of the 829 patients treated for a nephroblastoma, 18 had not undergone a nephrectomy of whom one had developed a second KC, 395 had undergone a right nephrectomy and 416 a left nephrectomy, among whom, respectively, two, and one later developed a second KC on the remaining kidney.

## DISCUSSION

Based on a cohort of 4,350 5-year survivors of childhood cancer followed up for an average of 27 years and 13 second KCs, this study showed that the main risk factor for a second KC is the radiation dose to kidneys, the risk increasing with increasing moderate doses but the trend seems to decrease at higher doses. As compared to that expected in the general population, the SIR of KC remained quite stable during the follow-up, but the annual excess incidence strongly increased with increasing follow-up. We identified a significant increase in the risk associated with chemotherapy, but we were unable to identify any specific drug associated with an increased risk.

Despite the relatively large size of the cohort and the long duration of the follow-up, the main limitation of our study is the small number of KCs, 13 cases, which strongly limits the analysis of risk factors.

Overall, the incidence of KC was 13.5-fold (95%CI: 7.4 to 22.2) higher in our cohort than that expected from the general French and UK population incidence rates. This ratio

is higher to that observed in the CCSS, SIR=8.0 (95%CI: 5.2-11.4) [5], but close to the one observed in the BCCSS, SIR=10.6 (95%CI: 5.5 to 20.4) [1].

We observed an increase in the risk of KC with increasing kidney radiation doses, up to 10 to 19.9 Gy (RR = 13.8, 95% CI 3.1-60.9), and a decrease for higher doses. For low doses and moderate doses, up to a tenth of a Gray, each Gray to the kidney increased the risk of KC by a factor 1.1 (95%CI: 0.1 to 9.8). Overall, our result is in agreement with the relative risk of 3.8 (95%CI 1.6-9.3) for radiation to kidney of 5 Gy or higher evidenced in the CCSS [5].

The shape of the dose-response pattern we evidenced for KC following radiation exposure is consistent with the cell-killing hypothesis proposed by Louis Gray in 1964 [20] and resembles findings for Thyroid cancer [21]. By contrast, results of two studies of breast [212] and lung cancer [213] after Hodgkin's lymphoma showed that second-cancer risks for both sites were linear over a wide range of radiation doses. The highest doses to the breast and lung exceeded 40 Gy and 30 Gy, respectively—i.e., within the range that we observed the fall in risk of KC. However, small numbers of patients who received low doses might have diminished the ability to detect a risk reduction at doses more than 30 Gy [212-23]. We presumed that the presence of these conditions in many of the patients who received high doses of radiation indicated that cells in the thyroid and kidney tissues were killed or that the surviving cells had lost their capacity to proliferate.

However, larger studies are needed to increase confidence in the shape of the dose-response curve.

If confirmed in analyses including more patients, the clinical implications of our finding is that radiation doses of 2-5 Gy delivered to a large volume of healthy tissue during intensity-modulated radiation therapy (IMRT) would be as carcinogenic for kidneys as the ones of 40 Gy or higher received when included or very near the target radiation therapy volume.

The magnitude of the excess risk we found for low and moderate radiation doses appears to be that evidenced in Hiroshima-Nagasaki survivors, in whom an ERR/Sv = 2.82 (90% CI: 0.45-8.89) [24]. This may probably be attributed to dose fractionation.

In our cohort, chemotherapy was associated with an increase in KC, but we were unable to identify any specific drug or drug category responsible for this increase, and did not confirm neither the specific role of cisplatin exposure (RR = 3.5, 95%CI: 1.0- 11.2) observed in the CCSS [5], nor the one of cyclophosphamide evidenced in a study of NHL survivors [25]. In fact, until now, the total number of second KCs observed in the main childhood cancer cohorts, including the CCSS (n=26), is certainly too small to investigate the role of a specific type of drugs.

Another important finding was the stability of the SIR compared to the incidence in the general population, during the follow-up since the childhood cancer (and therefore with attained age), even when adjusted on the kidney radiation dose. Due to the strong increase in KC with increasing age in the general population aged 50 years or more, the stability of the SIR in childhood cancer survivors will, as a consequence, shows a strong increase in the incidence of KC in childhood cancer survivors when they get older. This is what has been observed in the large scale Nordic Childhood Cancer Research Group cohort, in which KC was not specifically investigated, but in which urinary system cancer accounted for 2% of all second malignancies during the first 15 years of follow-up, but 60 years later, the figure had attained 10% [26].

Some authors suggested a genetic predisposition of neuroblastoma to the subsequent development of KC [27]. We were unable to confirm or to refute this result, but the small number of KCs in our study strongly limited our power to identify such a predisposition.

The findings in this paper may not be generalizable for children diagnosed after 1986. Further analyses have to be conducted on the extended French cohort, which includes 5-year survivors diagnosed from 1986 to 2000. That allows us to study a new radiotherapy

strategies such as IMRT and proton-therapy and also to study the risk related to the increasing in utility of the platinum-based agents as well as the introduction of the new chemotherapy agents.

As treatment-related complications may occur many years after radiotherapy, our findings support lifetime medical surveillance and screening for potential KC. We believe that ultrasound, computed tomography scanning and magnetic resonance imaging are the best available tools to screening for potential KC.

In conclusion, KC incidence will increase in the future in childhood cancer populations, because in our cohort, the ratio between expected and observed number of KC is constant during follow-up and the expected number will strongly increase when survivors will be older. The increase in risk of KC is similar after moderate kidney radiation dose (2-5 Gy) to the risk after high radiation doses. Chemotherapy increases KC risk, but we were not able to identify a specific drug responsive for this increase. Lastly urologists should inquire into the antecedents of their oncology patients and to stay informed that a history of chemotherapy or of radiation therapy is a risk factor for KC.

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## FIGURES LEGEND

FIGURE 1: Average radiation dose to kidneys in Wilms tumor survivors and in survivors in survivors from other cancer types.

FIGURE 2: Cumulative Kidney carcinoma incidence according to the kidney radiation dose, and expected incidence in the cohort, according to UK and French cancer registries.

FIGURE 3: Kidney carcinoma risk by radiation dose to kidney.

Linear dose-response model for relative risk calculated as:  $1+0.20(\text{dose})$ .

Linear-exponential dose-response model for relative risk calculated as  $1+(1.1\text{dose}) e^{(-0.067\text{dose})}$ . Vertical lines=95% CIs for RR.

Table I : General characteristics of the 4,350 5-years survivors from a childhood cancer.

|  | Secondary kidney<br>carcinoma (n=13) | No secondary<br>kidney carcinoma<br>(n=4337) |
|--|--------------------------------------|--|
| Years of treatment : mean (range)        | 1970 (1951-<br>1984)                 | 1974 (1942-1986)                             |
| Country of treatment : France / UK       | 12/1                                 | 3,121 / 1,216                                |
| Age at diagnosis in years : mean (range) | 6 (0-13)                             | 6 (0-16)                                     |
| Sex : males / females                    | 7 / 6                                | 2,405 / 1,932                                |
| 1 <sup>st</sup> cancer treatment n       |                                      |  |
| No Ct no Rt                              | -                                    | 432  |
| Rt no Ct                                 | 2                                    | 966  |
| Ct no Rt                                 | 2                                    | 927  |
| Rt & Ct                                  | 9                                    | 2012   |
| Mean follow-up in years (range)          | 27 (5-64)                            | 27 (5-64)                                    |

Table II: Kidney carcinoma risk according to the radiation dose to the kidney in a cohort of 4,350 5-year childhood cancer survivors.

|                                 | Patients | Observed /<br>Expected*<br>Kidneys<br>cancers | Standardized<br>Incidence Ratio<br>(95%CI) | Absolute Excess<br>Risk (AER) per<br>100.000 people per<br>year (95%CI) | Relative Risk<br>(95%CI)** |
|---------------------------------|----------|---|--|---|----------------------------|
| All cohort                      | 4,350    | 13 / 0.97                                     | 13.5 (7.4-22.2)                            | 7.9 (3.4-14.8)  | -                          |
| Years after childhood<br>cancer |          |   |  |   |                            |
| 5-19                            | 4,350    | 2 / 0.28                                      | 7.1 (1.2-21.9)                             | 2.3 (0.2-7.6)   | -                          |
| 20-29                           | 3,308    | 4 / 0.23                                      | 18.7 (5.8-43.3)                            | 14.4 (3.8-34.7)   | -                          |
| 30-39                           | 1,592    | 3 / 0.27                                      | 11.4 (2.8-29.6)                            | 27.0 (4.8-74.3)   | -                          |
| 40+                             | 519      | 4 / 0.19                                      | 21.6 (6.7-50.1)                            | 107.8 (24.1-269.4)  | -                          |
| Attained age                    |          |   |  |   |                            |
| 5-29                            | 4,350    | 3 / 0.33                                      | 9.1 (2.3-23.5)                             | 3.3 (0.7-8.9)   | -                          |
| 30-39                           | 2,693    | 5 / 0.22                                      | 22.8 (8.2-49.0)                            | 29.4 (9.6-64.8)   | -                          |
| 40-49                           | 1,189    | 3 / 0.27                                      | 11.1 (2.8-28.8)                            | 38.5 (3.6-113.0)  | -                          |

|  |       |           |                   |                   |                 |
|--|-------|-----------|-------------------|-------------------|-----------------|
| 50+                                      | 324   | 2 / 0.15  | 13.7 (2.3-42.4)   | 76.7 (13.4-440.7) | -               |
| Gender                                   |       |           |                   |                   |                 |
| Male                                     | 2412  | 7 / 0.60  | 11.8 (5.0-22.7)   | 6.5 (1.4-16.6)    | 1 (ref)         |
| Female                                   | 1938  | 6 / 0.37  | 16.2 (6.4-32.8)   | 10.1 (3.1-22.3)   | 0.9 (0.3-3.0)   |
| Chemotherapy                             |       |           |                   |                   |                 |
| No                                       | 1,400 | 2 / 0.43  | 4.6 (0.8-14.3)    | 4.6 (0.8-14.3)    | 1 (ref)         |
| Yes                                      | 2,950 | 11 / 0.54 | 20.6 (10.7-35.2)  | 14.6 (0.8-25.0)   | 5.1 (1.1-22.7)  |
| Average Kidney radiation dose (in grays) |       |           |                   |                   |                 |
| No Rt or < 1 Gy                          | 2,764 | 3 / 0.56  | 5.3 (1.3-13.8)    | 4.0 (1.0-10.5)    | 1 (ref)         |
| 1 to 4.9 Gy                              | 316   | 1 / 0.13  | 7.6 (0.4-33.5)    | 7.0 (0.4-30.9)    | 1.7 (0.2-17.4)  |
| 5 to 9.9 Gy                              | 203   | 2 / 0.09  | 22.2 (3.5-65.8)   | 19.9 (3.3-61.5)   | 5.3 (0.9-32.0)  |
| 10 to 19.9 Gy                            | 548   | 5 / 0.08  | 66.6 (23.2-138.8) | 47.7 (17.1-102.5) | 13.8 (3.1-60.9) |
| 20 Gy or more                            | 519   | 2 / 0.07  | 27.3 (4.5-84.3)   | 22.5 (3.7-69.5)   | 4.7 (0.7-31.8)  |

\* Expected number of kidney carcinoma in the cohort, from the incidence in French and UK population

\*\* Relative risk in a Cox proportional hazard model with clustering in order to take into account the fact that each patient has 2 kidneys, adjusted on gender, date and age of diagnosis, and chemotherapy.

Table III : Kidney carcinoma according to the type of first cancer, in a cohort of 4,350 5-year childhood solid cancer survivors patients, of whom 2,989 had received external beam radiation therapy.

| First cancer type             | Cases / Patients | Radiation therapy (%) | Kidney radiation dose: mean, median (range) | Absolute Excess of Risk per 100.000 people per year (95%CI) | Standardized Incidence Ratio (95%CI)* | Relative Risk (95%CI)** |
|-------------------------------|------------------|-----------------------|---|---|---------------------------------------|-------------------------|
| Nephroblastoma                | 4/829            | 73                    | 13.9, 14.6 (0.3-57.7)                       | 13.9 (2.5-36.6)   | 22.3 (6.3-51.7)                       | 1.5 (0.3-8.4)           |
| Neuroblastoma                 | 2/580            | 55                    | 5.5, 0.1 (0-48.4)                           | 12.9 (0.0-40.1)   | 19.4 (3.2 -59.9)                      | 1.5 (0.1-18.0)          |
| Gonadal tumor                 | 1/233            | 39                    | 5.3, 0.0 (0.1 - 44.8)                       | 15.2 (0.0-72.0)   | 17.4 (1.0-76.6)                       | 1.5 (0.2-11.1)          |
| Other 1 <sup>st</sup> cancers | 6/2708           | 72                    | 3.5, 0.1 (0 - 57.1)                         | 5.1 (0.6-3.0)   | 9.9 (3.4-20.1)                        | 1 (ref)*                |

\* As compared to the incidence in French and UK general population

\*\* Relative risk in a Cox proportional hazard model with clustering in order to take into account the fact that each patient has 2 kidneys, adjusted on gender, date and age of diagnosis, and chemotherapy.

Figure 1

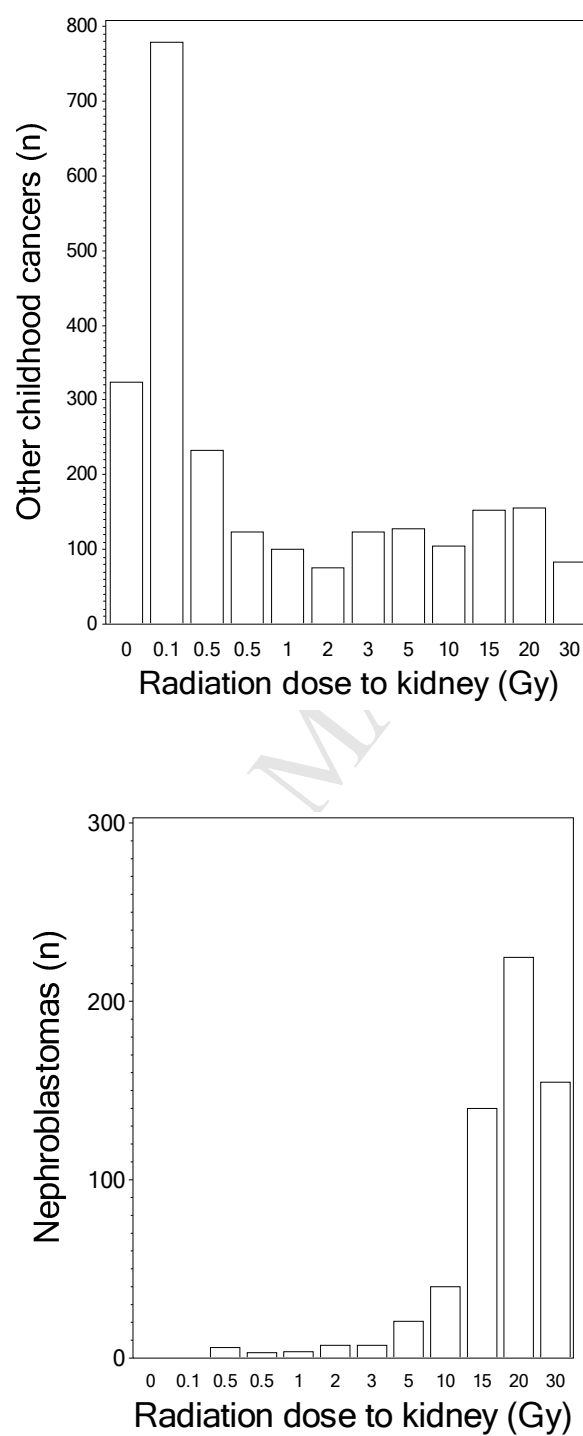


Figure 2

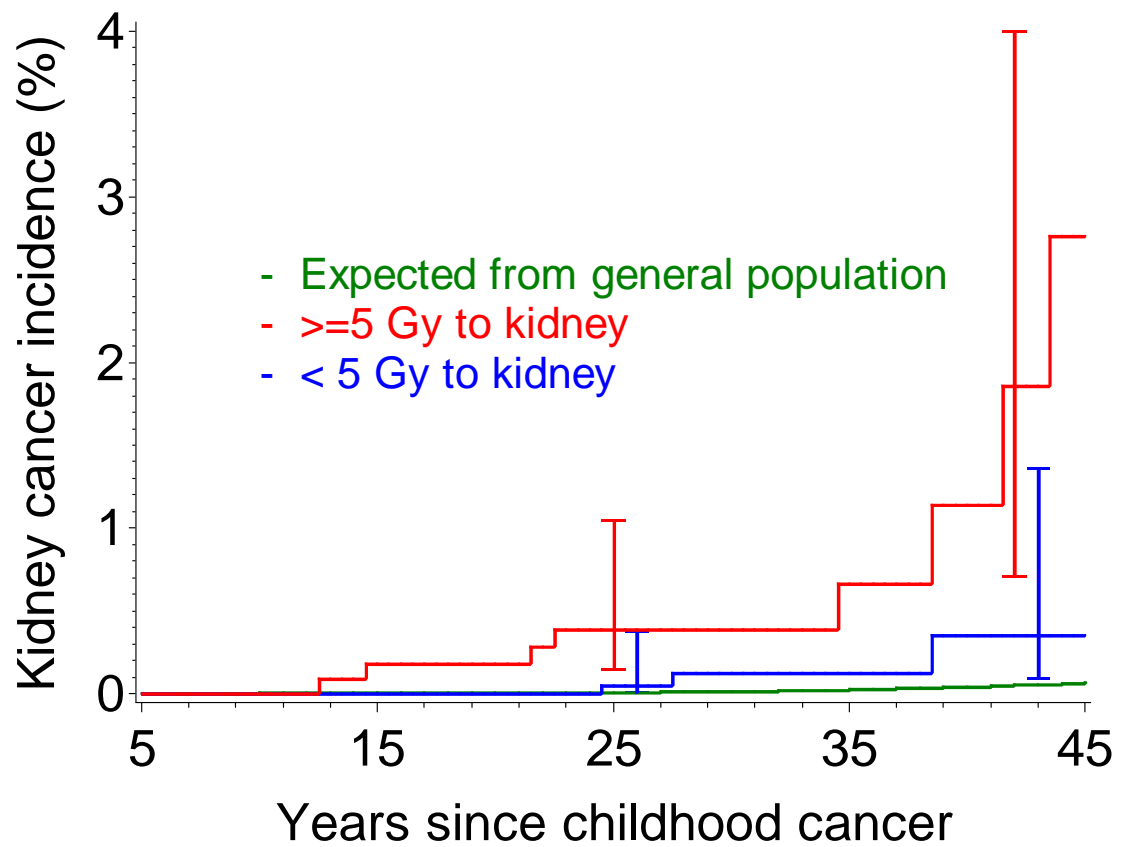
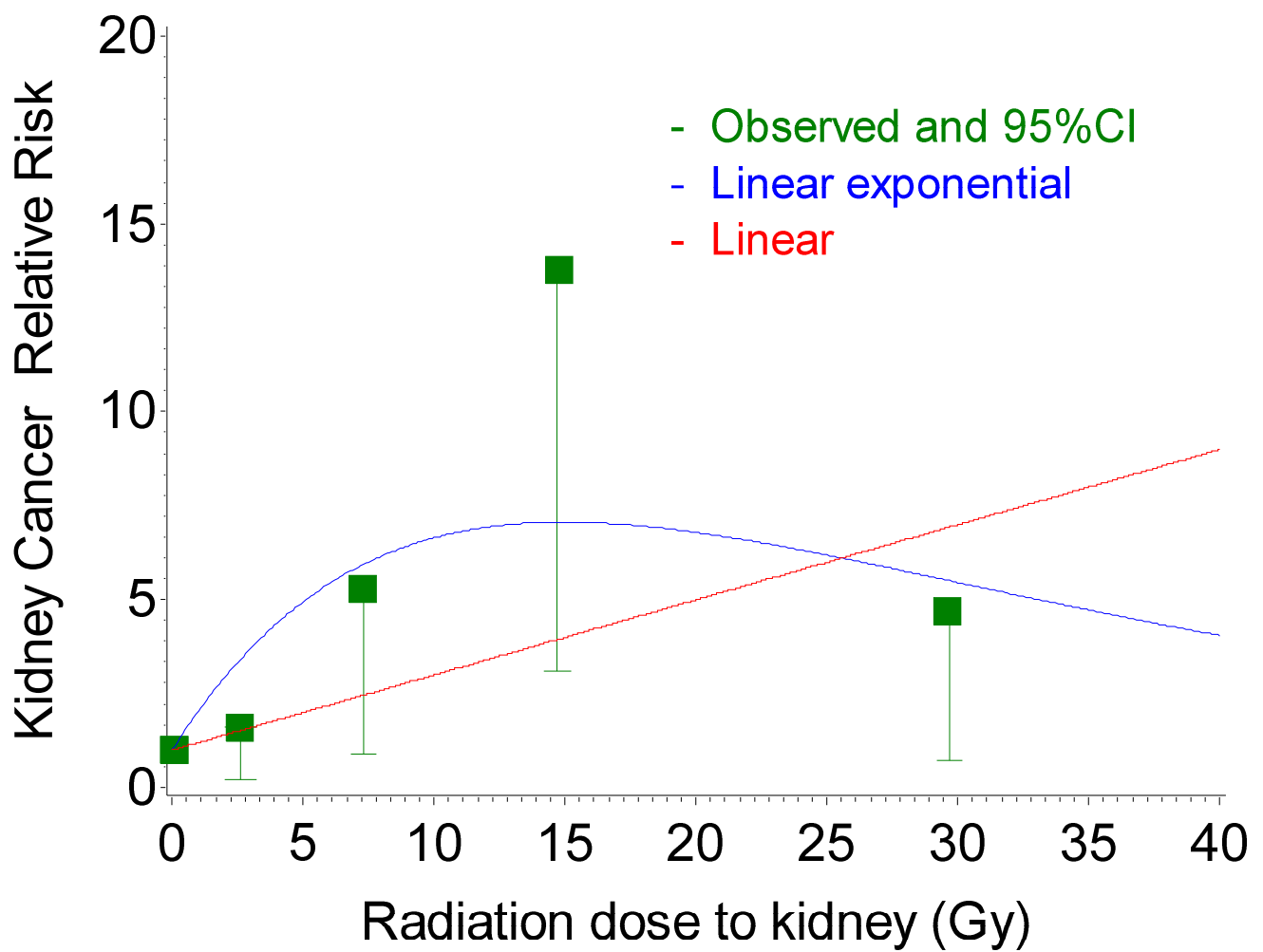




Figure 3



**KC:** Kidney Carcinoma

**CI:** Confidence Interval

**SIR:** Standardized Incidence Ratio

**CCSS:** Childhood Cancer Survivor Study

**Cst:** Constant

**Gy:** Gray