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Radiation Risks for the Incidence of Kidney, Bladder and Other Urinary Tract Cancers: 1958–2009

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As part of the recent series of articles to create a comprehensive description of the radiation risks of solid cancer incidence after ionizing radiation exposure, based on the atomic bomb survivors' Life Span Study (LSS), this work focuses on the risks of urinary tract cancer (UTC) and kidney cancer. Analyses covered a 52-year period of follow-up, through 2009, among 105,444 eligible survivors who were alive and cancer free in 1958. This represents an additional 11 years of follow-up since the last comprehensive report, with a total of 3,079,502 person-years. We observed 790 UTC and 218 kidney cancer cases. Adjusted for smoking, there was a strong linear radiation dose response for UTC. The sex-averaged excess relative risk per 1 Gy (ERR/Gy) was 1.4 (95% confidence interval, CI: 0.82 to 2.1). Both males and females showed significantly increased ERRs/Gy with female point estimates at a factor of 3.4 (95% CI: 1.4 to 8.6) greater than male estimates. UTC radiation risks were largely unmodified by age at exposure or attained age. The attributable fraction of UTC to radiation exposure was approximately 18% while that attributed to smoking was 48%. Kidney cancer showed an increased ERR due to smoking (0.56 per 50 pack-years; 95% CI –0.007 to 1.6; $P = 0.054$), but we did not observe any strong associations of kidney cancer with radiation exposure, although sex-specific dose responses were found to be statistically different.

INTRODUCTION

As part of the recent series of articles to create a comprehensive description of the radiation risks of solid cancer incidence based on the atomic bomb survivors' Life Span Study (LSS), this work focuses on the risk of urinary tract cancer (UTC) and kidney cancer due to ionizing radiation exposure among the atomic bomb survivors over the period 1958–2009. Previously published analyses have reported on the risks of solid cancers in aggregate and others have reported radiation risks for various organs or organ systems (*1–8*).

Urinary tract cancers, which include those occurring in the renal pelvis, are mostly transitional cell carcinomas and are known to be associated with cigarette smoking as well as exposure to other chemical carcinogens such as polyaromatic hydrocarbons and dyes (*9*). Most UTC occur in the bladder or renal pelvis (*10*). Kidney cancer (excluding the renal pelvis) develops in the kidney parenchyma and does not have strong known risk factors, but tobacco use, high blood pressure and obesity have all been reported as risk factors (*11*). Overall, kidney cancers accounted for approximately 2% of new cancers in Japan in 2000 (*12*). Japanese incidence rates of kidney cancer (excluding the renal pelvis) have been increasing in Japan (*13, 14*). However, the latest research indicates that trends for premature mortality due to malignancies of the kidney and bladder are improving (*15*).

Several previously reported studies from the LSS cohort have focused on the urinary tract and kidney cancer incidence using various outcome definitions. Thompson *et al*. (*16*) reported increased excess relative risk per Gy (ERR/Gy) for the bladder cancer [1.0; 95% confidence interval (CI): 0.27 to 2.1]. They also reported an estimate for the bladder, kidney, renal pelvis and ureter, and other urinary cancers in aggregate (ERR = 1.2; 95% CI: 0.62 to 2.1). Their study utilized the DS86 dosimetry system with follow-up for 1958–1987. Preston *et al*. (*17*) reported the sex-averaged ERR of bladder cancer as 1.23/Gy (90% CI: 0.59 to 2.1). They reported an ERR/Gy for kidney cancer (excluding cancers of the renal pelvis) of 0.13 (90% CI: –0.25 to 0.75). As an alternative, they used a sex-averaged, time-constant excess absolute risk model and reported a statistically significant increased risk of 0.25 excess cases/

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10,000 person-year-Gy ($P = 0.002$). In their work, Preston *et al*. utilized the DS02 dosimetry system with follow-up for 1958–1998. Over the same follow-up period, Richardson *et al*. reported strong radiation risks of the renal pelvis and ureter but non-significant radiation risks over all ages for kidney cancer in 2010 (*18*). However, they did note that in those with attained ages less than 55 years, a significant risk was observed for kidney cancer. In 2012, Grant *et al*. (*19*) reported on the radiation risks of urothelial carcinomas for the period 1958–2001. Cases included transitional cell carcinomas of the renal pelvis, ureter and bladder. Using DS02, they reported the sex-averaged ERR for urothelial carcinoma as 1.00 (95% CI: 0.43 to 1.78). The radiation risk changed little after adjusting for lifestyle factors, although a strong association with cigarette smoking was noted.

As in previous LSS analyses, we analyzed the radiation risks for the two groups of cancers defined by topography: 1. urinary tract cancer (''UTC'', i.e., urinary organs and renal pelvis); and 2. kidney cancer (all kidney excluding the renal pelvis). The purpose of this study was to update the radiation risk estimates using the most recent data for UTC and kidney cancer while adjusting for exposure to cigarette smoking to accompany the recent series of organ-specific risk estimates.

METHODS

This analysis used the same cohort and methods as reported in the literature on this solid cancer incidence series with follow-up through 2009. Please see Grant *et al*. (*1*), for a more complete description. Briefly, cancer incidence data were collected systematically in the Life Span Study of atomic bomb survivors using population-based cancer registries in Hiroshima and Nagasaki since 1958. The LSS consists of proximal survivors who responded to the 1950 Japanese national census and were residents of Hiroshima or Nagasaki at the time of census; additional distal survivors and persons who were not in city (NIC) at the time of the bombing were matched to proximal survivors on city, age and sex. After exclusion of those with known malignancies or death prior to 1958, and those without dose estimates, 105,444 subjects were eligible for analysis, including 42,910 males (41%) and 62,534 females (59%).

Cases were defined for separate analyses as the first primary malignant cancer of either the urinary tract, or the kidney (excluding the renal pelvis). UTC included the renal pelvis [International Classification of Disease (ICD) code C65], the ureter (C66), urinary bladder (C67) and urinary cancer ''not otherwise specified'' (NOS, C68). Cancers of the kidney (excluding the renal pelvis) were defined as cases with ICD code C64.

The primary exposure was RBE-weighted absorbed bladder dose (gamma plus 10*neutron) from the DS02 dosimetry system (*20*) with DS02R1 dose updates based on improved location data and shielding information (*21*). A neutron weight of 10 was consistent with previously reported studies (*1, 17, 22*). Doses were adjusted to allow for random errors (*23*) and truncated at 4 Gy. The 4 Gy dose is an arbitrary cut-off for assigned doses that are considered unrealistically high to be compatible with survival. Smoking data were collected by a series of clinical interviews and mail surveys [see Grant *et al*. for a more thorough description (*1*)]. All persons started with an ''unknown'' status of smoking. At the time smoking status became known, their cumulative pack-years-of-smoking value was calculated and was allowed to increase until they reported they had quit smoking.

We used Poisson regression models. Strata for the person-year table included city, sex, age at exposure (15 categories), attained age (18 categories), calendar year (13 categories), radiation dose (24 categories), smoking status (4 categories), smoking intensity (8 categories), smoking duration (7 categories) and a high-dose category for those with more than 4 Gy of shielded kerma exposure (as these doses may have unusually large errors). Radiation risk estimates were adjusted for cumulative pack-years of smoking. A multiplicative ERR model was used to model the observed rate of cancer incidence:

$$\lambda = \lambda_{background} * (1 + ERR_{radiation}) * (1 + ERR_{smoke}), \qquad (1)$$

where λ was the rate of cancer incidence and $\lambda_{background}$ was the cancer incidence rate for those not exposed to radiation and non-smokers. The background rates were modeled as sex-specific quadratic splines in log attained age with sex-specific log-linear trends in year of birth, which is co-linear with age at exposure as cohort members were exposed simultaneously. The baseline rate model included city specific effects for the NIC group so that all zero-dose survivors were included in the reference group (*24*). The background function was parameterized as:

$$\exp\left(\alpha_s + \gamma_s \ln\left(\frac{a}{70}\right) + \epsilon_s \ln^2\left(\frac{a}{70}\right) + \left[\eta_s \ln^2\left(\frac{a}{70}\right)\right]_{a>70} + \nu\left(\frac{byr - 1915}{10}\right) + \rho city * NIC\right). \qquad (2)$$

The ERR function for radiation exposure was modeled as a linear function (β_{1s}) with effect modification by attained age and age at exposure; the $ERR_{radiation}$ term was parameterized as:

$$\beta_{1s} d \exp\left(\delta_1 \ln\left(\frac{a}{70}\right) + \delta_2\left(\frac{e - 30}{10}\right) + [\phi I]_{d>4}\right), \qquad (3)$$

where all ''s'' subscripts indicate sex-specific parameters, ''a'' is attained age in years, *byr* is birth year, *NIC* is a ''not in city'' indicator, d is weighted absorbed dose in Gy, e is age at exposure in years, and I is an indicator for shielded kerma dose greater than 4 Gy. This indicator of a truncated dose allows the inclusion of the very proximal (high-dose) survivors who are particularly important for assessing the effect modifiers. Different parameterizations with the same numbers of terms allow for estimates of sex-averaged (i.e., the unweighted average of the male and female estimates) risks as well as the female-to-male ERR ratio. We also tested departure from linearity by including a quadratic dose term ($\beta_{1s} d + \beta_{2s} d^2$). Risk estimates were centered at an attained age of 70 years and an age at exposure of 30 years.

The ERR function for smoking (ERR_{smoke}) was parameterized as:

$$\left(\gamma \frac{packyears}{50} + Unk_{male}\right) \exp\left(\theta_1 \ln\left(\frac{cpd + 1}{20}\right) + \theta_2 \ln\left(\frac{smkdur + 1}{50}\right)\right), \qquad (4)$$

where *packyears* is the cumulative pack-years of smoking (i.e. time dependent), Unk_{male} is an indicator for unknown male smoking status, *cpd* is cigarettes per day, and *smkdur* is the duration of smoking in years (time dependent). Thus, γ is the ERR for smoking 50 pack-years and allows modification by smoking intensity and duration.

The excess absolute rates (EAR) of incident cancers were estimated using an EAR model as in Grant *et al*.

$$\lambda = \lambda_{background} + ERR_{radiation} + ERR_{smoke}. \qquad (5)$$

Briefly, baseline and radiation terms were parameterized as above while a richer parameterization for the age effects of smoking was included. For a more complete description, please see Grant *et al*. (*1*).

All confidence intervals (two-sided, 95% CI) were based on profile likelihood analyses. Using the ERR model, numbers of excess cases attributable to radiation and smoking were estimated for each strata by taking the difference between the estimated total number of cases and

the estimated number of background cases. From these values, the attributable fractions (AF) were calculated. Nested models were compared using a likelihood-ratio test (LRT). Statistical analyses were performed using Epicure version 2.0.3 (*25*).

This study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation (RP 1-75: Research plan for RERF Life Span Study of A-bomb survivors, Hiroshima and Nagasaki; RP 18-61: Tumor registry study in Hiroshima and Nagasaki). The Hiroshima and Nagasaki Prefectures and the city of Hiroshima approved linkage to data from the Cancer Registries. Data and analysis scripts are available for download at: http://www.rerf.or.jp.

RESULTS

From 1958 through 2009, there were a total of 3,079,502 person-years of observation. Over that period, we ascertained 790 UTC cases (males = 493; females = 297) with 86% having histological confirmation. UTC cases were primarily (90%) diagnosed with transitional cell morphology (611/790; 77%) or the non-specific ''epithelial'' morphology code (100/790; 13%). The most frequent location of the cancer was in the bladder with nearly 80% of the cases, followed by the renal pelvis, the ureter, and other locations (Table 1). The crude rates for UTC were approximately 3 times higher for men than for women. Incidence rates increased rapidly after about age 60 years and later birth cohorts tended to have higher rates than earlier birth cohorts. Fitted baseline rates are shown in Fig. 1.

The sex-averaged ERR for UTC was 1.4/Gy (95% CI: 0.82 to 2.1). The male ERR for UTC was 0.64/Gy (95% CI: 0.18 to 1.2) while the female ERR estimate was 2.2/Gy (95% CI: 1.2 to 3.5) (see Fig. 2 and Table 2). The female-to-male ERR ratio was 3.4 (95% CI: 1.4 to 8.6). The radiation risk estimates were not dependent on age-at-exposure ($P > 0.50$) nor attained age ($P > 0.50$). There was no evidence of a departure from a linear dose response for the sex-averaged model (LRT = 0.054 on one degree of freedom, $P > 0.5$) nor for males or females when checked separately. A secondary analysis of risks by calendar period showed no appreciable changes by calendar-year of follow-up. Sex-specific EAR point estimates at age 70 years were 4.4 (95% CI: 0.70 to 8.8) and 3.7 (95% CI: 2.0 to 5.8) excess cases per 10,000 person-year-Gy for males and females, respectively.

The sex-averaged ERR for tobacco intake was 1.3/50 pack-years (95% CI: 0.73 to 2.0). Overall, the AF for radiation exposure was 18% among those with >0.005 Gy while the AF for smoking was 48% for ever smokers. Smoking rates in males were much higher than in females, accounting for higher attributable fractions and total numbers of cases due to smoking (Table 3).

The radiation ERR models did not change appreciably in either magnitude or shape when not adjusted for smoking (data not shown). The multiplicative ERR model had a lower deviance than an additive ERR model (5963.7 and 5966.2, respectively). Further testing indicated that the joint effect of radiation and smoking was slightly super-multiplicative but an additive ERR model could not be statistically rejected.

For the non-pelvis region of the kidney (kidney cancer), there were 218 cases observed (118 among males and 100 among females). Incidence rates were approximately twice as high for males and were higher in more recent birth cohorts compared to early birth cohorts (Table 1 and Fig. 3). A sex-averaged, linear dose-response model did not converge. The estimate for the female linear response was 0.62/Gy (95% CI: –0.20 to 2.1; $P = 0.18$) with no evidence for curvature. Exposed males had unexpectedly low incidence rates among those with doses greater than about 100 mGy (see Table 1 and Fig. 4). This sex-specific difference in dose response explains the poor model fit when using a model common to both sexes. A ''U-shaped'' male dose response was significant using a linear-quadratic model (likelihood-ratio test on 2 degrees of freedom = 6.51; $P = 0.041$); the ERR point estimates were –2.1/Gy (linear) and 1.2/Gy^2 (quadratic) with indeterminate confidence intervals. The female dose response differed significantly from the male dose response ($P = 0.04$). Nineteen (9 male) of 118 cases were diagnosed prior to age 55. The most prevalent (specified) morphology was clear cell carcinoma (n = 40; 18%), but for most cases morphology was ''not otherwise specified'' (n = 118; 54%). Testing for an association with cumulative pack-years of smoking using a 1-degree-of-freedom likelihood-ratio test indicated a positive ERR point estimate of 0.56 per 50 pack-years of smoking and a marginal statistical significance (95% CI –0.007 to 1.6; $P = 0.054$).

DISCUSSION

In this prospective cohort analysis of the associations of radiation with UTC and kidney cancer we observed 790 UTC and 218 kidney cancers. Since the last comprehensive cancer incidence analysis in the LSS (*17*), this represents increases of 38% UTC cases and of 30% kidney cancer cases. Other recent analyses of LSS cancer incidence data include Richardson's 2010 analysis of renal parenchyma and the renal pelvis/ureter cancers (*18*), as well as an analysis of urothelial carcinomas (*19*), which focused on transitional cancers of the renal pelvis, ureter, bladder and other urinary tract sites. Despite the varying methods of defining cases, radiation risk estimates were generally consistent across the analyses with strong radiation risks observed for cancers occurring in the urinary tract. Most cancers occurring along the urinary tract were transitional cell carcinomas (accounting for 90% of cases in this analysis) occurring in the bladder (79% of cases). Due to this combination of topology and morphology, it follows that the conclusions across the various analyses were consistent despite minor differences in end points.

The etiologies of UTC and kidney cancer differ substantially. UTC are often associated with occupational and lifestyle exposures while the etiology of kidney cancer

TABLE 1
Counts of Persons, Person-Years, Cases and Crude Rates of Urinary Tract and Kidney Cancer Cases by Sex, City, Age at Exposure, Age and Radiation Dose to the Bladder

			Urinary tract cancer (UTC)						Kidney cancer	
	Count	Person-years	Bladder	Renal pelvis	Ureter	Other	Total	Rate per 10^4	(non-renal pelvis)	Rate per 10^4
Males										
City										
Hiroshima	29,498	807,727	311	30	25	7	373	4.6	86	1.1
Nagasaki	13,412	334,484	100	10	6	4	120	3.6	32	1.0
Age at exposure (years)										
0–19	21,588	727,787	174	32	14	5	225	3.1	67	0.9
20–39	8,525	238,550	113	6	14	4	137	5.7	24	1.0
40–	12,797	175,874	124	2	3	2	131	7.5	27	1.5
Attained age (years)										
<40	23,792	292,692	5	1	0	0	6	0.2	1	0.0
40–	4,889	187,443	8	1	1	0	10	0.5	3	0.2
50–	6,796	229,556	49	5	3	1	58	2.5	15	0.6
60–	5,228	238,161	120	16	9	5	150	6.3	40	1.7
70–	1,874	143,814	150	12	11	3	176	12.2	47	3.3
80–	331	50,545	79	5	7	2	93	18.4	12	2.4
Bladder dose (Gy)										
NIC	10,488	287,802	106	7	6	3	122	4.2	29	1.0
<0.005	14,561	378,373	139	13	5	3	160	4.2	45	1.2
–0.1	11,183	302,425	93	13	7	1	114	3.8	39	1.3
–0.2	2,143	58,151	21	2	3	1	27	4.6	0	0.0
–0.5	2,258	58,609	23	1	5	0	29	5.0	1	0.2
–1	1,293	32,604	14	3	2	1	20	6.1	1	0.3
–2	743	18,555	14	0	3	2	19	10.2	3	1.6
2+	241	5,692	1	1	0	0	2	3.5	0	0.0
Total (males)	42,910	1,142,212	411	40	31	11	493	4.3	118	1.0
Females										
City										
Hiroshima	43,903	1,385,561	163	23	22	7	215	1.6	70	0.5
Nagasaki	18,631	551,730	52	11	9	10	82	1.5	30	0.5
Age at exposure (years)										
0–19	24,199	901,253	45	7	9	4	65	0.7	41	0.5
20–39	21,564	749,970	107	23	17	9	156	2.1	43	0.6
40–	16,771	286,067	63	4	5	4	76	2.7	16	0.6
Attained age (years)										
<40	32,865	353,422	1	0	0	0	1	0.0	2	0.1
40–	10,371	298,868	2	0	0	0	2	0.1	6	0.2
50–	9,841	385,152	18	3	2	3	26	0.7	15	0.4
60–	6,030	413,010	46	5	8	3	62	1.5	38	0.9
70–	2,775	313,337	85	17	11	7	120	3.8	19	0.6
80–	652	173,501	63	9	10	4	86	5.0	20	1.2
Bladder dose (Gy)										
NIC	14,751	473,767	48	5	7	3	63	1.3	21	0.4
<0.005	21,374	652,995	58	13	11	5	87	1.3	34	0.5
–0.1	16,360	506,222	58	7	3	2	70	1.4	25	0.5
–0.2	3,452	105,828	13	1	2	0	16	1.5	7	0.7
–0.5	3,592	108,345	18	4	4	2	28	2.6	6	0.6
–1	1,891	58,029	12	2	2	1	17	2.9	4	0.7
–2	861	24,988	5	0	1	3	9	3.6	3	1.2
2+	253	7,115	3	2	1	1	7	9.8	0	0.0
Total (females)	62,534	1,937,290	215	34	31	17	297	1.5	100	0.5

is less clear. Due to these differences, we conducted separate analyses for UTC and kidney cancer. Overall, UTC was strongly associated with both radiation and smoking while we did not observe any strong associations of kidney cancer with radiation exposure or smoking.

Bladder cancers (and by extension transitional cell cancers) are known to have strong associations with exogenous carcinogens, primarily smoking, in most population-based studies (*26*). In our study, smoking had an attributable fraction of about 48% among current or former smokers, consistent with other reported values (*27*). Despite the strong association of smoking and UTC, ERR estimates for radiation exposure were unchanged with the adjustment for smoking. This is because the LSS cohort was a

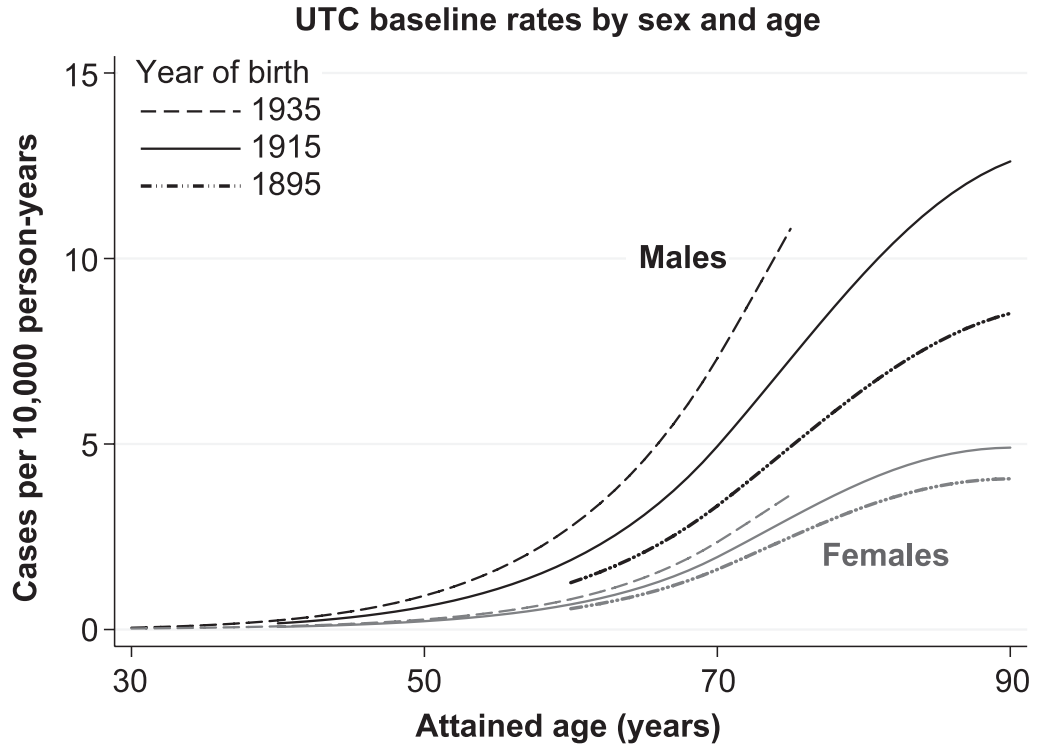

FIG. 1. Background rates of urinary tract cancer (UTC) by attained age, sex and birth cohort.

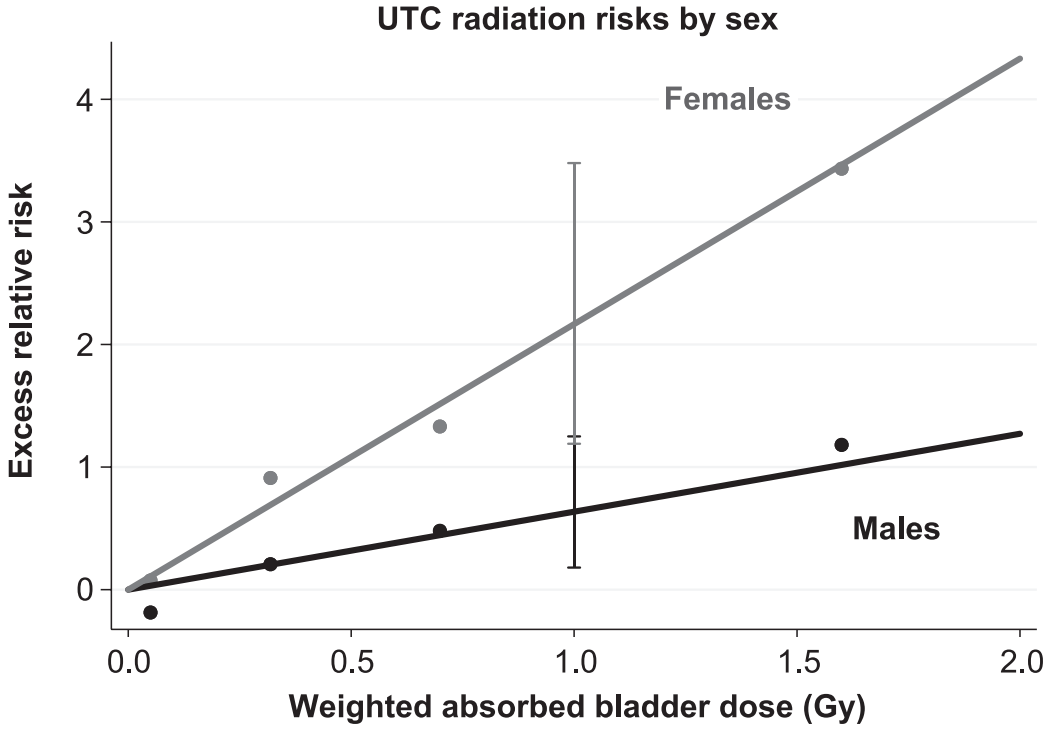

FIG. 2. Excess relative risk (ERR) per Gy of weighted absorbed bladder dose for urinary tract cancer by males and females using a linear dose-response model. Dots show arbitrarily chosen categorical risk estimates. The sex-specific whiskers at 1 Gy exposure are the 95% confidence intervals estimated using the linear ERR models (as shown in Table 2).

TABLE 2

Radiation risk estimates for urinary tract cancer (UTC) with age-related effect modifiers; and UTC risk of smoking	
Radiation risk fitted estimates	
Sex-averaged ERR/Gy (95% CI)	1.4 (0.82 to 2.1)
Male ERR/Gy (95% CI)	0.64 (0.18 to 1.2)
Female ERR/Gy (95% CI)	2.2 (1.2 to 3.5)
F:M ratio (95% CI)	3.4 (1.4 to 8.6)
Age-at-exposure (% change per decade) (CI)	0.067 (–0.23 to 0.45)
Attained age (95% CI) (power)	–0.43 (–2.8 to 2.4)
UTC smoking-related risk	
Smoking ERR/50 pack-years, sex-averaged (95% CI)	1.3 (0.73 to 2.0)

population exposed non-selectively to radiation with little chance for confounding by smoking status (*19, 28*). Our multiplicative model estimated that about 15 cases (attributable fraction = 4%) were due to a joint exposure effect from radiation and smoking. Due to the lack of confounding and lack of a strong joint effect, adjusting for smoking had little effect on our radiation risk estimates.

ERR estimates for UTC showed no strong dependence on either age at exposure or attained age. This is a somewhat unique feature of this organ system as most organs studied in the LSS (and solid cancer incidence risks in aggregate) show strong dependencies on age modifiers. Another exception is lung cancer, which is also highly smoking dependent. Lung cancer does not show a radiation risk dependence on age-at-exposure, although the ERR does decrease with attained age (*2*). While the female-to-male ratio of ERR/Gy estimates for UTC was significantly greater than unity, both sexes experienced excess cases due to radiation exposure. In this study, the EAR point estimates for males and females were approximately equal. Thus, the sex difference in ERR/Gy is a reflection of male-female difference in the background rates. The risk for second primary bladder cancers after radiotherapy for prostate cancers in men and gynecological cancers in women, among other sites, were increased (*29–32*). In the study of aggregate solid cancers in this cohort, significant curvature was observed in the male dose response (*1*). No evidence of curvature was observed in UTC for either sex.

TABLE 3
Attributable Fraction of Urinary Tract Cancer (UTC) by Radiation Dose and Smoking History (Males, Females, Both Sexes Combined)

Dose (Gy)	Cases	Fitted background	Fitted radiation excess	Fitted smoking excess	Radiation attributable fraction	Smoking attributable fraction
Male						
<0.005*	282	161.0	0.1	114.4	0.0%	41.5%
–0.1	114	69.1	2.5	52.7	2.0%	42.4%
–0.2	27	13.7	2.1	11.2	7.9%	41.4%
–0.5	29	13.9	4.9	12.6	15.6%	40.1%
–1.0	20	7.8	6.0	8.3	27.2%	37.4%
–2.0	19	4.3	6.5	6.2	38.2%	36.7%
2+	2	1.1	3.1	2.2	47.9%	34.7%
Total (all)	493	270.9	25.3	207.7	5.0%	41.2%
Total (dose >0.005 Gy)	211	109.9	25.2	93.3	11.0%	40.8%
Total (ever smokers)	308	143.0	17.6	156.5	5.6%	49.3%
Female						
<0.005*	150	140.9	0.2	7.5	0.1%	5.0%
–0.1	70	61.7	4.3	4.6	6.1%	6.6%
–0.2	16	13.4	4.5	1.6	23.1%	8.1%
–0.5	28	13.3	10.1	2.2	39.5%	8.5%
–1	17	6.8	10.9	1.6	56.6%	8.4%
–2	9	2.6	8.3	1.1	68.8%	9.5%
2+	7	0.7	3.9	0.4	78.5%	7.7%
Total (all)	297	239.4	42.2	19.0	14.0%	6.3%
Total (dose >0.005 Gy)	147	98.5	42.0	11.5	27.6%	7.6%
Total (ever smokers)	45	23.1	8.9	19.0	17.5%	37.2%
Both sexes						
<0.005*	432	301.9	0.3	121.9	0.1%	28.7%
–0.1	184	130.8	6.8	57.4	3.5%	29.4%
–0.2	43	27.1	6.6	12.8	14.3%	27.4%
–0.5	57	27.3	15.0	14.8	26.3%	25.9%
–1.0	37	14.6	17.0	9.9	40.9%	23.9%
–2.0	28	6.9	14.8	7.4	50.9%	25.4%
2+	9	1.8	6.9	2.6	61.2%	23.0%
Total (all)	790	510.4	67.4	226.7	8.4%	28.2%
Total (dose >0.005 Gy)	358	208.5	67.2	104.8	17.7%	27.6%
Total (ever smokers)	353	166.1	26.6	175.5	7.2%	47.7%

* Includes Not In City subjects.

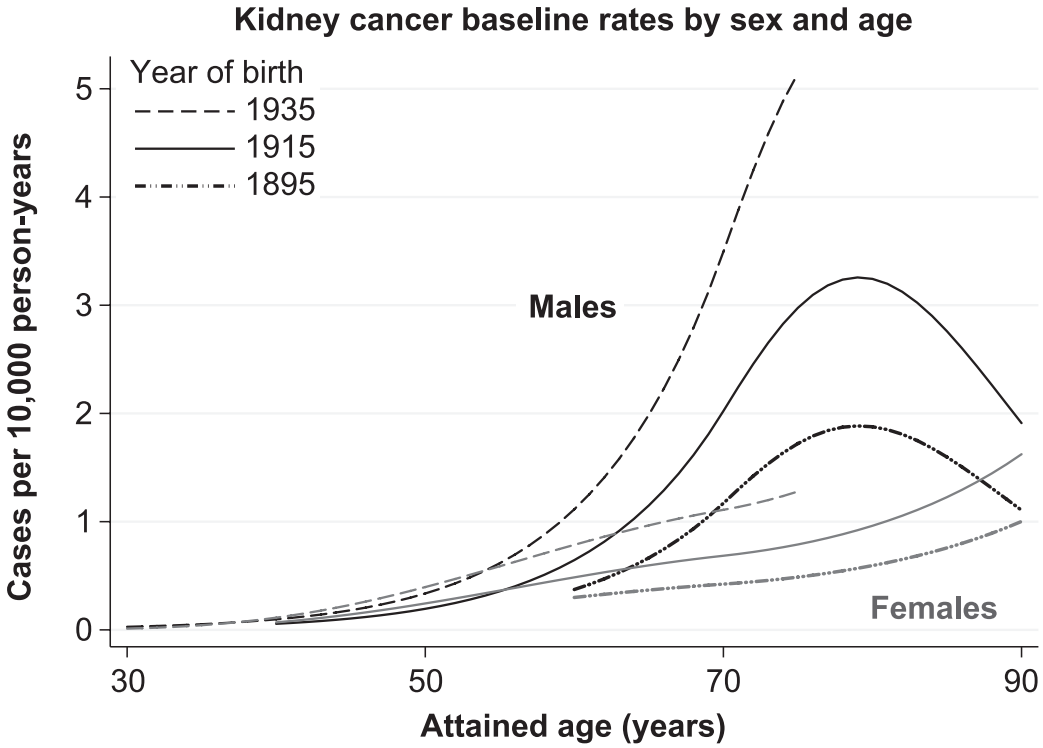

FIG. 3. Baseline rates for kidney cancer by birth cohort.

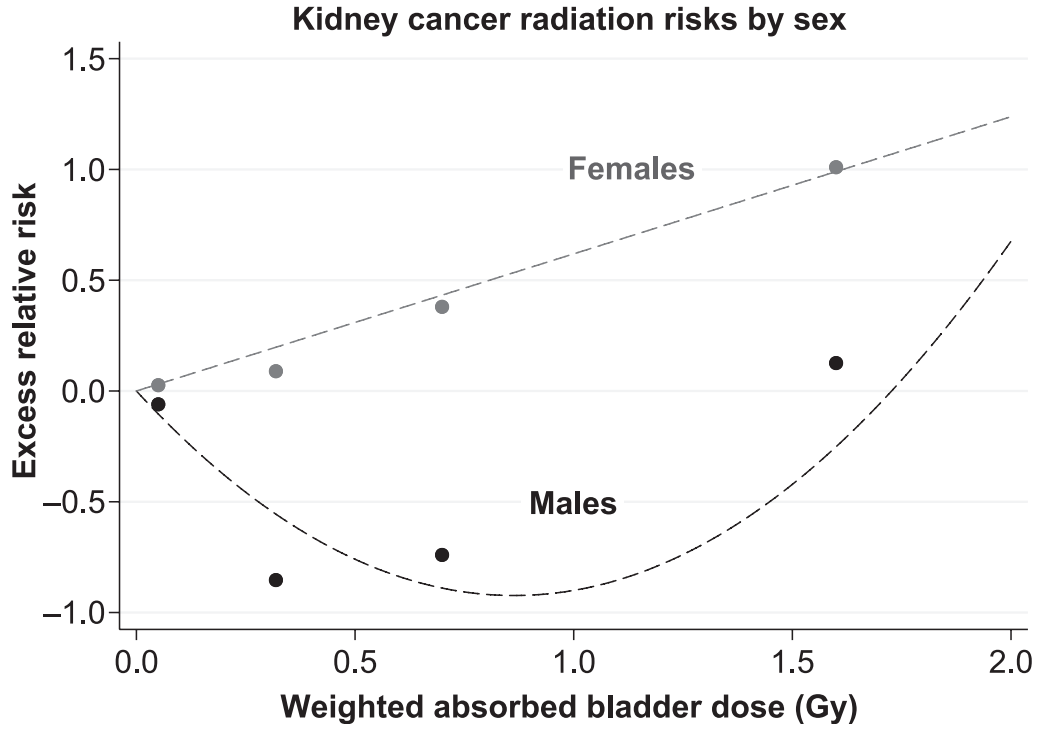

FIG. 4. Excess relative risk per Gy of weighted absorbed bladder dose for kidney cancer. The female dose response was modeled using a linear model while that of males used a linear-quadratic model. The sex-specific dose responses were statistically different from each other.

For kidney cancer, about 75% occurred in the renal parenchyma. The incidence rate in males was about twice that of females. Established risk factors for kidney cancer do not account for large fractions of the cases, although the most consistent risk factors are obesity, hypertension and cigarette smoking (*33–35*). We found that cigarette smoking appeared to be associated with kidney cancer and increased the risk by about 50% after 50 pack-years of smoking but with wide confidence intervals.

Our data did not show a strong radiation dose response, although there was an observed difference by sex. The female ERR increased linearly with dose; however, the male dose-response was ''U''-shaped, with negative ERR estimates at low-to-moderate doses. The non-intuitive shape of the male dose response coupled with small case numbers suggest that these findings were observed by chance and do not represent a real sex-based difference in radiation sensitivity. It is possible that further follow-up may clarify the reasons for this observation. Richardson (*18*) reported an elevated sex-averaged dose response for kidney cancer among those with attained age less than 55 years but only 8% of cases occurred prior to age 55 years.

Haylock *et al*. reported significant risk of bladder cancer mortality and incidence (1.489/Sv and 0.914/Sv, respectively) with occupational exposure among a cohort of 167,000 UK radiation workers, while finding no significant radiation risks for kidney cancer mortality or incidence (*36*). Lee *et al*. reported increased bladder cancer risks in diagnostic medical radiation workers from South Korea with higher relative risks in women compared to men (*37*). Sokolnikov *et al*. reported overall positive risks of mortality from solid cancers other than lung, liver and bone, including 78 kidney cancers with a positive point estimate and 62 bladder deaths (with a negative point estimate) in the Mayak Worker Cohort (*38*). Nekolla *et al*. observed higher risks of both bladder and kidney cancers among those injected with radium-224 for medical treatment (*39*). Other studies have not shown an association between radiation exposure and risk of urinary tract or kidney cancers. Richardson *et al*. reported an ERR of –0.17 for bladder cancer mortality and –0.16 for kidney cancer mortality in the International Nuclear Workers Study (INWORKS study, 87% male) (*40*). Davis *et al*. reported no increase in bladder or ''other urinary'' cancer incidence with radiation dose in the Techa River Cohort (*41*). Cohorts in these studies were all exposed to protracted doses of radiation over many years. Recently, Boice *et al*. reported no increased mortality risks from bladder and other urinary cancers as well as kidney cancer among 114,000 male military personnel exposed to atmospheric nuclear weapons tests, albeit at low estimated doses (*42*).

This study boasts high-quality dosimetry, consistent surveillance methods, long follow-up, a wide range of ages at the time of exposure, adjustment for smoking, and the inclusion of both males and females in approximately equal numbers. Despite these strengths, kidney cancer radiation risk estimates could not be estimated precisely due to small case numbers and low incidence rates among males in the low-dose range.

The results of this study are in agreement with previous results reported from this cohort, particularly for UTC where strong radiation risks have been consistently reported. Other cohorts generally report increased bladder cancer risks while not finding kidney cancer risks after radiation exposure.

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