eAPPENDIX A

SAMPLE DESIGN

Our basic approach for selecting cases and controls for the Kidney Cancer Study (KCS) was consistent with practices typically employed in population-based case-control studies. We selected cases that arose during a fixed period of time from a well-defined population and sampled controls from the general population in the same area and time period, frequency matching controls to cases on sex, age, and race. Our sample design incorporated scientifically and statistically sound procedures to address particular constraints in the KCS that may not be wholly familiar to those who generally employ traditional methods for sampling controls. These procedures are commonplace in the field of survey sampling and are appropriate to apply in population-based case-control studies where samples of cases and controls have been randomly selected and surveyed and inference is to be drawn to the target population of interest. This Appendix summarizes the important features of our sample design; additional detail may be obtained by contacting the author.

A main focus of the KCS was to examine kidney cancer risk factors separately for blacks and whites. Although kidney cancer incidence rates are higher among blacks, more white than black kidney cancer cases were diagnosed in the study catchment areas for Chicago and Detroit, as expected given the greater number of white residents. Therefore, our power to conduct race-specific analyses was limited by the number of black participants. We designed our sampling strategy to recruit the desired numbers of black cases and controls efficiently (i.e., without exceeding recruitment goals for whites) while retaining the targeted levels of power for analyses.

To maximize the number of black cases, we included all black cases and initially sampled from among some groups of white cases. To do this, we examined the distributions across sex/age strata of black and white individuals diagnosed with kidney cancer in the study areas during the four-year period preceding the study. At the beginning of the case accrual period, for those age groups expected to provide more white cases than needed, we sampled white cases at rates expected to provide twice as many participating whites as blacks within each sex/age stratum. Case and control accrual was terminated early in Chicago (12 months into the study, on December 31, 2003); subsequently, after July 1, 2004, we began sampling white cases in Detroit with certainty in all age strata to obtain a sufficient number of white cases for analysis. As a result of this design, white cases were selected at varying rates within sampling strata. We accounted for this aspect of the sample design through the use of sample weights, described in eAppendix B.

To further increase power for analyses restricted to blacks, we maintained a control:case matching ratio of 2 :1 for blacks throughout the study. For whites, whose targeted numbers of cases were about twice that of blacks, the need for additional power was not as compelling, so we deemed a control:case matching ratio of 1:1 to be sufficient for analytic purposes.

Samples of controls were selected periodically over the course of the case accrual period. The targeted sample sizes for controls for each stratum were based on case accrual data for the years just prior to the fielding of the KCS.

Controls 20-64 years of age. The study used population-based controls frequency matched to cases on age, sex, and race. We abandoned our original plan to select controls aged 20 to 64 using list-assisted random-digit dialing (RDD) because of low response rates to the RDD household screener. A suitable alternative was to use Department of Motor Vehicle (DMV) listings as a sample frame. The DMV listings provided date of birth and sex, but not race. Thus, finding sufficient black controls to achieve the specified matching rates through an efficient screening of the general population was a major component of the KCS sample design. To do so, we developed a strategy based on research by Waksberg, Judkins, and Massey (1997) showing that oversampling Census block groups with high percentages of blacks can be a relatively efficient approach to oversampling blacks in area-based sample designs.

To implement this sample design, we determined the proportion of the population that was black for each Census block group in the counties in the study based on 2000 Census data for men and women. We were able to identify a threshold or cut point that permitted the classification of block groups into two groupings: "high black" and "low black." The population of those block groups characterized as "high black" was at least 85% black based on these Census data. Overall, the "high black" block groups contained roughly 85% of the black population, about 5% of the white population, and about 25% of the total population. About 13% of the population found in the "high black" block groups was white. Within the "low black" block groups, only about 5% of the population was black. Through geocoding, we assigned each address on the DMV listing to a block group, and thus to either the "high" or "low" black grouping. Strata defined by the cross-classification of 5-year age group between 20 and 64 years, sex, and "high" or "low" black percentage were formed from the DMV sample frame. Random samples were selected within each stratum. To obtain the targeted number of black controls for frequency matching purposes, DMV records associated with persons in "high black" areas were selected at disproportionately high rates. In the analyses, to account for the different probabilities of selection in "high" and "low" black areas as well as for survey nonresponse, sampling weights were developed, as discussed in eAppendix B.

Controls 65-79 years of age. For controls aged 65 to79 years, the sample frames consisted of Medicare beneficiaries found on a data base provided by the Center for Medicare and Medicaid Services (CMS). The CMS data includes race as well as age and sex, allowing for sample selection in strata defined by the cross-classification of these three variables. The sample sizes for the black strata were determined to produce approximately twice as many participating controls as participating cases, and for whites, to produce about the same number of participating controls as participating cases. Since race was available on the sample frame, no special oversampling was called for. Nevertheless, as with virtually all case-control studies, sampling rates varied by stratum. Sample weights were developed to account for these different rates as well as for different rates of nonresponse (eAppendix B).

eAPPENDIX B

SAMPLE WEIGHTS

The Kidney Cancer Study (KCS) incorporated sample weights for most analyses based on established methods commonly used in other survey research settings (Korn and Graubard, 1999). The weighted analyses eliminate the potential for bias arising from the complex nature of the sample design, where some subsets of both cases and controls were oversampled (see eAppendix A). In addition, the sample weights serve to limit the potential for bias arising from nonresponse. Each participating case and control has an assigned sample weight reflecting (1) the probability of sample selection, (2) adjustment for nonresponse, and (3) post-stratification. The post-stratification was employed to achieve consistency between the weighted distribution of controls and cases on the variables used for frequency matching: age, sex, and race. In so doing, the post-stratification served to obtain the full benefits of matching controls to cases. A discussion of this weighting process, as well as an evaluation of this approach to weighting and corresponding analyses as applicable to case-control studies, is presented in Li et al. (2011). The important features of our sample weighting approach are summarized below, including a discussion of the replicate weights developed to permit appropriate variance estimation in light of the complex sample design employed. Additional detail may be obtained by contacting the author.

Base Weights

Cases. The base weight assigned to each case reflects the inverse of the probability of selection. Blacks, who were sampled with certainty throughout the case accrual period, were assigned a base weight of 1. During the period of time in which some white cases were subsampled, the reciprocal of the sampling rate was used as the base weight. After case accrual ended in Chicago, whites were sampled with certainty and were thus assigned a base weight of 1.

Controls were sampled from sampling strata several times over the course of the study. Small changes in sampling rates were made when called for to help achieve the targeted sample sizes. Base weights for controls were established as if the controls were sampled once from the general non-case population at roughly the midpoint of the case accrual period (the year 2004). This is consistent with the analytical approach commonly used in the absence of sample weights, where cases and controls are regarded as having been selected using stratified simple random sampling.

The same base weight was assigned to all controls within each age/sex/race stratum. The base weight was the ratio of the number of sampled controls selected from the stratum to the estimated number of people in that stratum in 2004. For people aged 65 to 79 (sampled from Center for Medicare and Medicaid Services [CMS] files), the denominator of the ratio was derived from Census estimates, which are available by age/sex/race for given years. For people aged 20 to 64 (sampled from Department of Motor Vehicle [DMV] files), we obtained estimates for each age/sex class from the Census. These estimates were multiplied by the percentage of people classified as living in "high" and "low" black areas within each such class (estimated from 2000 Census figures), providing the denominator for each age/sex/race stratum.

Nonresponse Adjustment

The adjustment of sample weights for nonresponse serves to limit the potential for bias in study estimates and analyses arising from differences in the characteristics between respondents and nonrespondents. The basic assumption in the nonresponse adjustment of sample weights is that respondents can be regarded as a random sample from among all of those sampled (respondents and nonrespondents) within the adjustment cells (subsets of the population formed by cross-classifying variables whose values are known for both respondents and nonrespondents). The nonresponse adjustment for each individual in a cell is the reciprocal of the (weighted) proportion of respondents for the cell. If the underlying assumption is appropriate, the nonresponse-adjusted weights will yield unbiased estimates; when the assumption is not appropriate, standard practice of no adjustment will not remove bias for nonresponse any better than adjustment (Little and Rubin, 2002).

The adjustment process was undertaken by computing the ratio of the sum of the base weights of all sampled cases (or controls) in an adjustment cell to the sum of the base weights of all participating cases (or controls) in the cell, and then multiplying the base weight of each participating case (or control) in the cell by this ratio. After nonresponse adjustment in the KCS, the weights of the participating cases reflected the population distribution of cases (for the age/sex/race groups of interest to the KCS), while the weights of the participating controls should reflect the population distribution of the corresponding control population.

Several methods are available for forming cells for the purpose of nonresponse adjustment. For the KCS, we used the Chi-Square Automatic Interaction Detector (CHAID) software (SPSS, 1993). CHAID first pools categories of predictor variables where there is evidence of statistical homogeneity with respect to the propensity to respond across these categories. All other categories, those with relatively distinct response rates, remain as is. CHAID then selects the most significant predictor (the one with the smallest p-value) as the best predictor of response and forms the first branch in the decision tree. It continues applying the same process within the subgroups (nodes) defined by the "best" predictor chosen in the preceding step. This process continues until no further significant predictor is found or a specified minimum node size is reached. The procedure is stepwise and creates a hierarchical tree-like structure.

When some nonrespondents are known to be members of the target population while the eligibility status of other nonrespondents is unknown, nonresponse adjustment of sample weights requires two steps: first, to estimate and adjust for those sampled nonrespondents whose eligibility status was not ascertained; and second, to further adjust the weights of the eligible respondents to account for the nonrespondents who were known to be eligible for the study. CHAID was used to form two different sets of cells to accomplish these two tasks.

For both cases and controls, nonresponse adjustment cells were formed based on data available for both respondents and nonrespondents. For controls sampled from the DMV listings, this included age group, sex, relative concentration of blacks in the residential area, and county of residence. For all cases and those controls sampled from the CMS listings, this included age group, sex, race, and county of residence.

Post-stratification

Post-stratification is the calibration of a set of sample weights to a set of population counts, generally obtained independently of the study (Korn and Graubard, 1999). In so doing, the weighted distribution of the study participants reflects the distribution of the corresponding population across the factors incorporated into the postratification. In the KCS, the weighted distribution of controls (after nonresponse adjustment) was poststratified to the weighted distribution of cases (after nonresponse adjustment) on the matching variables (5-year age group/sex/race). This served to frequency match the controls precisely to the estimated population distribution of cases (not simply the distribution of participating cases), the ultimate aim of frequency matching. Weighted analyses (e.g., logistic regression analyses to estimate the adjusted odd ratios) will thus fully reflect the desired matching.

Replicate Weights for Variance Estimation Purposes

For variance estimation in the weighted analysis, 90 replicate weights were created using the jackknife replication approach known as "Jackknife 2" or, more commonly, "JK2." This approach is appropriate when the sample design can be viewed as two primary sampling units (here, cases or controls) having been selected from each of L strata. In the KCS, the initial variance estimation strata were formed based on the sorting of cases and controls in their sample selection order. For the controls, where sorting on one or more variables was implemented prior to sample selection, this ensures that the resulting implicit stratification has been reflected in the variance estimation process. After the formation of the variance estimation strata, strata were "combined" to reduce the number of replicate weights to a manageable number for variance estimation purposes while still maintaining an ample number of degrees of freedom.

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eAppendix C, eTable C-1. Characteristics of cases and controls, by race, unweighted, Kidney Cancer Study, Detroit and Chicago, 2002-2007[a]

	Whites				Blacks			
	Cases n=843		Controls n=707		Cases n=358		Controls n=519	
	No.	%	No.	%	No.	Percent	No.	%
Study Site								
Chicago	115	14%	99	14%	79	22%	96	18%
Detroit	728	86%	608	86%	279	78%	423	82%
Age (years)								
20-44	103	12%	93	13%	40	11%	84	16%
45-54	180	21%	145	21%	102	28%	124	24%
55-64	254	30%	205	29%	117	33%	145	28%
65-74	218	26%	193	27%	81	23%	132	25%
75+	88	10%	71	10%	18	5%	34	7%
Sex								
Male	484	57%	435	62%	222	62%	246	47%
Female	359	43%	272	38%	136	38%	273	53%
Education								
<12 years	99	12%	62	9%	94	26%	100	19%
High school graduate	308	37%	213	30%	104	29%	172	33%
Some college	215	26%	183	26%	113	32%	172	33%
4+ years college	221	26%	249	35%	47	13%	75	14%
Body Mass Index (kg/m^2)								
<25	168	20%	215	30%	67	19%	147	28%
25<30	302	36%	291	41%	125	35%	198	38%
30<35	210	25%	125	18%	87	24%	95	18%
35+	156	19%	74	10%	74	21%	73	14%
Don't know	7	1%	2	<1%	5	1%	6	1%
Smoking Status								
Never	304	36%	285	40%	123	34%	184	35%
Occasional	34	4%	25	4%	21	6%	30	6%
Former	302	36%	273	39%	105	29%	167	32%
Current	203	24%	124	18%	109	30%	138	27%
Family History of Kidney Cancer								
None with cancer	329	39%	276	39%	180	50%	284	55%
Cancer other than kidney	476	56%	410	58%	152	42%	220	42%

Kidney cancer	33	4%	15	2%	19	5%	9	2%
Don’t know	5	1%	6	1%	7	2%	6	1%
Ever Diagnosed with hypertension	398	47%	445	63%	102	28%	273	53%
No	445	53%	262	37%	256	72%	246	47`%
Yes								

[a]Excludes 16 cases and 9 controls with unknown history of hypertension.

eAppendix C, eTable C-2. Hypertension and renal cell carcinoma risk, by race, unweighted

	All Participants[a]			Whites[b]			Blacks[b]		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Ever diagnosed with hypertension[e]									
No	500/718	1.0		398/445	1.0		102/273	1.0	
Yes	701/508	2.1	1.7, 2.5	445/262	1.8	1.45 2.3	256/246	2.8	2.0, 3.9
Years since hypertension diagnosis[c]									
Never had hypertension	500/718	1.0		398/445	1.0		102/273	1.0	
>0-5	180/160	1.7	1.3, 2.2	124/83	1.7	1.1, 2.3	56/77	1.9	1.2, 3.0
6-15	215/154	2.0	1.5, 2.6	147/85	1.8	1.3, 2.5	68/69	2.6	1.7, 4.1
16-25	158/100	2.4	1.8, 3.3	93/55	1.8	1.2, 2.7	65/45	4.0	2.5, 6.8
26+	146/92	2.8	2.0, 3.9	80/37	2.5	1.6, 3.9	66/55	4.2	2.5, 6.8
		$p_{trend}<0.001$			$p_{trend}<0.001$			$p_{trend}<0.001$	
Blood pressure control[d]									
Never had hypertension	500/718	1.0		398/445	1.0		102/273	1.0	
Always well controlled	176/163	1.5	1.2, 2.0	134/98	1.5	1.1, 2.1	42/65	1.7	1.03, 2.8
Usually well controlled	293/204	2.2	1.7, 2.7	175/101	1.8	1.3, 2.4	118/103	3.3	2.2, 4.8
Rarely well controlled	97/65	2.3	1.6, 3.3	62/23	3.0	1.8, 5.0	35/42	2.2	1.3, 3.7
Almost never controlled	78/45	2.6	1.7, 3.9	41/24	1.9	1.1, 3.2	37/21	4.3	2.3, 8.0
		$p_{trend}<0.001$			$p_{trend}<0.001$			$p_{trend}<0.001$	

[a]Adjusted for study center, race, sex, age, education, smoking status, body mass index, and family history of kidney cancer

[b] Adjusted for study center age, sex, education, smoking status, body mass index, and family history of kidney cancer

[c]Excludes 2 hypertensive cases and 2 hypertensive controls with unknown years since hypertension diagnosis

[d]Excludes 57 hypertensive cases and 31 hypertensive controls with unknown blood pressure control

[e]$P_{interaction}$ by race=0.040

eAppendix C, eTable C-3. Odds ratios for renal cell carcinoma by years since hypertension diagnosis and level of blood pressure control, unweighted[a]

Blood Pressure Control	Years Since Hypertension Diagnosis <=5	6-15	16-25	26+
WHITES AND BLACKS[b]				
Well controlled[c]	1.6 (1.2, 2.2)[d] 123/113[e]	1.7 (1.3, 2.3) 150/120	2.4 (1.7, 3.3) 113/72	2.4 (1.6, 3.5) 83/62
Poorly controlled[f]	1.6 (0.95, 2.7) 34/31	2.5 (1.5, 4.0) 52/32	2.6 (1.5, 4.4) 41/25	3.7 (2.2, 6.4) 48/22
WHITES[g]				
Well controlled[c]	1.6 (1.1, 2.3) 87/61	1.6 (1.1, 2.3) 108/70	1.6 (1.04, 2.45 65/42	2.2 (1.3, 3.7) 49/26
Poorly controlled[f]	1.7 (0.8, 3.4) 22/14	2.3 (1.2, 4.6) 30/14	2.5 (1.2, 5.0) 26/12	4.0 (1.7, 9.7) 25/7
BLACKS[g]				
Well controlled[c]	1.9 (1.1, 3.1) 36/52	2.2 (1.3, 3.7) 42/50	4.4 (2.5, 7.8) 48/30	3.6 (2.0, 6.4) 34/36
Poorly controlled[f]	1.7 (0.7, 3.8) 12/17	3.2 (1.6, 6.4) 22/18	3.1 (1.3, 7.1) 15/13	4.2 (2.0, 9.2) 23/15

[a]Referent group is respondents with no history of hypertension (500 cases, 718 controls). Table excludes 57 cases and 31 controls with unknown years since hypertension diagnosis or unknown level of blood pressure control.

[b]Adjusted for study center, race, sex, age, education, smoking status, body mass index, and family history of kidney cancer

[c]Participant reported that blood pressure was higher than the doctor wanted it to be "some of the time" or "almost never or never." If participant answered in terms of the number of times blood pressure was too high, we estimate that blood pressure was too high ≤50% of the time.

[d]Odds ratio and 95% confidence interval

[e]Cases/controls

[f]Participant reported that blood pressure was higher than the doctor wanted it to be "most of the time" or "all or almost all of the time." If participant answered in terms of the number of times blood pressure was too high, we estimate that blood pressure was too high >50% of the time.

[g]Adjusted for study center, sex, age, education, smoking status, body mass index, and family history of kidney cancer

eAppendix C, eTable C-4. Hypertension, use of prescription antihypertensive medications, and renal cell carcinoma risk, by race, unweighted[a]

Ever Diagnosed with Hypertension	Ever Took Prescription Antihypertensive Medication[b]	All Participants[c]			Whites[d]			Blacks[d]		
		Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
No	No (referent)	427/621	1.0	--	341/386	1.0	--	86/235	1.0	--
	Yes	69/87	1.1	0.8, 1.6	55/54	1.0	0.7, 1.5	14/33	1.3	0.6, 2.6
Yes	No	14/38	0.5	0.3, 0.9	9/25	0.4	0.2, 0.9	5/13	0.9	0.3, 2.7
	Yes	681/466	2.3	1.8, 2.8	433/236	2.0	1.6, 2.6	249/231	3.1	2.1, 4.4

[a]Excludes 9 cases and 13 controls with unknown use of antihypertensive medications

[b]For high blood pressure, heart problems, weight control, or swelling

[c]Adjusted for study center, race, sex, age, education, smoking status, body mass index, and family history of kidney cancer

[d] Adjusted for study center, sex, age, education, smoking status, body mass index, and family history of kidney cancer

eAppendix C, eTable C-5. Population attributable risk for hypertension and contribution of hypertension to black excess in renal cell cancer incidence, Detroit residents aged 50-79 years, unweighted

Race and Sex	Population Attributable Risk for Hypertension (PAR)[a]	Renal Cell Carcinoma Incidence Rate (per 100,000 per year)	
		SEER Rate[b]	Calculated Rate in the Absence of Hypertension[c]
Black Men	47%	62.1	32.9
White Men	34%	49.1	32.3
		Black:white ratio = 1.26	Black:white ratio = 1.02
Black Women	51%	29.8	14.6
White Women	27%	28.3	20.6
		Black:white ratio = 1.05	Black:white ratio = 0.71

Abbreviations: PAR, population attributable risk; SEER, Surveillance, Epidemiology, and End Results

[a]Adjusted for age (5-year intervals), education, smoking status, body mass index, and family history of cancer, weighted

[b]Microscopically-confirmed cases of adenocarcinoma of the kidney (renal parenchyma) or renal pelvis at ages 50-79, Detroit SEER, 2002-2006

[c]RCC incidence rate in the absence of hypertension (i.e., if nobody had a history of hypertension) = SEER rate x (1-PAR)

eAppendix D. Hypertension and renal cell cancer risk, by race and sex, weighted, Kidney Cancer Study, Detroit and Chicago, 2002-2007

	All Participants[a]			Whites[b]						Blacks[b]					
				Men			Women			Men			Women		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Ever diagnosed with HYP															
No	500/718	1.0	--	221/261	1.0	--	177/184	1.0	--	70/128	1.0	--	32/145	1.0	--
Yes	701/508	2.0	1.7, 2.5	263/174	1.8	1.3, 2.5	182/88	2.1	1.4, 3.1	152/118	2.5	1.6, 4.0	104/128	3.7	2.0, 7.1
Years since HYP diagnosis[c]															
Never had HYP	500/718	1.0	--	221/261	1.0	--	177/184	1.0	--	70/128	1.0	--	32/145	1.0	--
>0-5	180/160	1.7	1.2, 2.2	74/49	1.8	1.2, 2.8	50/34	1.3	0.7, 2.5	35/41	1.6	0.9, 3.0	21/36	2.7	1.3, 5.9
6-15	215/154	1.9	1.4, 2.6	87/63	1.5	1.003, 2.4	60/22	2.6	1.4, 4.9	47/32	2.7	1.4, 5.2	21/37	2.5	1.02, 6.1
16-25	158/100	2.3	1.7, 3.3	52/34	1.9	1.1, 3.2	41/21	2.2	1.1, 4.4	42/21	4.0	2.0, 7.8	23/24	3.9	1.4, 10.5
26+	146/92	2.9	2.0, 4.1	49/26	2.3	1.3, 4.0	31/11	3.6	1.8, 7.1	27/24	2.6	1.2, 5.7	39/31	7.3	3.0, 18
		$p_{trend}<0.001$			$p_{trend}=0.002$			$p_{trend}<0.001$			$p_{trend}=0.002$			$p_{trend}<0.001$	
Blood pressure control[d]															
Never had HYP	500/718	1.0	--	221/261	1.0	--	177/184	1.0	--	70/128	1.0	--	32/145	1.0	--
Always well controlled	176/163	1.6	1.2, 2.1	87/68	1.6	1.02, 2.4	47/30	1.8	1.01, 3.3	27/34	1.6	0.8, 3.3	15/31	1.7	0.7, 3.9
Usually well controlled	293/204	2.0	1.6, 2.6	93/64	1.6	1.05, 2.5	82/37	1.9	1.2, 3.2	68/41	3.1	1.8, 5.3	50/62	4.2	2.1, 8.4
Rarely well controlled	97/65	2.6	1.9, 3.7	40/16	2.9	1.4, 5.9	22/7	3.1	1.04, 9.2	21/19	2.8	1.3, 5.9	14/23	2.5	0.9, 7.2
Almost never controlled	78/45	2.6	1.7, 4.0	25/12	2.9	1.3, 6.6	16/12	1.5	0.6, 3.7	21/11	3.7	1.3, 10	16/10	6.6	2.4, 18
		$p_{trend}<0.001$			$p_{trend}<0.001$			$p_{trend}=0.008$			$p_{trend}<0.001$			$p_{trend}<0.001$	

Abbreviations: HYP, hypertension

[a]Adjusted for race, sex, age, education, smoking status, body mass index, and family history of kidney cancer

[b] Adjusted for age, education, smoking status, body mass index, and family history of kidney cancer

[c]Excludes 2 hypertensive cases and 2 hypertensive controls with unknown years since hypertension diagnosis

[d]Excludes 57 hypertensive cases and 31 hypertensive controls with unknown blood pressure control