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Cancer risk in living kidney donors

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Abstract

Living kidney donors are screened for transmissible diseases including cancer. Outcomes following donation are excellent, but concern exists regarding development of chronic kidney disease, and cancer risk is unknown. We used linked transplant and cancer registry data to identify incident cancers among 84,357 kidney donors in the United States (1995–2017). We compared risk to the general population using standardized incidence ratios (SIRs). For selected cancers, we used Poisson regression to compare donors to 47,451 Adventist Health Study 2 (AHS-2) participants, who typically have healthy lifestyles. During follow-up, 2843 cancers were diagnosed in donors, representing an overall deficit (SIR 0.79, 95%CI 0.76–0.82). None of 46 specified cancer sites occurred in excess relative to the general population, and 15 showed significant deficits (SIR<1.00). Compared with AHS-2 participants, donors had similar incidence of liver cancer, melanoma, breast cancer, and non-Hodgkin lymphoma but, starting seven years after donation, elevated incidence of colorectal cancer (adjusted incidence rate ratio 2.07, 95%CI 154–2.79) and kidney cancer starting (2.97, 1.58–5.58, accounting for the presence of a single kidney in donors). Elevated kidney cancer incidence may reflect adverse processes in donors' remaining kidney. Nonetheless, cancer risk is lower than in the general population, suggesting that enhanced screening is unnecessary.

Background

In the United States, living donors play a crucial role in providing needed kidneys to people on the transplant waitlist. In 2019, a total of 6626 US kidney transplants (28% of all kidney transplants) were from living donors (1). Living kidney donors are carefully evaluated for transmissible diseases (specifically including cancer and infections) as well as for other

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chronic medical conditions that might impact the viability of the transplanted kidney or put the donor's health at risk (2, 3). As a result, living donors are relatively healthy compared with the general population. Outcomes following donation are generally excellent. The main health consequence is that donors must live with only a single kidney. There has been concern that donors may have an elevated risk of developing chronic kidney disease in their remaining kidney (4, 5), although recent longitudinal data indicate that kidney function is stable for up to 9 years after donation (6).

Little is known about cancer risk in living kidney donors following donation. Given donors' good overall health, one might expect that cancer risk would not be increased, but this has been assessed in only one study (7). Lentine *et al.* evaluated 4650 US kidney donors covered in an insurance database. Overall cancer incidence appeared lower than in control subjects from the same insured population (relative risk 0.74, 95% confidence interval [CI] 0.55–0.99). For most specific cancer types, incidence was similar to or lower than in controls, with the exception of prostate cancer, for which incidence was increased (relative risk 3.80, 95%CI 1.42–10.2).

Of note, no potential biologic mechanism is apparent to explain an elevated risk of prostate cancer following kidney donation. Limitations of the Lentine *et al.* study include the modest number and possible non-representative sampling of donors, and reliance on insurance claims for ascertainment of cancer diagnoses. Because of the possibility of developing chronic kidney disease after donation, kidney donors may have elevated risk for kidney cancer (8), although that was not observed in the Lentine study (7).

Additional data on cancer risk in living kidney donors are important for advising potential donors about possible complications of donation and planning appropriate follow-up care (e.g., cancer screening). We therefore assessed cancer risk in a large sample of US living kidney donors using data from the Transplant Cancer Match (TCM) Study.

Methods

Living kidney donor population and outcome ascertainment

The TCM Study is a linkage of the Scientific Registry of Transplant Recipients (SRTR), which contains data on all US solid organ recipients, candidates, and donors, with multiple central cancer registries (http://transplantmatch.cancer.gov/). As shown in Figure 1, for the present study we assessed living kidney donors registered in the SRTR during 1995–2017, who resided at the time of donation within the catchment area of one of 32 participating TCM Study cancer registries (see Table 1 note for list). We excluded donors outside the four major racial/ethnic groups (see Table 1) or with missing age to allow calculation of expected cancer counts.

Each donor was followed from kidney donation until the earliest of death or the end of cancer registry coverage (December 31, 2017 was the last follow-up date). Using the linked cancer registry data, we ascertained invasive malignancies diagnosed in the donors during follow-up. Cancers were classified using a modified version of the Surveillance, Epidemiology, and End Results (SEER) site recode (9).

Comparison of cancer risk with general population

We present standardized incidence ratios (SIRs, defined as the ratio of the observed and expected number of cases) as a measure of risk relative to the general population. The expected number of cases was based on general population rates from SEER (SEER13 database, https://seer.cancer.gov/registries/), calculated in strata defined by sex, age, race/ethnicity, and calendar year. Because the vast majority of donors had no prior history of cancer, these expected rates were restricted to include only first cancers. For kidney and renal pelvis cancers, the expected counts were divided by 2 to account for the presence of only one kidney in donors (i.e., the SIR reflects per-kidney cancer risk). We also present SIRs for kidney cancer according to stage at diagnosis, to evaluate whether increased medical surveillance of donors might have led to an increase in local-stage cases (10), and time since donation (less than 3, 3.00–6.99, 7.00–9.99, 10+ years).

To assess whether some cancer registries did not identify all incident cancers, we calculated SIRs for overall cancer for each cancer registry separately. Also, some donors would have moved out of the state in which they lived at the time of donation, which would lead cancer registries to miss their cancer diagnoses and cause an apparent decline in cancer risk with increasing time since donation. To evaluate this possibility, we assessed SIRs for overall cancer as a function of time since donation.

Comparison of cancer risk with Adventist Health Study 2 participants

Because living kidney donors are typically healthier than the general population, we also compared donors to individuals in the Adventist Health Study 2 (AHS-2). AHS-2 is a US nationwide cohort study of more than 90,000 individuals who are members of the Adventist church, which promotes a healthy lifestyle including abstinence from smoking and alcohol, and a vegetarian or low-meat diet (11). Follow-up started in 2001–2002, and cancers were ascertained through 2012 using periodic questionnaires and linkages to 50 US cancer registries (12).

We restricted the AHS-2 cohort to individuals with non-missing/valid data on the variables required for analysis, who were at least 30 years old at cohort entry, and who were in the same four racial/ethnic groups as donors (Figure 1). We further excluded individuals with any of the following relative or absolute contraindications for donation: extreme obesity (body mass index [BMI] 35 kg/m^2 or greater), heavy current smoking (more than 1/2 pack/day), heavy alcohol use (more than 1 drink/day), prior cancer diagnosis (except for cutaneous basal or squamous cell carcinoma), or a serious medical condition (diabetes mellitus, cardiovascular disease, congestive heart failure, stroke/transient ischemic attack, chronic bronchitis, emphysema, ulcerative colitis, Crohn’s disease, Parkinson’s disease, or lupus). In addition, we required AHS-2 participants to have had baseline screening for colorectal cancer within the previous 10 years (for individuals age 50 years or older) and breast cancer screening within the previous year (women age 40 years or older).

We used Poisson regression to compare cancer incidence in kidney donors and AHS-2 participants. To make the cohorts more comparable for the regression analyses, we excluded individuals who were less than 30 years old at entry (donors) or resided in Puerto Rico,

outside the US, or in an unknown state (donors and AHS-2). We limited analysis to selected cancers of interest *a priori* (kidney cancer) or when there was a plausible reason for an observed decreased SIR in donors (i.e., lower risk than in the general population). The latter group included colorectal cancer, breast cancer, and melanoma, for which prospective donors would have been screened, and liver cancer and non-Hodgkin lymphoma (NHL, including chronic lymphocytic leukemia), which in some cases are caused by viruses for which prospective donors would have been screened. We did not include prostate cancer because we did not observe a difference in incidence in donors compared with the general population.

The Poisson regression analyses were adjusted for attained age during follow-up and, in a full multivariable model, for sex, attained age, race/ethnicity, and US geographic region (12). For kidney cancer, we considered the kidney the unit of analysis; statistical adjustment of the variance for the correlation in outcomes for the two kidneys in each AHS-2 participant did not affect the results (data not shown), and therefore we present results without this variance adjustment. For two cancers we stratified the follow-up in donors according to time since transplant: colorectal cancer (for which incidence was increased overall) and kidney cancer (because of a clear deficit in cases early in follow-up that likely reflected screening at donation). We also show results for kidney cancer separately comparing related and unrelated donors to AHS-2 participants.

In a sensitivity analysis, we further adjusted the regression models of colorectal and kidney cancers for BMI. We present results of additional multivariate models for colorectal and kidney cancers restricted to donors. Finally, we used an exact test to assess whether a prior diagnosis of these two cancers was a risk factor for a new cancer diagnosis after donation.

We considered $p<0.05$ as significant. The TCM Study is considered non-human subjects research at the National Cancer Institute and was approved, as required, by participating cancer registries.

Results

We evaluated 84,357 living donors who donated a kidney during 1995–2017 (Table 1). These individuals comprised 65.7% of all US living kidney donors (N=128,452) during this period. As shown in Supplementary Table 1, included and excluded donors were largely similar, although included donors had a larger proportion of Hispanic individuals and were less likely to have donated in 2010–2017.

Among included kidney donors, 63.0% were related to the organ recipient. Most donors (59.8%) were female, the mean age at donation was 40.7 years, and the most common race/ethnicity was non-Hispanic White (68.0%). The mean BMI was 26.9 kg/m^2, approximately one-quarter of donors (24.1%) were current or former smokers, and hepatitis B and C virus infections were uncommon (0.3% and 0.4%, respectively). As shown in Table 1 and Supplementary Table 2, a prevalent (baseline) cancer diagnosis was documented by cancer registries in 390 donors (0.5%), including 26 with colorectal cancer, 37 with melanoma,

and 34 with kidney cancer (including 13 whose kidney cancer was diagnosed at the time of donation).

During 836,955 person-years of follow-up (median 9.6 years, interquartile range 4.9–14.5 years, per donor), 2830 incident cancers were diagnosed in these donors, whereas 3594 were expected based on general population cancer rates, corresponding to a 21% deficit in cancer risk (SIR 0.79, 95%CI 0.76–0.82). Cancer risk was significantly decreased for donors living in 16 of the included cancer registry areas considered separately (SIRs in the range 0.48–0.84) and was not significantly elevated in any of the 16 remaining areas (SIRs 0.65–1.03).

As shown in Table 2, none of 46 specified cancer sites occurred in excess (i.e., SIR significantly above 1.00), and there were significant deficits (SIR<1.00) for 15 cancer sites: cancers of the oral cavity/pharynx, stomach, colorectum, liver, pancreas, lung, breast, cervix, uterus, testis, bladder, and kidney as well as melanoma, Hodgkin lymphoma, and NHL. For kidney cancer, in particular, risk relative to the general population was reduced by 38% (SIR 0.62, 95%CI 0.43–0.87). SIRs for kidney cancer were 0.53 (0.33–0.81) for localized stage cases, 0.87 (0.35–1.79) for regional stage cases, and 0.52 (0.14–1.32) for distant stage cases.

The overall deficit in incident cancers among donors was similar across follow-up intervals, with an overall SIR (95%CI) of 0.70 (0.65–0.77) less than 3 years, 0.79 (0.74–0.85) during years 3.00–6.99, 0.84 (0.77–0.91) during years 7.00–9.99, and 0.81 (0.76–0.86) for 10+ years after donation. For kidney cancer, there were no cases in the first 3 years of follow-up, and the SIRs (95%CIs) were 0 (0–0.35), 0.41 (0.15–0.89), 1.05 (0.53–1.89), and 0.87 (0.52–1.38) for less than 3, 3.00–6.99, 7.00–9.99, and 10+ years after donation, respectively.

We also compared donors to 47,451 AHS-2 participants (Table 1). Seventy percent of the AHS-2 cohort were female, and the mean age at entry was 55.1 years. Compared to living kidney donors, AHS-2 participants were more frequently of non-Hispanic Black race/ethnicity (28.3%), less frequently Hispanic (4.9%), and had higher educational attainment. The mean BMI of participants was 25.7 kg/m^2, 15.7% reported current or former smoking, and none had a prior cancer diagnosis (other than basal or squamous cell skin cancer).

During 375,977 person-years of follow-up, AHS-2 participants were diagnosed with 1230 cases of the six cancers of interest (compared with 1200 cases in living kidney donors, Table 3). In unadjusted analyses, incidence of each cancer was lower or similar in donors compared with AHS-2 participants. However, these deficits in donors disappeared with age-adjustment, and after age adjustment there were significant elevations observed in donors for colorectal cancer and melanoma (Table 3). In the final multivariable model, donors exhibited significantly higher incidence than AHS-2 participants only for colorectal cancer (adjusted incidence rate ratio [IRR] 1.38, 95%CI 1.06–1.80). Donors did not exhibit elevated risk compared with AHIS-2 participants in an analysis of breast cancer restricted to females (adjusted IRR 1.04, 95%CI 0.90–1.21) or for melanoma restricted to non-Hispanic White subjects (1.36, 0.96–1.92).

As shown in Table 3, compared with AHS-2 participants, during the first 7 years of follow-up donors had similar incidence of colorectal cancer and tended to have lower

incidence of kidney cancer. However, incidence was elevated for both cancers 7+ years after donation (adjusted IRR 2.07, 95%CI 1.54–2.79 for colorectal cancer; 2.97, 1.58–5.58 for kidney cancer). Finally, the incidence of kidney cancer appeared similar for both related and unrelated donors (Table 3).

Data on BMI were available among donors for 136 colorectal cancer cases and 17 kidney cancer cases (including 73 colorectal cancers and 14 kidney cancers diagnosed 7+ years after donation). In a sensitivity analysis, we further adjusted for BMI among individuals with known values, and the results were similar to the main analysis (7+ years after donation: adjusted IRR 2.20, 95%CI 1.57–3.08, for colorectal cancer, and 2.98, 1.41–6.32, for kidney cancer).

Multivariable models restricted to donors show that older attained age and greater time since donation were independent risk factors for colorectal and kidney cancers (Supplementary Table 3). Among donors with a history of colorectal cancer or kidney cancer before donation, only one donor in each group developed a new diagnosis of the same cancer after donation. Nonetheless, these individual cases represent an excess risk compared to donors without a prior cancer diagnosis (Supplementary Table 4; p=0.002 for colorectal cancer, p=0.01 for kidney cancer).

Discussion

An understanding of health risks associated with kidney donation is important to advise potential donors and plan appropriate medical care. In the present study, we comprehensively evaluated cancer risk in a large sample of living kidney donors. We observed an overall deficit in cancer risk compared with the US general population, and risk was decreased for many specific cancers. To a great extent, this decreased risk likely reflects the good general health of donors and cancer screening prior to donation. We therefore also compared donors to the AHS-2 cohort, which comprises individuals who follow a healthy lifestyle advocated by the Adventist church. The most notable finding in that analysis is that, after seven years following donation, donors had elevated incidence of kidney and colorectal cancers.

Our use of cancer registry data as a reference allowed a broad and systematic evaluation of cancer risk (Table 2), but the observed deficits compared with the general population likely reflect the evaluation and selection by transplant providers of relatively healthy donors. For example, exclusions of people with human immunodeficiency virus (HIV), and the relative rarity of hepatitis B and C infections among donors, could explain the decreased SIRs for lymphomas and liver cancer, respectively (13, 14).

Notably, potential donors are recommended to undergo cancer screening following age-appropriate guidelines (2, 3). This screening likely contributed to the reduced incidence that we observed for some malignancies (e.g., colorectal, cervical, and breast cancers, and melanoma), due to effective treatment for screen-detected precursor lesions (e.g., excision of colorectal polyps) or exclusion of some potential donors due to detection of early-stage asymptomatic cancers that would have become clinically manifest later. There is

no consensus regarding the advisability of general population screening for prostate cancer with prostate-specific antigen testing. We did not confirm an increased incidence of prostate cancer among donors as reported by Lentine et al. in a much smaller study (7), although our risk estimate for cancer overall is essentially identical (SIR 0.79 vs. relative risk 0.74).

As a result of careful donor selection, donors had a lower baseline prevalence of cancer (0.5%) than individuals in the general population (Table 1 and Supplementary Table 5). This difference may partly explain why donors exhibited lower cancer risk than the general population, since a previous cancer diagnosis is a risk factor for developing a new cancer (15). Potential donors are screened for kidney cancer, and some might have been excluded from donation if one had been detected, which would explain the absence of cases in the first three years following donation. Of interest, 34 donors still had a prevalent diagnosis of kidney cancer before or at the time of donation, the vast majority of whom donated their affected kidney (Supplementary Table 2) (16). Donors with a prior diagnosis of colorectal or kidney cancer had an elevated incidence of developing a second such cancer after donation, but the number of such cases was far too small to affect our study results (Supplementary Table 4).

For a subset of cancers, our comparison of kidney donors with participants in the AHS-2 cohort allowed us to control, to some extent, for the selection of donors to be relatively healthy. Indeed, AHS-2 participants have decreased incidence for certain cancers compared with the US general population (12), which likely arises from practices promoted by the Adventist church. For example, the prevalence of ever-use of tobacco is much lower than in the general population, and only 1% of AHS-2 participants are current smokers. In our study, we excluded AHS-2 members with a history of cancer or other serious medical conditions, and we required recent age-appropriate cancer screening at baseline. AHS-2 participants were not tested for HIV and hepatitis virus infections, but the prevalence was most likely very low. As a result, the AHS-2 participants were much more similar to donors than was the US general population, although the younger age of AHS-2 participants required statistical adjustment. In the adjusted analyses shown in Table 3, donors and AHS-2 participants had similar incidence of breast cancer, liver cancer, and NHL, suggesting that the decreased SIRs that we observed (Table 2) reflect the differences between donors and the US general population described above.

Notably, after seven years following donation, donors had approximately three times the risk of developing kidney cancer compared with AHS-2 participants. This increase is a biologically plausible effect of donation: after donation the remaining kidney experiences hyperfiltration related to hemodynamic changes, which may eventually lead to proteinuria, hypertension, and (rarely) end-stage kidney disease (4, 5), all of which are risk factors for kidney cancer (8, 17, 18). We used a correction factor of 2 to account for the presence of only one kidney in donors, based on the plausible hypothesis that cancer risk is proportional to the number of cells susceptible to cancer (19). In support of this model, the size of many organs (including the kidney) increases with body height, and body height is a strong risk factor for kidney cancer (20). Thus, we assumed that removing one kidney would lead directly to halving of a person’s risk of kidney cancer, before the onset of any compensatory

changes in the remaining kidney, and that any increase in the subsequent occurrence of kidney cancer should be attributed to adverse downstream effects of donation.

Our results thus suggest that the cumulative effects of donation may eventually lead to a tripling of kidney cancer risk on a per-kidney basis. Non-causal explanations of the elevated risk of kidney cancer should be considered but seem less likely. First, the apparent increase could be artifactual, because kidney cancer is subject to overdiagnosis that may result when patients undergo frequent medical evaluation (10), which could occur, e.g., if donors are more likely to receive imaging of their kidney than individuals in the general population. Arguing against this possibility, we did not observe an elevated SIR for localized stage kidney cancer which would have resulted from over-detection of small, clinically insignificant lesions. Another possibility is that hereditary renal diseases shared by donors with their recipients may increase the risk of kidney cancer. However, kidney cancer incidence appeared similar in related and unrelated donors (Table 3).

The increased risk for colorectal cancer among living kidney donors compared with AHS-2 participants is also noteworthy. Chronic kidney disease is associated with increased risk of colorectal cancer (17), and the elevation in colorectal cancer incidence that we observed was only present with extended follow-up after donation. Importantly, AHS-2 participants have lower incidence of colorectal cancer relative to the US general population, which is partly due to the healthy diet encouraged by the Adventist church (12, 21). The dietary patterns among kidney donors are unknown but probably somewhat typical of the US general population, so the elevated incidence of colorectal cancer in donors documented in Table 3 may partly reflect comparison to an especially low-risk population.

Our study has several important strengths, including its large size, representativeness of the US living kidney donor population, and extended follow-up. We also acknowledge several limitations. Notably, we could not identify a perfect reference population, and we therefore view the comparison groups in our study as complementary, trading off large size (US general population) and relatively good general health (AHS-2). While AHS-2 might be considered more appropriate as a comparison group, “general health” is a vague construct, and there were likely relevant differences between AHS-2 and donors that we could not measure. Indeed, we lacked detailed information on cancer risk factors for donors and/or the reference populations (e.g., diet, detailed smoking history, kidney function, family history of cancer) that likely confounded some comparisons. Our data on BMI were incomplete, but adjustment for BMI in a sensitivity analysis produced similar results to the main analysis. We also lacked data on cancer screening among donors and AHS-2 participants during follow-up.

Cancer registries may vary in the completeness of their ascertainment of cancer. We considered the possibility that donors could have moved out of the cancer registry region in which they resided at the time of donation, which would have led to us to increasingly miss cancer diagnoses with longer follow-up. However, the similarity in the SIR results across cancer registries and follow-up time supports the robustness of our cancer ascertainment in donors. We made multiple comparisons, which could lead to some associations arising due to chance. However, the main findings of increased incidence of kidney and colorectal

cancer after 7 years following donation were based on a smaller targeted list of comparisons, and the elevated risk of kidney cancer seen in that analysis has biological plausibility.

Based on the formula for attributable fraction of (adjusted IRR – 1) / (adjusted IRR) and the results in Table 3, we calculate that the excess cancer incidence attributable to donation is 6.2 and 23.4 per 100,000 person-years for kidney cancer and colorectal cancer, respectively, after seven years post-donation. Cancer screening approaches are typically predicated on absolute risk measures (e.g., number needed to screen) (22), and donors' risk for most cancers is similar to or lower than in the general population, suggesting that enhanced screening is unnecessary. Because the absolute increase in colorectal cancer relative to AHS-2 participants is modest, it is reasonable that kidney donors should be screened for colorectal cancer also following general population guidelines (23). There are no currently recommended screening approaches for kidney cancer.

In conclusion, it is reassuring that we did not observe an increase in cancer risk among living kidney donors, overall or for any specific cancer site, compared with the US general population. There were elevated risks of kidney and colorectal cancers after extended follow-up when donors were compared to a cohort of individuals with better-than-average health behaviors and outcomes. Future studies on health consequences of kidney donation should incorporate prospective enrollment of donors and appropriate controls, detailed baseline questionnaire assessment of health behaviors and disease risk factors, collection of biospecimens for measurement of disease biomarkers, and follow-up for multiple outcomes including cancer (6, 24). Finally, we note that the exclusion of potential living donors with a history of cancer in transplant practice is mainly due to the need to prevent inadvertent transmission of cancer to recipients. We therefore believe that our data on cancers that arise after donation should not influence the currently accepted procedures for careful selection of donors based on a thorough medical evaluation, including assessment for a history of cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

AHS-2	Adventist Health Study 2
BMI	body mass index
CI	confidence interval
HIV	human immunodeficiency virus
HPV	human papillomavirus
IRR	incidence rate ratio
NHL	non-Hodgkin lymphoma
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SRTR	Scientific Registry of Transplant Recipients
TCM	Transplant Cancer Match
US	United States

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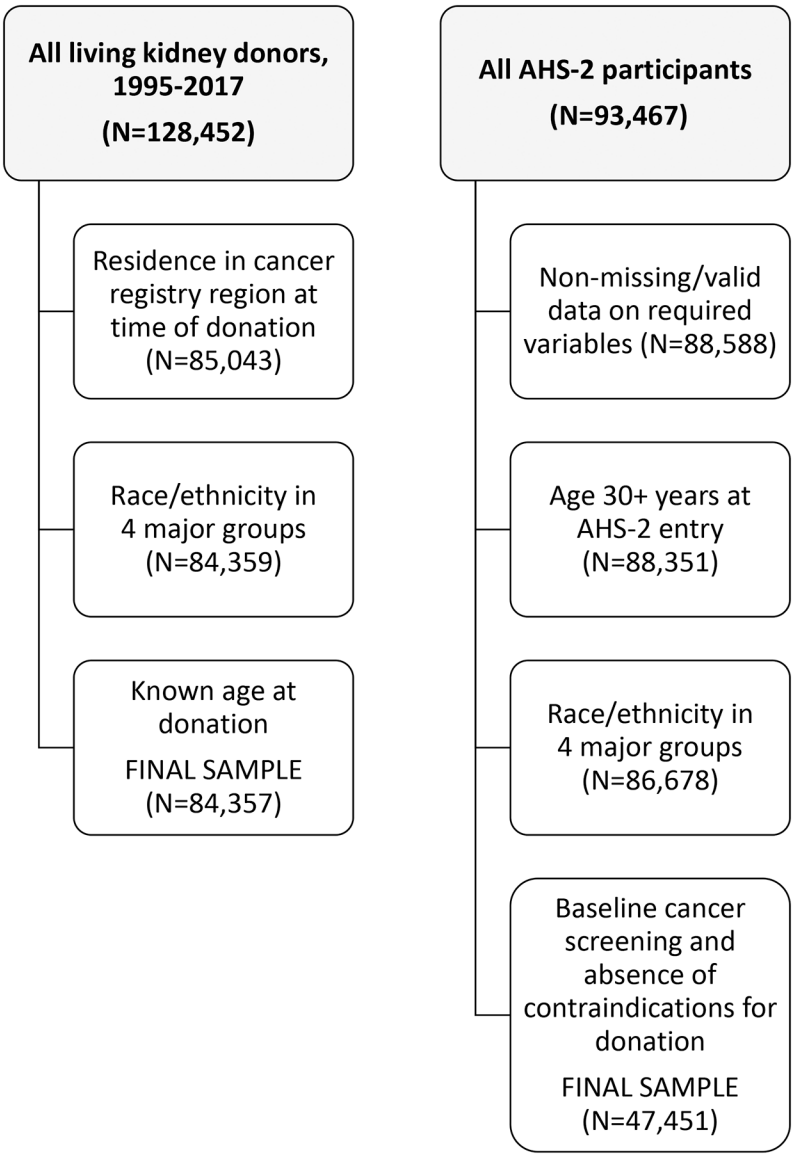

Figure 1.

Subject selection. The figure shows the number of potentially eligible living kidney donors and participants in the Adventist Health Study 2, the number remaining after each exclusion, and the final number of included individuals. Abbreviation: AHS-2 Adventist Health Study 2.

Table 1.

Baseline characteristics of living kidney donors and participants in the Adventist Health Study 2

Characteristic	Living kidney donors (N=84,357)	AHS-2 participants (N=47,451)
Relation to transplant recipient, N (%)[a]		
Related	53,103 (63.0)	--
Unrelated	31,179 (37.0)	--
Sex, N (%)		
Male	33,878 (40.2)	14,179 (29.9)
Female	50,479 (59.8)	33,272 (70.1)
Age at donation or cohort entry in years, mean (sd)	40.7 (11.3)	55.1 (14.0)
Race/ethnicity, N (%)		
White, non-Hispanic	57,336 (68.0)	29,936 (63.1)
Black, non-Hispanic	10,652 (12.6)	13,409 (28.3)
Hispanic	13,176 (15.6)	2308 (4.9)
Asian/Pacific Islander	3193 (3.8)	1798 (3.8)
Region of United States, N (%)		
New England/Mid-Atlantic	20,518 (24.3)	4723 (10.0)
South Atlantic	13,187 (15.6)	9256 (19.5)
East North Central	14,238 (16.9)	5139 (10.8)
East South Central	1387 (1.6)	3394 (7.2)
West North Central	2707 (3.2)	2544 (5.4)
West South Central	10,970 (13.0)	2990 (6.3)
Mountain	5750 (6.8)	3352 (7.1)
Pacific	14,997 (17.8)	14,203 (29.9)
Other/unknown	603 (0.7)	1850 (3.9)
Education level[a]		
Grade school or less	1130 (2.0)	2939 (6.3)
High school	17,797 (31.3)	5632 (12.0)
College or trade school	31,418 (55.3)	29,349 (62.5)
Post-graduate	6427 (11.3)	9019 (19.2)
Body mass index in kg/m^2, mean (sd)[a]	26.9 (4.3)	25.7 (4.0)
Obesity[a,b], N (%)	14,511 (23.1)	7751 (16.3)
Tobacco use, current or former, N (%)[a]	10,580 (24.1)	7443 (15.7)
Hepatitis B virus surface antigen positive, N (%)[a]	251 (0.3)	--
Hepatitis C virus antibody positive, N (%)[a]	282 (0.4)	--
Prior cancer diagnosis (other than basal or squamous cell skin cancer)	390 (0.5)	0 (0)

Data on donors were included from the following cancer registries: Alaska, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kentucky, Louisiana, Michigan, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Texas, Utah, and Virginia.

Abbreviations: AHS-2 Adventist Health Study 2

Donors were included from the following states/territories that provided cancer registry data: Alaska, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kentucky, Louisiana, Michigan, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Texas Utah, and Virginia.

[a]Missing data are excluded from the percentage calculations. Data on donor relationship to transplant recipient were missing for 75 living kidney donors. Data on education were missing for 27,585 donors and 512 AHS-2 participants. Data for donors were missing for body mass index (N=21,404, mostly for donations before 2001, so results are restricted to 2001 and after), hepatitis B surface antigen (N=9759), and hepatitis C virus antibody (N=8683). Data for tobacco use were not collected on donors before 2006; results for donors are presented for 2006–2017. AHS-2 did not collect information on hepatitis B and C infection.

[b]Obesity was defined based on a body mass index greater than 30 kg/m^2.

Table 2.

Standardized incidence ratios for cancer among living kidney donors in the United States

Cancer site	Observed cases	SIR	95% confidence interval		p-value
Total	2830	0.79	0.76	0.82	<0.001
Lip	2	0.43	0.05	1.54	0.307
Salivary gland	11	1.22	0.61	2.18	0.592
Nasopharynx	7	1.55	0.62	3.20	0.340
HPV-related oropharynx	42	1.03	0.74	1.40	0.879
Other oral cavity/pharynx	17	0.53	0.31	0.85	0.005
Esophagus	20	0.72	0.44	1.11	0.152
Stomach	30	0.66	0.45	0.94	0.020
Small intestine	14	0.81	0.44	1.35	0.506
Colorectum	216	0.75	0.65	0.85	<0.001
Anus	11	0.59	0.29	1.05	0.080
Liver	6	0.11	0.04	0.24	<0.001
Intrahepatic bile duct	3	0.42	0.09	1.22	0.143
Gallbladder	6	0.81	0.30	1.77	0.790
Other biliary tract	6	0.58	0.21	1.27	0.222
Pancreas	48	0.64	0.47	0.85	0.001
Larynx	15	0.67	0.38	1.11	0.133
Lung	219	0.71	0.62	0.81	<0.001
Bone	2	0.33	0.04	1.20	0.123
Soft tissue	17	0.68	0.40	1.10	0.129
Melanoma	172	0.86	0.73	0.99	0.041
Other non-epithelial skin	11	0.89	0.45	1.60	0.854
Breast	701	0.87	0.80	0.93	<0.001
Cervix	27	0.53	0.35	0.77	<0.001
Uterus	98	0.56	0.45	0.68	<0.001
Ovary	70	0.99	0.77	1.25	1.000
Vagina	5	2.01	0.65	4.69	0.214
Vulva	6	0.59	0.21	1.27	0.231
Prostate	412	0.95	0.86	1.04	0.264
Testis	12	0.46	0.24	0.81	0.004
Penis	2	1.00	0.12	3.59	1.000
Bladder	29	0.29	0.19	0.41	<0.001
Kidney	35	0.62	0.43	0.87	0.003
Renal pelvis	1	0.51	0.01	2.82	0.826
Eye	12	1.70	0.88	2.97	0.113
Brain	46	0.94	0.69	1.26	0.753
Thyroid	176	1.14	0.97	1.32	0.102

Cancer site	Observed cases	SIR	95% confidence interval		p-value
Hodgkin lymphoma	8	0.35	0.15	0.68	0.001
Non-Hodgkin lymphoma	117	0.64	0.53	0.77	<0.001
Myeloma	37	0.81	0.57	1.11	0.208
Acute lymphocytic leukemia	4	0.69	0.19	1.77	0.631
Acute myeloid leukemia	26	1.20	0.79	1.76	0.394
Chronic myeloid leukemia	10	0.75	0.36	1.39	0.460
Acute monocytic leukemia	1	0.72	0.02	4.00	1.000
Other acute leukemia	0	0.00	0.00	4.22	0.834
Mesothelioma	1	0.24	0.01	1.31	0.151
Kaposi sarcoma	1	0.82	0.02	4.54	1.000
Miscellaneous	102	1.23	1.00	1.49	0.046
Tumors with poorly specified morphology	16	0.39	0.22	0.63	<0.001

Standardized incidence ratios incorporate a calculation of the expected number of cancer cases, based on SEER cancer registry data and stratification of rates by sex, age, race/ethnicity, and calendar year.

Abbreviations: HPV human papillomavirus, SIR standardized incidence ratio

Table 3.

Comparison of cancer incidence among living kidney donors and Adventist Health Study 2 participants

Cancer site	Incidence in donors, per 100,000 person-years (N)	Incidence in AHS-2 participants, per 100,000 person-years (N)	Unadjusted IRR[b] (95%CI)	Age-adjusted IRR[b] (95%CI)	Multivariate adjusted model[b]	
					IRR (95%CI)	p-value
Colorectum	30.9 (206)	67.6 (254)	0.46 (0.38–0.55)	1.32 (1.03–1.69)	1.38 (1.06–1.80)	0.02
By years since donation						
<7	20.6 (80)	67.6 (254)	0.30 (0.24–0.39)	0.90 (0.66–1.22)	0.94 (0.68–1.30)	0.70
7+	45.3 (126)	67.6 (254)	0.67 (0.54–0.83)	1.99 (1.50–2.63)	2.07 (1.54–2.79)	<0.0001
Liver	0.9 (6)	3.2 (12)	0.28 (0.11–0.75)	1.07 (0.29–3.97)	--	0.92
Melanoma	24.3 (162)	26.9 (101)	0.90 (0.70–1.16)	1.73 (1.25–2.39)	1.33 (0.96–1.84)	0.09
Breast	100.4 (670)	174.5 (656)	0.58 (0.52–0.64)	1.01 (0.88–1.15)	1.04 (0.90–1.21)	0.58
Kidney[a]	4.8 (32)	14.6 (55)	0.66 (0.42–1.01)	1.56 (0.89–2.72)	1.48 (0.82–2.68)	0.19
By donor relatedness						
Related	4.5 (20)	14.6 (55)	0.62 (0.37–1.03)	1.52 (0.80–2.87)	1.37 (0.70–2.69)	0.36
Unrelated	5.4 (12)	14.6 (55)	0.74 (0.40–1.38)	1.71 (0.84–3.50)	1.75 (0.82–3.73)	0.15
By years since donation						
<7	1.5 (6)	14.6 (55)	0.21 (0.09–0.49)	0.53 (0.21–1.35)	0.50 (0.19–1.31)	0.16
7+	9.3 (26)	14.6 (55)	1.28 (0.80–2.04)	3.14 (1.73–5.69)	2.97 (1.58–5.58)	0.0007
Non-Hodgkin lymphoma	16.8 (112)	40.4 (152)	0.42 (0.33–0.53)	1.24 (0.89–1.72)	1.08 (0.76–1.52)	0.68

Abbreviations: AHS-2 Adventist Health Study 2, CI confidence interval, IRR incidence rate ratio

Statistically significant incidence rate ratio estimates are underlined.

[a]Counts of kidney cancer reflect the presence of 1 kidney in donors and 2 kidneys in AHS-2 participants. The IRR calculations adjust for this difference in the number of kidneys per person (see Methods).

[b]Incidence rate ratios compare incidence in donors to AHS-2 participants, i.e., IRR > 1 implies greater incidence in donors. Multivariable models are adjusted for sex, attained age (ordinal variable using 5-year categories from 30–34 to 85+ years), race/ethnicity, and United States region. The multivariate model for liver cancer did not converge, and the p-value shown in the multivariable adjusted model results is instead from the age-adjusted model. The multivariate model for melanoma did not converge, and the results are shown from a model without United States region.