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Racial/Ethnic Differences in Cancer Risk After Kidney Transplantation

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Abstract

Transplant recipients have elevated cancer risk, but it is unknown if cancer risk differs across race and ethnicity as in the general population. U.S. kidney recipients (N=87,895) in the Transplant Cancer Match Study between 1992 and 2008 were evaluated for racial/ethnic differences in risk for six common cancers after transplantation. Compared to white recipients, black recipients had lower incidence of non-Hodgkin lymphoma (NHL) (adjusted incidence rate ratio [aIRR] 0.60, p<0.001) and higher incidence of kidney (aIRR 2.09, p<0.001) and prostate cancer (aIRR 2.14, p<0.001); Hispanic recipients had lower incidence of NHL (aIRR 0.64, p=0.001), and lung (aIRR 0.41, p<0.001), breast (aIRR 0.53, p=0.003) and prostate cancer (aIRR 0.72, p=0.05). Colorectal cancer incidence was similar across groups. Standardized incidence ratios (SIRs) measured the effect of transplantation on cancer risk and were similar for most cancers (p≥0.1). However, black and Hispanic recipients had larger increases in kidney cancer risk with transplantation (SIRs: 8.96 in blacks, 5.95 in Hispanics vs. 4.44 in whites), and only blacks had elevated prostate cancer risk following transplantation (SIR: 1.21). Racial/ethnic differences in cancer risk after transplantation mirror general population patterns, except for kidney and prostate cancers where differences reflect the effects of end-stage renal disease or transplantation.

Keywords

ethinic/racial disparities in cancer risk; cancer risk attributable to transplantation; cumulative incidence of cancer

Introduction

Kidney transplantation offers improved survival and quality of life compared to other treatments for end-stage renal disease (ESRD) [1]. These benefits are not without risk, however, including increased risk for cancer after transplantation [2-4]. The reasons for this increased risk are multifactorial and stem from a combination of decreased control of

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oncogenic viruses due to the chronic immunosuppression necessary to prevent rejection, the high prevalence of certain chronic medical conditions associated with ESRD, and the intrinsic oncogenic properties of maintenance immunosuppression medications that may also contribute.

In the U.S. general population, cancer risk varies substantially across different races and in people of Hispanic ethnicity compared with non-Hispanics. Compared to whites, blacks have increased risk for cancers of the lung (among men), kidney, colorectum, prostate, pancreas, liver, and esophagus, as well as for multiple myeloma [5-10]. Blacks have decreased risk for non-Hodgkin lymphoma (NHL), breast cancer, and endometrial cancer compared to whites in the general population [5, 11-13]. Hispanics have increased risk for cancers of the cervix, liver, gall bladder, and stomach, and for acute lymphocytic leukemia, and decreased risk for cancers of the lung, colorectum, prostate, and breast compared to whites [14]. Many factors contribute to these differences, including differing environmental exposures, diets, occupations, health behaviors, genetics, socioeconomic status, access to health care, and cancer screening behaviors [15-22].

We are unaware of any previous research into racial/ethnic differences in cancer risk after transplantation. In the present study, we used several approaches to understand if different racial/ethnic groups face different risks for cancer after transplantation. First, we compared the incidence of common cancers among kidney recipients according to race/ethnicity. Since baseline (general population) cancer risks vary by race/ethnicity, we also explored whether the risk attributable to the transplant differed across groups. Finally, since risk of one of the cancers of interest (namely, kidney cancer) is elevated among people with ESRD [23, 24], and this increase could vary by race/ethnicity, we compared the risk of kidney cancer between kidney recipients and candidates on the transplant waitlist. We used data on more than 87,000 U.S. kidney recipients from the Transplant Cancer Match Study.

Methods

The Transplant Cancer Match Study links data from the Scientific Registry of Transplant Recipients (SRTR, 1987-2008) with 14 population-based U.S. cancer registries (http://transplantmatch.cancer.gov/) [4]. The SRTR includes data on all solid organ transplants in the United States. Participating cancer registries, which together cover approximately 43% of the U.S. transplant population, ascertained the occurrence of malignancies (other than basal cell and squamous cell skin cancer) based on mandatory reporting from hospitals, medical providers, and pathology laboratories. Following linkage with the SRTR, investigators retain only anonymized data from the cancer registries. The study was approved by human subjects committees at the National Cancer Institute and, as required, at participating cancer registries.

In the present study, we included kidney-only recipients classified by the SRTR as white, black/African American, or Hispanic/Latino. The SRTR race/ethnicity variable is derived from kidney transplant candidate registry forms completed by transplant centers as required by participation in the U.S. transplant network. Multiple races/ethnicities may be marked for a given individual, although in practice more than 99% of candidates have a single race/

ethnicity entered. In our analysis, any recipient with the category Hispanic/Latino indicated was included in our Hispanic category. This approach assumes that remaining recipients categorized as white are non-Hispanic whites, and those categorized as black are non-Hispanic black, although it is likely that the white and black categories include some Hispanics.

For kidney recipients, follow-up started at transplantation and ended at death, graft failure, retransplantation, loss of follow-up by the transplant registry, or end of cancer registry coverage. Recipients were further restricted to those who received their transplant during years of cancer registry coverage between 1992 and 2008. We used the linked cancer registry data to identify incident cancers following transplantation. We focused on the six most common cancers after kidney transplantation: NHL, and cancers of the lung, kidney, colorectum, prostate, and breast. Breast cancer analyses were limited to female recipients; prostate cancer analyses were limited to male recipients.

Because kidney cancer incidence is markedly elevated in ESRD patients [23, 24], we assessed data for this cancer in candidates as well as recipients. We evaluated first-time candidates for kidney transplantation who were listed in the SRTR. Follow-up started on the date of first active waitlisting or January 1, 1992 (whichever was later) and continued until transplantation, death, or end of cancer registry coverage. We included 132,308 candidates residing in areas covered by participating cancer registries and followed during 1992-2008. As for recipients, kidney cancers were identified using linked cancer registry data.

Statistical analyses

For kidney recipients, we used Poisson regression to quantify racial/ethnic differences in cancer incidence (the number of cases observed per unit person-time at risk) after transplantation. Incidence rate ratios (IRRs) comparing recipients were adjusted for age at transplant (0-35, 36-50, 51-60, >60), gender, calendar year of transplant (1987-1996, 1997-2003, 2004-2008), retransplantation (i.e., whether this was a first kidney vs. subsequent kidney transplant), and HLA mismatch (1-6 vs. 0).

As noted above, racial/ethnic differences in cancer incidence after transplantation could be caused by different baseline cancer incidence in the general population, different risks attributable to transplantation, or both. To test for differences in the effect of transplantation, we calculated the standardized incidence ratio (SIR) of each cancer of interest separately for each racial/ethnic group. The SIR compares cancer risk in kidney transplant recipients to people in the general population who are demographically similar, including in terms of race/ethnicity. The SIR is the observed count of cancers divided by the expected count, which is calculated by applying general population rates to person-time in the transplant cohort stratified by gender, age, race/ethnicity, and calendar year. For whites and blacks, the general population rates were derived from data from all participating cancer registries. For Hispanics, general population rates were from NCI's Surveillance, Epidemiology, and End Results program (SEER, www.seer.cancer.gov); because SEER data on Hispanics were first available in 1992, all kidney recipients transplanted in earlier years were excluded. We calculated 95% confidence intervals for the SIR using an exact method. We compared SIRs across racial/ethnic groups using Poisson regression. An elevated SIR (SIR>1) indicates an

increased risk for that cancer type after transplantation compared to the same racial/ethnic group in the general population, while a difference in SIRs between racial/ethnic groups implies that transplantation has a different effect on cancer risk across racial/ethnic groups.

Since kidney cancer is associated with ESRD, we did an additional set of analyses to clarify the relationship between race/ethnicity, ESRD, and kidney cancer risk. First, we calculated SIRs for kidney candidates vs. the general population, similar to the approach for recipients stratified by race/ethnicity. Second, we compared kidney cancer incidence in kidney recipients and candidates separately for each race/ethnic group, adjusting for attained age (0-14, 15-29, 30-44, 45-59, >59), gender, and attained calendar year (1992-1996, 1997-2003, 2004-2008) using Poisson regression. We then assessed whether these IRRs differed across the race/ethnicity groups by testing for an interaction between candidate/recipient status and race/ethnicity.

All p-values were two-sided and a p-value of 0.05 was considered significant. Analyses were performed using Stata 12.0/MP for Linux (StataCorp, www.stata.com, College Station, TX).

Results

There were 87,895 patients in the Transplant Cancer Match Study who underwent kidney transplantation between 1992 and 2008, of whom 56.7% were white, 23.5% black, and 19.8% Hispanic. Demographic characteristics differed slightly among the racial/ethnic groups (Table 1). Black and Hispanic recipients were slightly younger (median age at transplant 45 years in blacks, 43 in Hispanics, vs. 47 in whites), less likely to have received a retransplantation, less likely to have zero HLA mismatches, and more likely to have undergone transplantation in the most recent calendar years.

As shown in Table 2, black kidney recipients had lower incidence of NHL (adjusted incidence rate ratio [aIRR] 0.60, 95% CI 0.46-0.77) and breast cancer (aIRR 0.62, 95% CI 0.43-0.91), and higher incidence of kidney cancer (aIRR 2.09, 95% CI 1.68-2.60) and prostate cancer (aIRR 2.14, 95% CI 1.75-2.63) compared to white recipients. Hispanic recipients had lower incidence of NHL (aIRR 0.64, 95% CO 0.49-0.82), lung cancer (aIRR 0.41, 95% CI 0.28-0.60), prostate cancer (aIRR 0.72, 95% CI 0.52-0.99) and breast cancer (aIRR 0.53, 95% CI 0.35-0.80) compared to white recipients.

Compared to the same racial/ethnic group in the general population, kidney recipients in all racial/ethnic groups had higher risk of NHL and kidney cancer (Table 3). SIRs for NHL were similar in the three racial/ethnic groups (ranging from 4.87 to 6.02), but the SIRs for kidney cancer in blacks and Hispanics were significantly higher than in whites (8.96 and 5.95 vs. 4.44, Table 3). Lung cancer risk was approximately 30-40% higher than in the general population, with similar SIRs (1.33-1.39) in the three racial/ethnic groups. Colorectal cancer risk was similar to risk in the general population, and SIRs did not vary among the three groups. For breast cancer, female recipients in all groups had lower risk than the general population, although the deficit was most pronounced and statistically significant only for blacks (SIR 0.61, 95% CI 0.43-0.86). Among males, white and Hispanic

kidney recipients had lower risk of prostate cancer than the general population (SIRs 0.70-0.75), but black recipients had a higher risk than the general population (SIR 1.21, 95% CI 1.03-1.42).

As shown in Table 4, kidney candidates in all racial/ethnic groups had increased risk of kidney cancer compared to the same racial/ethnic group in the general population. The SIR for kidney cancer in black candidates (14.20) was higher than in whites or Hispanics (5.87 and 6.99, respectively; Table 4). Furthermore, kidney cancer risk was actually lower after transplant than in candidates of the same race/ethnicity. The degree of this reduction was similar across race/ethnicity (adjusted IRRs vs. candidates 0.68-0.86, p-values for interaction with race/ethnicity 0.28 for blacks and 0.61 for Hispanics).

Discussion

Among kidney recipients, risk for several common cancers differs by race/ethnicity. Black kidney recipients have a higher risk for kidney cancer and prostate cancer, and lower risk for NHL and breast cancer than white kidney recipients. Hispanic kidney recipients have a lower risk for NHL, lung cancer, prostate cancer, and breast cancer compared to white kidney recipients. We found that most of these racial/ethnic differences after transplantation were attributable to baseline differences in risks of cancer, since the cancer risk attributable to transplantation (as assessed by the SIR) was similar between races/ethnicities. We discuss below two exceptions to this pattern—kidney and prostate cancers—for which varying SIRs suggest different effects of transplantation and ESRD on risk across racial/ethnic groups.

First, though, we highlight that in the U.S. general population, racial/ethnic groups have different risks for each of the cancers that we studied. Compared to whites, blacks have increased risk for lung, kidney, colorectal, and prostate cancers while Hispanics have decreased risk for lung, kidney, and colorectal cancers [5, 14]. Causes for these racial/ethnic differences in baseline risk are varied and are posited to include differences in exposures, diet, health conditions, lifestyle, genetics, and screening rates [15-22]. In addition, cancer risk factors might have different effects across groups. For instance, there is evidence that blacks may have an increased susceptibility to cigarette smoke, while Hispanics may have decreased susceptibility [25, 26]. The incidence of NHL is lower for blacks than whites in the U.S. general population, although the explanation is unclear [27]. Differences in breast cancer risk may reflect differences in genetics or lifetime reproductive history, or perhaps variation in breast cancer screening related to healthcare access [19, 28-31].

Transplantation has a variable effect on risk for specific cancers [2-4]. A markedly elevated risk of NHL is largely due to the adverse effects of immunosuppression on control of Epstein-Barr virus infection [2-4]. An elevated risk for lung cancer with kidney transplantation has been demonstrated across studies and, among smokers, could be partly caused by chronic pulmonary inflammation or repeated lung infections [2-4, 32]. Among kidney recipients, risk for colorectal cancer is typically similar to the general population or slightly increased, while the risks of breast and prostate cancers are decreased [2, 3]. The reasons for the deficits in breast and prostate cancers are unclear, but one possibility is the effect of pre-transplant cancer screening. It is recommended that ESRD patients undergo

age-appropriate cancer screening before placement on the kidney waitlist [33]. If breast or prostate cancer were found, those patients would be ineligible for transplantation. Removal of such patients with cancer from the transplant population would lessen the incidence of these cancers among recipients after transplantation.

SIRs were similar across races/ethnicities with the exception of kidney cancer and prostate cancer. This finding suggests that for many cancer outcomes, the cancer risk attributable to transplantation is similar across racial/ethnic groups. That is, the biological effects of transplantation add to other risk factors to promote the development of cancer similarly across racial/ethnic groups, and transplantation preserves the relative ranking in cancer risk among groups. For example, in lung cancer, the prevalence of smoking or its effects may differ by race/ethnicity, but immunosuppression or other transplant-related factors amplify the risk associated with smoking with the same intensity across racial/ethnic categories. Among female recipients, the deficit of breast cancer appeared to be stronger in blacks than whites (Table 3), but the difference was of borderline significance (p=0.04).

In contrast, kidney cancer risk was elevated for all kidney recipients compared to the general population, but it increased more for black kidney recipients than for white or Hispanic recipients. However, when compared to kidney candidates, we observed that recipients actually had less risk. Thus, the increased risk for kidney cancer among black kidney recipients does not appear to be attributable to transplantation: instead there are strong racial/ethnic differences in risk among kidney candidates. Given the association of kidney cancer with acquired polycystic kidney disease (APKD) and the increased prevalence of APKD with time on dialysis [34, 35] the difference among black candidates may partly result from longer waitlist time and time on dialysis for blacks compared to whites [36, 37]. The amplification of kidney cancer risk associated with ESRD in blacks could also be a result of racial differences in the primary cause of ESRD or the prevalence of obesity or uncontrolled hypertension [38]. The effect of hypertension on development of kidney cancer may be stronger in blacks than whites and could explain our findings [39].

For prostate cancer, the risk was lower in white and Hispanic kidney recipients than in the general population, while for black men the risk was actually increased after transplantation. Because a large fraction of prostate cancers are detected in asymptomatic men due to screening [40], one possibility is that black kidney recipients received more prostate cancer screening than whites and Hispanics. In turn, higher rates of screening in black kidney recipients could have been driven by clinicians' recognition of a higher risk of prostate cancer among black men in the general population.

Strengths of our study include use of a large, nationally representative cohort of ethnically diverse kidney recipients. Cancer ascertainment was based on cancer registry data with mandatory reporting, and was reliable and uniform across racial/ethnic groups. Nonetheless, any study that examines differences in racial/ethnic groups must acknowledge the imperfect nature of these classifications. We relied on transplant centers' classification of recipients at the time of initial evaluation for transplantation, and the white and black categories likely included an unknown proportion of Hispanics. Furthermore, our Hispanic category represents a heterogeneous population in terms of genetic background, culture, and duration

of U.S. residence. In general, race/ethnicity serves as a marker for other genetic, exposure, and lifestyle factors [41]. Although we conjectured that racial/ethnic differences in screening rates for cancers before and after transplantation could have contributed to variation in cancer risk, we do not have data on cancer screening practices among transplant candidates or recipients. In addition, we lacked data on other health behaviors and exposures that could have impacted cancer risk.

To conclude, we found that cancer risk varies by race/ethnicity in kidney recipients. For the most part, these differences parallel the patterns seen in the general population, suggesting that transplantation has a consistent effect across groups on underlying biological processes and preserves the underlying racial/ethnic differences in cancer risk. Nonetheless, the risk attributable to transplantation or ESRD for kidney and prostate cancer was increased in blacks compared to whites or Hispanics. Further research should aim to elucidate the mechanisms that underlie racial/ethnic differences in cancer risk among transplant recipients and candidates and to determine optimal cancer screening and prevention measures.

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Abbreviations

NHL	non-Hodgkin lymphoma
aIRR	adjusted incidence rate ratio
SIR	standardized incidence ratio

ESRD	end-stage renal disease
U.S.	United States
SRTR	Scientific Registry of Transplant Recipients
SEER	Surveillance Epidemiology and End Results
APKD	acquired polycystic kidney disease

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Table 1

Demographic characteristics of U.S. kidney recipients in the Transplant Cancer Match Study by race/ethnicity

	White N (%) 49,827 (100)	Black N (%) 20,678 (100)	Hispanic N (%) 17,390 (100)
Age at transplant, years			
0-35	12,709 (25.5)	5,635 (27.3)	6,176 (35.5)
36-50	16,415 (32.9)	7,420 (35.9)	5,428 (31.2)
51-60	11,863 (23.8)	4,951 (23.9)	3,543 (20.4)
>60	8,840 (17.7)	2,672 (12.9)	2,243 (12.9)
Gender			
Male	30,139 (60.5)	12,094 (58.5)	10,363 (59.6)
Female	19,688 (39.5)	8,584 (41.5)	7,027 (40.4)
Calendar year of transplant			
1992-1996	12,176 (24.4)	4,190 (20.3)	3,215 (18.5)
1997-2003	23,056 (46.3)	9,545 (46.1)	7,772 (44.7)
2004-2008	14,595 (29.3)	6,943 (33.6)	6,403 (36.8)
Retransplantation			
No	44,052 (88.4)	19,051 (92.1)	15,992 (92.0)
Yes	5,775 (11.6)	1,627 (7.9)	1,398 (8.0)
HLA mismatches			
0	8,406 (16.9)	1,409 (6.8)	2,539 (14.6)
1-6	40,935 (82.2)	19,129 (92.5)	14,670 (84.4)
Missing	486 (1.0)	140 (0.7)	181 (1.0)

Table 2

Incidence of cancer among kidney recipients according to race/ethnicity.

Cancer Outcome	Incidence per 100,000 person years (n)			Adjusted incidence rate ratio (95% CI), p-value	
	White	Black	Hispanic	Black vs. white	Hispanic vs. white
NHL	167.3 (360)	95.7 (71)	105.6 (74)	0.60 (0.46-0.77) <0.001	0.64 (0.49-0.82) 0.001
Lung cancer	126.0 (271)	129.4 (96)	41.4 (29)	1.17 (0.93-1.49) 0.2	0.41 (0.28-0.60) <0.001
Kidney cancer	93.4 (201)	190.0 (141)	98.5 (69)	2.09 (1.68-2.60) <0.001	1.16 (0.88-1.53) 0.3
Colorectal cancer	60.0 (129)	64.7 (48)	31.4 (22)	1.21 (0.87-1.69) 0.3	0.65 (0.41-1.02) 0.06
Prostate cancer	171.5 (221)	373.5 (157)	108.4 (45)	2.14 (1.75-2.63) <0.001	0.72 (0.52-0.99) 0.05
Breast cancer	184.3 (164)	105.7 (34)	91.1 (26)	0.62 (0.43-0.91) 0.04	0.53 (0.35-0.80) 0.003

Poisson models are adjusted for age at transplant, gender, calendar year of transplant, retransplantation and zero mismatch.

Table 3

Comparison of cancer risk in kidney recipients with risk in the general population, according to race/ethnicity

Cancer Outcome	Standardized incidence ratio (95% CI)			P-value for difference in SIRs	
	White	Black	Hispanic	Black vs. white	Hispanic vs. white
NHL	6.02 (5.43-6.68)	4.87 (3.80-6.14)	5.57 (4.37-6.99)	0.1	0.5
Lung cancer	1.39 (1.23-1.57)	1.34 (1.08-1.63)	1.33 (0.89-1.91)	0.7	0.8
Kidney cancer	4.44 (3.84-5.09)	8.96 (7.54-10.57)	5.95 (4.63-7.53)	<0.001	0.02
Colorectal cancer	0.94 (0.78-1.12)	0.93 (0.68-1.23)	0.75 (0.47-1.13)	0.9	0.3
Prostate cancer	0.75 (0.65-0.85)	1.21 (1.03-1.42)	0.70 (0.51-0.94)	<0.001	0.7
Breast cancer	0.91 (0.77-1.06)	0.61 (0.43-0.86)	0.77 (0.50-1.12)	0.04	0.4

Standardized incidence ratios (SIR) are the observed count of each cancer divided by the expected count calculated by applying general population rates to person-time in the transplant cohort stratified by gender, age at transplant, race/ethnicity, and calendar year of transplant. General population rates were derived from all participating cancer registries (whites and blacks) and SEER registries (Hispanics). Poisson regression was used to compare SIRs between racial/ethnic groups.

Table 4

Comparison of kidney cancer risk in candidates for kidney transplantation, kidney recipients, and the general population, according to race/ethnicity.

	White	Black	Hispanic
SIR in candidates (95% CI)	5.87 (5.15-6.65)	14.20 (12.85-15.64)	6.99 (5.77-8.40)
SIR in recipients (95% CI)	4.44 (3.84-5.09)	8.96 (7.54-10.57)	5.95 (4.63-7.53)
aIRR for recipients vs. candidates (95% CI)	0.80 (0.65-0.97)	0.68 (0.57-0.81)	0.86 (0.66-1.13)

Standardized incidence ratios (SIR) are the observed count of each cancer divided by the expected count calculated by applying general population rates to person-time in the cohort stratified by those variables available for both recipients and candidates, namely: gender, attained age, race/ethnicity, and attained year. General population rates were derived from all participating cancer registries (whites and blacks) and SEER registries (Hispanics). Poisson regression was used to compare adjusted incidence rates (aIRR) between recipients and candidates and to test for interaction by racial/ethnic group.