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Article

Sex differences in cancer incidence among solid organ transplant recipients

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Abstract

Background: Males have 2–3-fold greater risk of cancer than females at most shared anatomic sites, possibly reflecting enhanced immune surveillance against cancer in females. We examined whether these sex differences remained among immunocompromised adults.

Methods: Using the Transplant Cancer Match (TCM) study, we estimated the male-to-female incidence rate ratio in TCM (M:F $IRR_{Transplant}$) for 15 cancer sites diagnosed between 1995 and 2017 using Poisson regression. Male to female IRRs in the general population (M:F IRR_{GP}) were calculated using expected cancer counts from the Surveillance, Epidemiology, and End Results Program, standardized to the transplant population on age, race and ethnicity, and diagnosis year. Male to female IRRs were compared using a chi-square test.

Results: Among 343 802 solid organ transplants, 211 206 (61.4%) were among men and 132 596 (38.6%) among women. An excess cancer incidence in males was seen in transplant recipients, but the sex difference was attenuated for cancers of the lip (M:F $IRR_{Transplant}$: 1.81 vs M:F IRR_{GP}: 3.96; $P < .0001$), stomach (1.51 vs 2.09; $P = .002$), colorectum (0.98 vs 1.43; $P < .0001$), liver (2.39 vs 3.44; $P = .002$), kidney (1.67 vs 2.24; $P < .0001$), bladder (2.02 vs 4.19; $P < .0001$), Kaposi sarcoma (1.79 vs 3.26; $P = .0009$), and non-Hodgkin lymphoma (1.34 vs 1.64; $P < .0001$). The M:F $IRR_{Transplant}$ was not statistically different from the M:F IRR_{GP} for other cancer sites.

Conclusions: Although male solid organ transplant recipients have higher cancer incidence than female recipients, the attenuation in the male to female ratio for many cancers studied relative to the general population might suggest the importance of immunosurveillance, with some loss of advantage in female recipients due to immunosuppression after transplantation.

Cancer is a major cause of morbidity and mortality in the United States. For unclear reasons, the burden of nonreproductive cancer is significantly higher among men than women, with men having at least twice the risk of most cancers compared to women at most shared anatomic sites (1). A higher risk of non-sex-specific cancers among men often has been attributed to sex-based differences in carcinogenic exposures or behaviors—for example, those related to smoking, alcohol use, diet, or physical activity. However, even after adjustment for these risk factors, the male bias in cancer incidence at most sites remains (2).

These differences in cancer incidence by sex suggest that there are underlying biological sex differences in cancer susceptibility. Sex differences in cancer risk may arise from genetic mechanisms, such as the escape of tumor suppressor genes located on the inactivated X-chromosome (Xi) (3,4). The sex hormones progesterone and estrogen are also associated with a lower risk of some nonreproductive cancers in women (4,5), whereas testosterone has been shown to promote tumor growth in both sexes (6,7).

An additional possible explanation is that females may have enhanced "immunosurveillance," in which the immune system recognizes and targets premalignancies (8). Females are observed to have more robust innate and adaptive immune responses than males (9,10). This enhanced immune surveillance results in increased susceptibility to autoimmune diseases among females and may contribute to a decreased incidence of many tumor types (9).

Exploring sex differences in cancer incidence within an immunocompromised population, such as solid organ transplant recipients, may help clarify the role of sex-specific immune differences in carcinogenesis. The use of immunosuppressive medications to prevent graft rejection after organ transplantation results in a state of poor immune surveillance. This immunosuppression is associated with a 2- to 4-fold elevated risk of cancer overall and even stronger increases for malignancies caused by viral infections (11,12).

If differences in cancer incidence are explained by differences in immunity, then the female advantage may be reduced in a

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population of solid organ transplant recipients due to decreased immune surveillance with immunosuppressive therapy use. Several studies have shown that cancer incidence rates are elevated in both sexes among solid organ transplant recipients compared to the general population (11,13,14). However, these studies have not addressed whether sex differences in cancer incidence are present to the same degree among transplant recipients as in the general population. Furthermore, these studies were conducted mostly among kidney transplant recipients (13,14), and sex-based differences in cancer risk may vary by transplanted organ due to the degree of immunosuppression. In the present study, we examined the male-to-female ratio in the risk of incident cancer among solid organ transplant recipients in the United States.

Methods

The Transplant Cancer Match (TCM) study links data from the US Scientific Registry of Transplant Recipients (SRTR) with 33 population-based cancer registries (11). The TCM study includes cancer data for two-thirds of solid organ transplant recipients the United States since 1995. SRTR contains information on all solid organ transplants beginning in 1987, including demographic characteristics, transplanted organs, indication for transplantation, and medical comorbidities. This study was considered not human subjects research by the National Cancer Institute and was approved by the institutional review boards at the participating cancer registries.

There was a total of 591 780 solid organ transplants in the SRTR during 1995–2017. We excluded transplants from individuals who did not reside in regions covered by participating cancer registries at the time of transplantation or that did not have follow-up (n = 181 929). We also excluded recipients less than 18 years old at transplantation (n = 27 700), and those whose race and ethncity was not reported as non-Hispanic White, non-Hispanic Black, Hispanic, or Asian or Pacific Islander (n = 3513) to allow comparison with cancer rates from the US general population. Finally, we excluded recipients who had a cancer diagnosis prior to transplantation (n = 34 836). The final analysis cohort consisted of 343 802 transplants in 322 007 individuals.

We used linked cancer registry data to identify incident cancers after transplantation, focusing on the 15 most common non-sex-specific cancer sites after transplantation: cancers of the lip, oral cavity, oropharynx, esophagus, stomach, colorectum, liver, larynx, lung, kidney, bladder, and thyroid, along with melanoma of the skin, non-Hodgkin lymphoma ([NHL], including chronic lymphocytic leukemia), and Kaposi sarcoma (Supplementary Table 1, available online). Due to known sex differences in colorectal cancer incidence for various subsites (15,16), we also separately examined incidence at the proximal colon, distal colon, and rectum. Important sex differences have been noted for histologic subtypes for esophageal cancer (17), lung cancer (18,19), and lymphoma (20). Consequently, we examined sex differences separately for esophageal squamous cell carcinoma and adenocarcinoma; lung squamous cell carcinoma, adenocarcinoma, and small cell carcinoma; and diffuse large B-cell lymphoma.

We used Poisson regression models to estimate the male-to-female incidence rate ratio for each cancer and the corresponding 95% confidence interval (95% CI) in the TCM population (M:F $IRR_{Transplant}$). Follow-up began at transplantation and ended at the earliest of graft failure or retransplantation, death, loss to follow-up by SRTR, or end of cancer registry coverage. We calculated the M:F IRR for the general population (M:F IRR_{GP}) for each cancer type using expected cancer counts from the US Surveillance, Epidemiology, and End Results (SEER) Program (SEER13) cancer registries (21), standardized to the transplant population on age, race and ethnicity, and year of cancer diagnosis. The M:F IRR_{GP} for the Kaposi sarcoma analysis used data from SEER9 (1973–1979) to reflect population estimates before the HIV epidemic (22). The analyses for Kaposi sarcoma were restricted to White and Black individuals as Hispanic and Asian Pacific Islander ethnicity were not captured in SEER9. We tested differences in the M:F $IRR_{Transplant}$ to the M:F IRR general population (M:F IRR_{GP}) for each cancer type with a chi-square test using the formula $[\log(\text{M:F } IRR_{Transplant}) - \log(\text{M:F } IRR_{GP})]^2 / \text{Var}[\log(\text{M:F } IRR_{Transplant})]$ with 1 degree of freedom, assuming that the M:F IRR_{GP} was estimated without variation as it was based on very large numbers. Two-sided *P* values less than .05 were considered statistically significant.

We conducted several additional analyses. First, we stratified the analysis for each cancer site by age at transplantation (<55 and ≥55 years) to evaluate the role of sex hormones in shaping the immune response. Because the sex bias among older people in the general population already reflects the reduction of estrogen and progesterone levels in women after menopause, we hypothesized that any attenuation in transplant recipients resulting from immunosuppression would be less apparent in older than younger women. We statistically compared the M:F $IRR_{Transplant}$ to the M:F IRR_{GP} within each age group for each cancer type using the chi-square test described in the previous paragraph.

Second, to assess the extent to which confounding could account for sex differences in cancer incidence among transplant recipients, we adjusted the M:F $IRR_{Transplant}$ estimates for the categorical variables of age at transplantation (in 5-year increments), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or Asian or Pacific Islander), Yost index (a measure of socioeconomic status at the Census group level) (23), transplanted organ (kidney, liver, heart and/or lung, or other/multiple), calendar year of transplantation (1995–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2017), and time since transplantation (modeled as a time-dependent variable). Because there are notable gender disparities in transplantation, with women often waiting longer for organs than men (24), we also adjusted for time on the transplant waitlist (continuous). Models for melanoma and lip cancer were additionally adjusted for prior diagnosis of a posttransplant squamous cell carcinoma or basal cell carcinoma (time-dependent) and annual average daily ultraviolet B radiation exposure (based on location of residence). Models for several cancers included additional adjustments: kidney and colorectal cancers, for body mass index (BMI, <18.5, 18.5–24.9, 25.0–29.9, or ≥30 kg/m^2) and diabetes mellitus (yes, no, or missing); thyroid cancer, for BMI; NHL, for Epstein-Barr virus (EBV) status at transplantation (positive, negative, or missing); and liver cancer, for diabetes, BMI, and hepatitis B and C virus status (HBV or HCV; positive, negative, or missing).

We also estimated M:F $IRR_{Transplant}$ separately by transplanted organ. We did not have information on the dose of immunosuppressive medications, so this analysis allowed us to assess the sex bias according to degree of immunosuppression: liver recipients (least immunosuppression), kidney recipients (intermediate), and heart/lung recipients (greatest). We used Poisson regression models to test for interactions of sex and transplanted organ. Finally, smoking status was available only for lung transplant recipients. Therefore, we conducted a sensitivity analysis restricted to lung recipients and evaluated models for smoking-

related cancers (cancers of the esophagus, oral cavity, lip, larynx, lung, and bladder) with additional adjustment for smoking status.

All analyses were conducted using SAS, version 9.4 (SAS System, Cary, NC).

Results

Among 343 802 solid organ transplants occurring between 1995 and 2017, 211 206 (61.4%) were among men and 132 596 (38.6%) were among women (Table 1). Men and women differed significantly with respect to all the examined characteristics, although these differences were small in magnitude. Compared to women, men were slightly older at transplantation (median 51.0 years vs 50.0 years), were more likely to be non-Hispanic White (61.9% vs 58.0%), and had higher socioeconomic status (median Yost Index 0.45 vs 0.40). Men were more likely to receive a heart and/or lung transplant (16.2% vs 12.0%). Women had been on the transplant waitlist longer than men (median of 257 days vs 230 days). Men were more likely than women to have a higher BMI (median 26.7 vs 26.0), diabetes (31.8% vs 28.2%), HBV infection (10.1% vs 7.9%), and HCV infection (10.5% vs 6.7%).

For nearly all cancer sites examined, male transplant recipients had a higher incidence than female recipients (M:F $IRR_{Transplant}$ >1; Table 2). For 8 of the 15 cancer sites examined (excluding subsites or histologic subtypes), the M:F $IRR_{Transplant}$ was significantly lower than the M:F IRR_{GP}: lip (M:F $IRR_{Transplant}$: 1.81 vs M:F IRR_{GP}: 3.96; $P < .0001$), stomach (1.51 vs 2.09; $P = .002$), colorectum (0.98 vs 1.43; $P < .0001$), liver (2.39 vs 3.44; $P = .002$), kidney (1.67 vs 2.24; $P < .0001$), bladder (2.02 vs 4.19; $P < .0001$), Kaposi sarcoma (1.79 vs 3.26; $P = .0009$), and NHL (1.34 vs 1.64; $P < .0001$). The M:F $IRR_{Transplant}$ was also significantly lower than the M:F IRR_{GP} for three of the cancer subsites and subtypes we examined: rectum (1.26 vs 1.71; $P = .019$), lung squamous cell carcinoma (1.76 vs 2.15; $P = .002$), and diffuse large B-cell lymphoma (1.25 vs 1.59; $P < .0001$). Proximal colon cancer showed a female predominance in the transplant population but not the general population (M:F $IRR_{Transplant}$ 0.82 vs M:F IRR_{GP} 1.18; $P < .0001$). Thyroid cancer showed a female predominance in the transplant and the general populations, but the M:F IRR was attenuated in the transplant population compared to the general population estimate (M:F $IRR_{Transplant}$ 0.49 vs M:F IRR_{GP} 0.41; $P = .022$) The M:F $IRR_{Transplant}$ was not statistically different from the M:F IRR_{GP} at the other main cancer sites (oral cavity, oropharynx, esophagus, and melanoma).

Table 1. Characteristics of US transplant recipients by sex (1995–2017)[a]

Characteristic		Total N = 343 802	Males n = 211 206	Females n = 132 596	P-value
Age at transplantation, years	Median (IQR)	51.0 (40, 59)	51.0 (41, 60)	50.0 (38, 59)	<.0001
Race and ethnicity	Asian or Pacific Islander	18 561 (5.4)	10 559 (5.0)	8002 (6.0)	<.0001
	Black, non-Hispanic	66 959 (19.5)	39 066 (18.5)	27 893 (21.0)	
	Hispanic	50 687 (14.7)	30 917 (14.6)	19 770 (14.9)	
	White, non-Hispanic	207 595 (60.4)	130 664 (61.9)	76 931 (58.0)	
Transplanted organ	Kidney	214 537 (62.4)	128 537 (60.9)	86 000 (64.9)	<.0001
	Liver	56 458 (16.4)	34 857 (16.5)	21 601 (16.3)	
	Heart and/or lung	49 993 (14.5)	34 132 (16.2)	15 861 (12.0)	
	Other or multiple	22 814 (6.6)	13 680 (6.5)	9134 (6.5)	
Time on wait list, days	Median (IQR)	240 (59, 694)	230 (56, 673)	257 (63, 729)	<.0001
Calendar year of transplantation	1995-1999	65 961 (19.2)	40 080 (19.0)	25 881 (19.5)	<.0001
	2000-2004	80 992 (23.6)	49 306 (23.3)	31 686 (23.9)	
	2005-2009	87 071 (25.3)	54 101 (25.6)	32 970 (24.9)	
	2010-2014	71 922 (20.9)	44 510 (21.1)	27 412 (20.6)	
	2015-2017	37 856 (11.0)	23 209 (11.0)	14 647 (11.1)	
Education	None	1353 (0.4)	774 (0.4)	579 (0.4)	<.0001
	Grade school (0-8)	15 800 (4.6)	9787 (4.6)	6013 (4.5)	
	High school	124 615 (36.3)	76 318 (36.1)	48 297 (36.4)	
	Some college/technical school	74 399 (21.6)	44 914 (21.3)	29 485 (22.2)	
	Associate/bachelor's degree	49 932 (14.5)	30 568 (14.5)	19 364 (14.6)	
	Post-college/graduate degree	20 381 (5.9)	13 860 (6.6)	6521 (4.9)	
	Unknown	57 322 (16.7)	34 985 (16.6)	22 337 (16.9)	
Yost index	Median (IQR)	0.43 (-0.5, 1.2)	0.45 (-0.4, 1.2)	0.40 (-0.5, 1.2)	<.0001
Body mass index, kg/m^2	Median (IQR)	26.5 (23, 30)	26.7 (24, 30)	26.0 (22, 31)	<.0001
Diabetes mellitus	No	230 442 (67.0)	138 859 (65.8)	91 583 (69.1)	<.0001
	Yes	104 682 (30.5)	67 243 (31.8)	37 439 (28.2)	
	Missing	8678 (2.5)	5104 (2.4)	3574 (2.7)	
Smoking (among lung recipients only)	No	6988 (34.4)	3323 (31.6)	3365 (38.1)	<.0001
	Yes	11 431 (56.3)	6979 (60.9)	4452 (50.4)	
	Missing	1876 (9.2)	856 (7.5)	1020 (11.5)	
Hepatitis B virus	Active infection	7395 (2.2)	4906 (2.3)	2489 (1.9)	<.0001
	Resolved infection	24 556 (7.1)	16 525 (7.8)	8031 (6.1)	
	Uninfected	288 707 (84.0)	175 550 (83.1)	113 157 (85.3)	
	Unknown	23 144 (6.7)	14 225 (6.7)	8981 (6.7)	
Hepatitis C virus	Positive	31 114 (9.1)	22 174 (10.5)	8940 (6.7)	<.0001
	Negative	282 532 (82.2)	170 525 (80.7)	112 007 (84.5)	
	Unknown	30 156 (8.8)	18 507 (8.8)	11 649 (8.8)	
Epstein-Barr virus	Positive	222 124 (64.6)	85 189 (64.3)	136 935 (64.8)	<.0001
	Negative	1860 (0.5)	1169 (0.6)	691 (0.5)	
	Unknown	119 818 (34.9)	46 716 (35.2)	73 102 (34.6)	

[a] Results are presented as N (%) unless otherwise noted. Categorical variables were compared with a chi-square test and continuous variables with a Wilcoxon test. IQR = interquartile range; kg = kilogram; m^2 = meters squared.

Table 2. Incidence rates and male-to-female incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for cancer among transplant recipients and in the general US population standardized to transplant population[a]

Cancer site	Incidence in transplant recipients, per 100 000 person-years		Incidence in the general population, per 100 000 person-years		M:F $IRR_{Transplant}$ (95% CI)	M:F IRR_{GP}	P-value for difference[b]
	Males	Females	Males	Females			
Lip	16.6	9.2	1.9	0.5	1.81 (1.37 to 2.38)	3.96	<.0001
Oral cavity	22.6	12.2	11.5	5.2	1.85 (1.46 to 2.34)	2.23	.121
Oropharynx	0.4	0.3	0.4	0.1	1.62 (0.31 to 8.33)	3.29	.399
Esophagus	21.1	5.6	14.4	3.1	3.77 (2.72 to 5.23)	4.59	.238
Adenocarcinoma	13.3	1.5	9.2	1.1	9.11 (4.94 to 16.78)	8.74	.894
Squamous cell carcinoma	6.7	3.7	4.3	1.9	1.80 (1.17 to 2.77)	2.29	.273
Stomach	26.1	17.3	17.5	8.4	1.51 (1.23 to 1.85)	2.09	.002
Colorectum	73.1	74.3	85.6	59.7	0.98 (0.89 to 1.10)	1.43	<.0001
Proximal colon	36.1	44.1	30.2	25.5	0.82 (0.71 to 0.95)	1.18	<.0001
Distal colon	18.6	14.5	24.2	15.7	1.28 (1.02 to 1.61)	1.54	.112
Rectum	15.3	12.1	28.8	16.9	1.26 (0.98 to 1.63)	1.71	.019
Liver	35.3	14.8	26.4	7.7	2.39 (1.94 to 2.95)	3.44	.002
Larynx	20.3	5.6	11.7	2.4	3.63 (2.62 to 5.04)	4.97	.060
Lung	212.5	160.1	113.4	82.0	1.33 (1.24 to 1.42)	1.38	.286
Adenocarcinoma	70.9	69.9	44.6	39.1	1.02 (0.91 to 1.13)	1.14	.044
Squamous cell carcinoma	79.8	45.4	27.2	12.6	1.76 (1.55 to 1.99)	2.15	.002
Small cell carcinoma	20.3	13.2	14.4	11.6	1.54 (1.22 to 1.95)	1.25	.081
Kidney	147.4	88.5	38.7	17.2	1.67 (1.52 to 1.82)	2.24	<.0001
Bladder	39.5	19.6	55.3	13.2	2.02 (1.68 to 2.43)	4.19	<.0001
Thyroid	24.3	49.9	11.0	27.1	0.49 (0.42 to 0.57)	0.41	.022
Melanoma skin	66.8	33.7	48.1	26.7	1.99 (1.72 to 2.29)	1.80	.169
Kaposi sarcoma[c]	12.4	6.9	0.4	0.1	1.79 (1.30 to 2.46)	3.26	.0009
Non-Hodgkin lymphoma	180.5	134.7	53.8	32.9	1.34 (1.24 to 1.45)	1.64	<.0001
Diffuse large B-cell lymphoma[h]	110.4	88.4	14.4	9.1	1.25 (1.14 to 1.37)	1.59	<.0001

[a] M:F IRR_{GP} estimates are standardized to the transplant population on age, race and ethnicity, and year of diagnosis. M:F IRR = male to female incidence rate ratio.
[b] P-values were estimated from a chi-square test using the formula $\log(\text{M:F } IRR_{Transplant} - IRR_{GP})^2/\text{Var}(\text{M:F } IRR_{Transplant})^2$ with 1 degree of freedom.
[c] Estimates of the M:F $IRR_{Transplant}$ were restricted to non-Hispanic White and non-Hispanic Black participants in SEER9 (1973-1979) to calculate the M:F IRR_{GP}.

Analyses stratified by age at transplantation (<55 vs ≥55 years) generally demonstrated a similar pattern to the main analysis in which the same cancers showed significant attenuation of the M:F IRRs in the transplant population from the general population regardless of age (Supplementary Table 2, available online). There were a few exceptions to this pattern. The M:F $IRR_{Transplant}$ for stomach cancer was significantly attenuated from M:F IRR_{GP} in recipients less than 55 years of age, but not for those aged ≥55 years. For laryngeal cancer and lung squamous cell carcinoma, the M:F $IRR_{Transplant}$ estimates were attenuated from the M:F IRR_{GP} estimates in recipients aged ≥55 years, but not in those aged less than 55 years.

We also present adjusted M:F $IRR_{Transplant}$ estimates for each cancer site and stratified the analyses by transplanted organ (Supplementary Table 3, available online). When adjusted for known cancer risk factors, the M:F $IRR_{Transplant}$ estimates were not appreciably different from the unadjusted estimates, with one exception: the male predominance of distal colon cancer was no longer statistically significant (adjusted M:F $IRR_{Transplant}$ 1.23 [95% CI = 0.96 to 1.56]). For cancers of the stomach, colorectum, kidney, and for Kaposi sarcoma and NHL, M:F $IRR_{Transplant}$ varied significantly by transplanted organ. However, these differences did not follow a clear pattern of increasing attenuation with increasing intensity of immunosuppression, from liver to kidney to heart and/or lung recipients. There was no difference in M:F $IRR_{Transplant}$ by transplanted organ for the other cancers. Finally, among lung recipients, additional adjustment for smoking did not appreciably affect the estimated M:F $IRR_{Transplant}$ for smoking-related cancers (Supplementary Table 4, available online).

Discussion

In this population-based study of solid organ transplant recipients in the United States, we found that the sex ratio for cancer incidence showed a male predominance for most cancers. However, the notable finding was that these male to female ratios were significantly attenuated compared to the expected sex ratio in the general population for several cancers: lip, stomach, colorectum, liver, squamous cell carcinoma of the lung, kidney, and bladder as well as NHL (including diffuse large B-cell lymphoma) and Kaposi sarcoma. Two cancer subsites and subtypes, proximal colon and lung adenocarcinoma, had a female predominance in the transplanted population not seen in the general population. The sex ratios among transplant recipients were not significantly different from the sex ratio in the general population for the other cancer sites.

We conducted additional analyses to confirm our main results. First, we adjusted the M:F $IRR_{Transplant}$ estimates for known cancer risk factors for each cancer site to account for possible exposure differences between men and women in the transplant population. We found no substantial differences between the fully adjusted and unadjusted M:F $IRR_{Transplant}$ estimates. Importantly, the male bias persisted for most of the cancers we examined. Second, we could not adjust our primary estimates for smoking, because smoking data were available only for lung recipients in the SRTR. Nonetheless, we found no difference between the unadjusted and smoking-adjusted M:F $IRR_{Tansplant}$ estimates when we restricted the analysis to lung recipients.

A possible explanation for the excess of cancer among males in the general population is that it reflects stronger immune

function in females, which could eliminate premalignant cells. Solid organ transplant recipients are administered potent immunosuppressive medications to prevent graft rejection. These medications inhibit both innate and adaptive immunity, especially related to T-cell function (25,26). These agents also upregulate vascular endothelial growth factor and increase the expression of transforming growth factor beta 1, potentially facilitating cancer cell growth and metastasis (26). As a result, transplant recipients have increased risk for a broad range of cancers, especially those with viral etiologies (11).

We hypothesized that if differences in immune surveillance explain the excess cancer risk in males, then immunosuppression in the setting of transplantation would tend to equalize cancer risk and attenuate the male to female ratio. Consistent with this hypothesis, we saw the sex differences attenuated for 8 of the 15 cancers. The attenuation of the male to female ratio is driven by the greater increase in cancer incidence in females (compared to females in the general population) than for males (compared to males in the general population). This pattern was borne out for 7 of the 8 cancers, as shown in Table 2.

Two cancers that showed more complicated results are bladder and colorectal cancers. Bladder cancer incidence was increased among female transplant recipients but decreased in male recipients relative to the general population, leading to an attenuation of the male to female ratio. Female patients are less likely than male patients to be referred to a urologist and have cystoscopy when presenting with symptoms (even after adjusting for demographic characteristics and risk factors), possibly leading to delays in diagnosis of bladder cancer (27-29). We hypothesize that, among transplant candidates, males may have been more likely than females to be diagnosed with early bladder cancer, leading them to be deferred from transplantation and excluded from our analysis. This selection effect would have contributed to an apparently high risk of bladder cancer among female but not male recipients.

Both distal colon and rectal cancers had lower incidence among male and female transplant recipients than among their counterparts in the general population. Similarly, a previous analysis of the TCM data by Safaeian and colleagues (30) found that transplant recipients had reduced risk of distal colon cancer (standardized incidence ratio [SIR] 0.93, 95% CI = 0.80 to 1.07) and rectal cancer (0.64, 95% CI = 0.54 to 0.76) (30). Because of these decreased risks, the immunosurveillance model is not directly supported by our data for distal colon and rectal cancers. For proximal colon cancer, Safaeian et al. found that the risk was increased in transplant recipients (SIR 1.69, 95% CI = 1.53 to 1.87) compared to the general population (30), suggesting that immunosurveillance plays a protective role for proximal colon cancer. However, Safaeian et al. did not disaggregate their results by sex. We show in Table 2 that the elevation in transplant recipients is present for females but to a much smaller degree in males.

In the Safaeian et al. study, the decreased risks of distal and rectal cancers were attributed to colorectal cancer screening in transplant candidates and recipients, which would allow for detection and removal of precancerous polyps or (in the case of transplant candidates) detect invasive cancers and result in deferral of affected individuals from transplantation. Along these lines, we believe that the attenuation in the male to female ratios for colorectal cancer that we show in Table 2 largely reflect less effective cancer screening in women than men. Randomized clinical trials have found that women do not benefit as much as men with respect to decreased incidence or mortality from colon cancer screening, regardless of the screening method (31,32).

Hormonal differences between men and women likely contribute to differences in immunity (9,10). For example, signaling via estrogen receptor alpha can lead to reduced proinflammatory and tumor-promoting properties of macrophages, whereas androgen receptors promote the release of proinflammatory cytokines (5). The enhanced innate and adaptive immune response mediated by sex hormones may reduce susceptibility to infection-associated cancers among females (10). When we stratified our results by age at transplantation to capture the effect of menopause among women, there was only one cancer (stomach cancer) for which the attenuation of the male to female ratio in transplant recipients was present only in younger individuals. Thus, for most cancers we examined, our findings suggest that, to the extent that immune responses play a role in the development of cancer, hormonal mechanisms do not appear to drive the relevant immune differences between men and women. We note, however, that we did not directly measure hormone levels. Our study design only addresses immune mechanisms, and there may be nonimmune effects of hormones that contribute to the greater cancer risk in men.

Finally, we estimated M:F $IRR_{Transplant}$ separately by transplanted organ as a proxy for degree of immunosuppression. The M:F IRRs in transplant recipients were largely similar across transplanted organ for most cancer sites. On their face, these results might suggest another explanation than immunosuppression for the attenuation in the sex bias among transplant recipients. Alternatively, the lack of variation in M:F $IRR_{Transplant}$ may reflect that all transplant recipients are immunosuppressed to a substantial degree, sufficient to remove much of the benefit in females that derives from their heightened immunity.

In the setting of immune suppression, it is likely that other nonimmune factors contribute to protection of females against cancer. Several tumor suppressor genes located on Xi are known to escape X-inactivation and may contribute to lower cancer risk in females (3). Six of these genes (*ATRX*, *CNKSR2*, *DDX3X*, *KDM5C*, *KDM6A*, and *MAGEC3*) have loss-of-function mutations that are seen more frequently in males across cancer types (3). Biallelic expression of these genes may give females an advantage in the presence of immunosuppression. Indeed, loss of Xi is associated with increased cancer risk among females (33). Compared with the autosomes, the X chromosome contains a higher number of long non-coding RNAs and microRNAs, both of which can escape X-inactivation and act as tumor suppressors (34,35). Furthermore, mutations of the tumor suppressor gene *TP53* located on chromosome 17 occur more frequent among males than females (36). X-linked tumor suppressor genes interact with the p53 regulatory process to control apoptosis, cell cycle, DNA structural integrity, and hypoxic response (36). The disruption of this network may contribute to heightened carcinogenesis in males (36).

Our analysis has several strengths, including the large size and representativeness of the TCM study population. The large sample size allowed for subgroup analyses and the examination of less common cancers. We were able to build on prior literature to examine sex differences among transplant recipients outside of kidney transplants (13,14). There were also some limitations to our analysis. Notably, we lacked data on some important confounding factors, such as smoking for transplant recipients other than lung, and for people in the general population. However, our sensitivity analyses that included additional adjustments suggested that these factors were unlikely to completely explain away our observations. Finally, we were not able to look at

immune function directly to validate our immunosurveillance hypothesis.

In conclusion, we found that for many cancer sites, the male sex bias in cancer incidence seen in the general population was attenuated among solid organ transplant recipients. These results may suggest that immunity contributes to these sex differences and that females lose some of their immune advantage in the setting of immunosuppression. Future work should examine sex differences in cancer incidence among other immunosuppressed populations, such as people living with HIV, and by directly measuring markers of immune function. Understanding the mechanisms underlying the apparent female immune advantage in carcinogenesis could lead to the development of novel chemopreventive or immune therapies.

Data availability

The data are available to researchers upon request by submitting a proposal in writing to the Principal Investigator of the Transplant Cancer Match study, Dr Eric Engels in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute.

Author contributions

Sarah S. Jackson (Conceptualization; Formal analysis; Writing—original draft), Ruth M. Pfeiffer (Formal analysis; Methodology; Writing—review & editing), Mei-chin Hsieh (Data curation; Resources; Writing—review & editing), Jie Li (Data curation; Resources; Writing—review & editing), Margaret Madeleine (Data curation; Resources; Writing—review & editing), Karen Pawlish (Data curation; Resources; Writing—review & editing), Yun Zheng (Data curation; Resources; Writing—review & editing), Kelly Yu (Resources), Eric Engels (Project administration; Resources; Supervision; Writing—review & editing).

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Conflicts of interest

The authors have no disclosures to report.

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