



Published in final edited form as:

Int J Cancer. 2025 August 01; 157(3): 427–435. doi:10.1002/ijc.35415.

Sex differences in cancer mortality among solid organ transplant recipients

Sarah S Jackson^{1,*}, Ruth M Pfeiffer¹, Erin Gardner², Mei-Chin Hsieh³, Tabassum Insaf⁴, Charles F Lynch⁵, Bozena Morawski⁶, Shuhui Wang⁷, Kelly J Yu¹, Eric A Engels¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD

²Texas Cancer Registry, Texas Department of State Health Services, Austin, TX

³Louisiana Tumor Registry and Epidemiology & Population Health Program, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA

⁴Bureau of Cancer Epidemiology, New York State Department of Health and Department of Epidemiology and Biostatistics, University at Albany, Albany, NY

⁵Department of Epidemiology, The University of Iowa, Iowa City, IA

⁶Cancer Data Registry of Idaho, Idaho Hospital Association, Boise, ID

⁷Division of Population Health Data, Virginia Cancer Registry, Virginia Department of Health, Richmond, VA

Abstract

Males have increased mortality after a cancer diagnosis than females, possibly due to poorer immunosurveillance. We tested whether the female survival advantage is lost with immunosuppression by evaluating 17,048 cancer patients (68% male) with a prior solid organ transplant using data from the US Transplant Cancer Match Study and 1,221,914 cancer patients (58% male) from the general population using data from the Surveillance, Epidemiology, and End Results Program. We evaluated 13 solid cancers that occur in both sexes. We compared mortality due to cancer in males and females using a male:female hazard ratio (M:F HR) derived from Cox proportional hazards models adjusted for age, race/ethnicity, diagnosis year, stage, and cancer treatment. Among cancer patients in the general population, males had higher cancer-specific mortality than females for cancers of the lip, stomach, colorectum, anus, liver,

***Corresponding Author:** Sarah S. Jackson, PhD, MPH, Infections and Immunology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850-9761, sarah.jackson@nih.gov. Author contributions

SSJ conceived of the project, completed the data analysis, and drafted the manuscript. RMP supervised the statistical analysis. EAE supervised the project and analysis. EG, MCH, TI, CFL, BM, SW, KJY, and EAE were responsible for data curation. All authors reviewed the manuscript and provided substantive edits.

Conflict of interest statement

The authors declare that they have no competing interests

Ethics statement

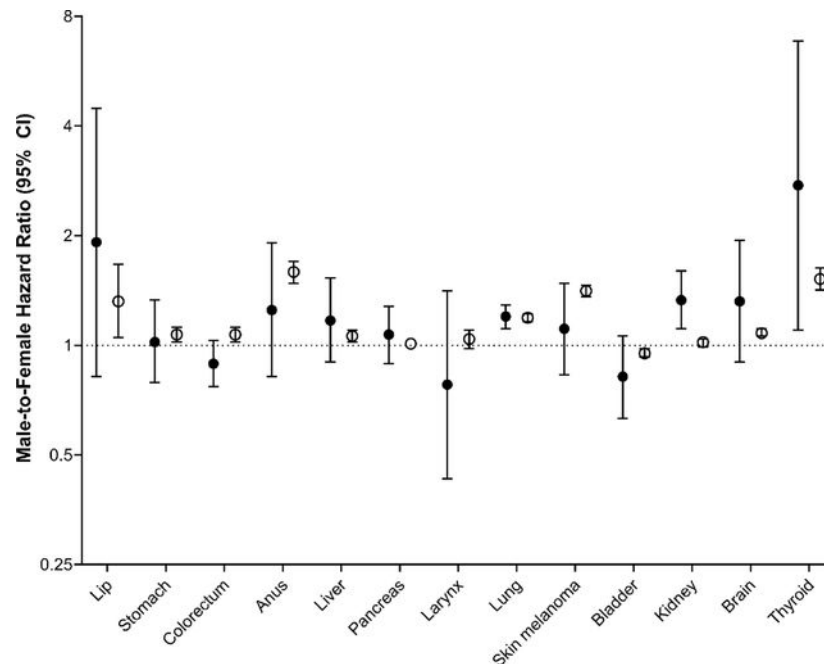
This study was considered not human subjects research by the National Cancer Institute and approved by the institutional review boards at the participating cancer registries.

Previous presentation

Preliminary results from this report were presented at the Organization for the Study of Sex Differences annual conference in May 2024 in Bergen, Norway.

lung, skin, brain, and thyroid, with M:F HRs ranging from 1.06 to 1.59. Only colorectal cancer showed an attenuation in the female mortality advantage in transplant recipients (M:F HR_{Transplant}: 0.89; 95% CI: 0.77, 1.03; vs. M:F HR_{GenPop}: 1.07; 95% CI: 1.06, 1.08; $P_{\text{interaction}}=0.007$). Among kidney cancer patients, the female mortality advantage was stronger in the transplant population (M:F HR_{Transplant}: 1.33; 95% CI: 1.11, 1.60; M:F HR_{GenPop}: 1.02; 95% CI: 0.99, 1.04; $P_{\text{interaction}}=0.003$). Overall, we did not find consistent evidence that the female advantage in cancer mortality is weakened among immunosuppressed transplant recipients, suggesting that non-immune factors contribute to the female advantage among cancer patients in the general population.

Graphical Abstract



Male-to-female cancer-specific mortality ratios in cancer patients with a prior solid organ transplant (black circles) compared to those in the general population (open circles)

Keywords

Sex differences; cancer; mortality; immunosurveillance; organ transplantation

Introduction

Cancer is a major cause of morbidity and mortality in the United States (US), with an estimated 1,958,310 cases and 609,820 deaths in 2023 [1]. The cancer mortality rate, which reflects both cancer incidence and survival after a cancer diagnosis, is 177.5 per 100,000 persons for males and 128.7 per 100,000 persons for females [1]. This sex difference in overall cancer mortality also holds for most cancers at shared anatomic sites (excluding sex-specific cancers), where males typically have higher cancer mortality, with the highest

male-to-female mortality ratios seen for melanoma of the skin, head and neck, and thyroid cancers [2, 3].

Importantly, males are more likely than females to die from their cancer after diagnosis [3]. Increased mortality among males with cancer may be due to weaker immune control of cancer after diagnosis compared to females, a process referred to as immunosurveillance or immunocontainment [4]. In support of this hypothesis, females exhibit a more robust cell-mediated and humoral immune response to a host of antigenic challenges [5]. Sex steroid hormones may mediate these immune differences [6]. Further, many genes related to immunity and tumor suppressor genes, escape X-inactivation, resulting in biallelic expression in females [7]. Females also have increased response rates and survival after chemotherapy compared to males [8], which may be because the half-life of many chemotherapeutics is longer in females [9]. Mortality from bladder cancer is an exception, as males have better 5-year survival than females after adjustment for age, stage, and grade [10].

Exploring sex differences in cancer mortality among solid organ transplant recipients can help clarify the role of immunity in driving sex differences in cancer mortality. Transplant recipients are immunosuppressed due to the requirement for lifelong use of post-transplantation immunosuppressive medications to prevent graft rejection. Transplant recipients with cancer have elevated cancer-specific mortality compared to other individuals with cancer, which could be due to the effects of this immunosuppression [11]. If sex differences in mortality among cancer patients in the general population are explained by differences in immunity, then the female advantage may be reduced in a population of solid organ transplant recipients.

Methods

We used data from the Transplant Cancer Match (TCM) Study, which links the US national solid organ transplant registry (Scientific Registry of Transplant Recipients [SRTR]) to 30 population-based cancer registries [12]. The TCM Study includes cancer registry data on cancer diagnoses for two-thirds of US solid organ transplant recipients since 1995. Along with demographic and transplant data, the TCM Study includes data on dates of cancer diagnoses, first course of cancer treatment (chemotherapy, radiation, and surgery), vital status, and cause of death. This study was not considered human subjects research by the National Cancer Institute. The TCM Study was approved by institutional review boards at participating cancer registries as required.

From TCM cancer registries, we identified cancer patients diagnosed between January 1, 1995 and December 31, 2019, and we used the linked SRTR data to select those who had had a solid organ transplant before their cancer diagnosis. We excluded individuals outside the four race/ethnic groups of non-Hispanic White, non-Hispanic Black, Hispanic, and Asian American/Pacific Islander due to small numbers. We included first malignant cancer diagnoses and evaluated non-sex-specific solid tumors with at least 200 cases among transplant recipients. The examined cancers included lip, stomach, colorectum, anus, liver (including intrahepatic bile duct), pancreas, larynx, lung, melanoma of the skin, kidney

(including renal pelvis), urinary bladder, brain, and thyroid. For comparison, we also evaluated individuals in the general US population with the same types of cancer, using data from 12 Surveillance, Epidemiology, and End Results Program (SEER) cancer registries for the same calendar years [13]. Cancers diagnosed at autopsy were excluded in both datasets. Due to the rarity of organ transplantation, the general population patients can be considered to lack a prior transplant.

We identified deaths due to cancer among transplanted and general population cancer patients based on cause of death information as described by Howlader [14], and calculated corresponding cancer-specific mortality rates (we note that these mortality rates are restricted to cancer patients and thus reflect only mortality after cancer diagnosis). Separately for cancer patients with a prior transplant in the TCM study and cancer patients in the general population in SEER, we compared cancer-specific mortality in males and females using a Cox proportional hazards model. Specifically, we calculated male-to-female hazard ratios (M:F HRs) for death due to cancer, with follow-up from the time of the cancer diagnosis until death from cancer or censoring due to death from other causes or end of cancer registry follow-up (the latest follow-up date was December 31, 2019).

To detect a difference in the M:F HR between cancer patients in the transplant and general populations, we combined the TCM and SEER populations and tested for an interaction in the Cox model between sex and cohort (TCM vs. SEER) using the *P*-value from a Wald chi-square test. To understand whether an effect of estrogen on immunity may play a role in cancer mortality, we also performed separate analyses according to age at cancer diagnosis (<50 vs ≥50 years based on the typical age of menopause). We also conducted an analysis restricted to cancer patients diagnosed with localized stage cancer who had received treatment (one or more of chemotherapy, radiation, and surgery). To examine whether the degree of immunosuppression affects the results, we also stratified by transplanted organ. Liver transplant recipients receive the lowest dose of immunosuppressant medications, followed by kidney recipients, with recipients of lung and heart transplant receiving the largest doses. If immunity explains the sex difference in cancer-specific mortality, we would hypothesize that the M:F HR would be greatest among liver recipients and more attenuated for heart/lung recipients. Differences between the M:F HR among the three organ groups were tested using an interaction in the Cox model between sex and organ using the *P*-value from a Wald chi-square test. All models were adjusted for age at cancer diagnosis (<40 years, 40–79 years in 10-year increments, and 80+ years), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Asian-American Pacific Islander), stage of cancer (localized, regional, distant, or unknown), year of diagnosis (1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2019), and first course of cancer treatment based on receipt of chemotherapy (yes, no/unknown), radiation (yes, no/unknown), and surgery (yes, no/unknown) where applicable.

All analyses were conducted in SAS version 9.4 (The SAS System, Cary, NC). We present 95% confidence intervals (CIs) based on a level of statistical significance of $P < 0.05$.

Results

The analysis cohort comprised 17,048 cancer patients with a prior transplant (11,535 males and 5,513 females) and 1,221,914 patients from the general population (702,758 males and 569,156 females) with cancers of the lip, stomach, colorectum, anus, liver, pancreas, larynx, lung, skin (melanoma), bladder, kidney, brain, and thyroid (Table 1). The most common cancer was lung cancer among patients both with a prior transplant and in the general population. Cancer patients with a prior transplant were younger than patients in the general population (median age 60 vs. 65–69 years). The majority of both groups were non-Hispanic White (67.5% in the transplant population vs. 70.1% in the general population), and the cancer stage distribution was similar.

Cancer-specific mortality rates were highest for patients with pancreatic, lung, stomach, and liver cancers (Table 2). Among cancer patients with a prior transplant, males had significantly higher cancer-specific mortality than females for cancers of the lung (M:F HR: 1.20; 95% CI: 1.11, 1.29), kidney (M:F HR: 1.33; 95% CI: 1.11, 1.60), and thyroid (M:F HR: 2.75; 95% CI: 1.10, 6.85). Among cancer patients in the general population, males had higher cancer-specific mortality than females for cancers of the lip, stomach, colorectum, anus, liver, lung, skin, and thyroid, with M:F HRs ranging from 1.06 to 1.59, while females had higher cancer-specific mortality for bladder cancer (M:F HR: 0.95; 95% CI: 0.93, 0.98).

When comparing the M:F HRs for cancer-specific mortality between cancer patients with a prior transplant and those in the general population, we found a significant interaction only for colorectal and kidney/renal pelvis cancers. Specifically, for colorectal cancer, males had increased cancer-specific mortality compared with females among patients in the general population, but no sex difference in cancer-specific mortality was observed among patients with a prior transplant (M:F HR_{GenPop}: 1.07; 95% CI: 1.06, 1.08; M:F HR_{Transplant}: 0.89; 95% CI: 0.77, 1.03; *P*-interaction=0.007). In contrast, for kidney cancer, there was no sex difference for patients in the general population, but cancer-specific mortality was higher for males than females among patients with a prior transplant (M:F HR_{GenPop}: 1.02; 95% CI: 0.99, 1.04; M:F HR_{Transplant}: 1.33, 95% CI: 1.11, 1.60; *P*-interaction=0.003).

We next looked at results stratified by age at cancer diagnosis (Table 3). Among cancer patients aged <50 years in the general population, males had worse survival than females for cancers of the lip, colorectum, anus, liver, pancreas, lung, skin, kidney, and thyroid with M:F HRs ranging from 1.11 to 4.61. The number of cancer patients with a prior transplant in this age group was somewhat limited, ranging from 25 to 1,240 patients across the cancer types. In this age group, only the M:F HRs for anal cancer differed significantly between the two populations, with a two-fold increase in cancer-specific mortality for males in the general population but no sex difference among those with a prior transplant (M:F HR_{GenPop}: 2.02; 95% CI: 1.71, 2.39 vs. M:F HR_{Transplant}: 0.67; 95% CI: 0.24, 1.89; *P*-interaction=0.024).

In the general population, M:F HRs were mostly weaker among patients aged ≥50 years at diagnosis compared with younger patients (Table 3). Among cancer patients in the general population aged ≥50 years, males had increased mortality compared to females for cancers of the stomach, colorectum, anus, liver, lung, skin, and thyroid with M:F HRs ranging from

1.03 to 1.50. The M:F HR estimates for colorectal and kidney cancers differed significantly between the two populations. Specifically, for colorectal cancer, there was an increased risk of mortality among male patients in the general population but no sex difference in cancer-specific mortality among patients with a prior transplant (M:F HR_{GenPop}: 1.07; 95% CI: 1.05, 1.08 vs. M:F HR_{Transplant}: 0.87; 95% CI: 0.75, 1.02; *P*-interaction=0.018). For kidney cancer, in contrast, there was no sex difference in cancer-specific mortality among patients the general population but a male bias for patients with a prior transplant (M:F HR_{GenPop}: 1.00; 0.97, 1.03 vs. HR_{Transplant}: 1.31; 95% CI: 1.07, 1.61; *P*-interaction=0.025).

When we restricted to cancer patients in the transplant and general populations who were diagnosed with localized stage cancer receiving treatment (Supplemental Table 1), we did not see substantial differences from the main results. The exception is for larynx cancer where females had worse cancer-specific mortality than males in the general population (M:F HR_{GenPop}: 0.89, 95% CI: 0.80, 0.99) and this association was stronger in the transplant population (M:F HR_{Transplant}: 0.42; 95% CI: 0.18, 0.97; *P*-interaction=0.035). As shown in Supplemental Table 2, we found interactions between sex and transplanted organ type (a proxy for degree of immunosuppression) for only two cancer sites: melanoma of the skin (*P*-interaction=0.016) and brain tumors (*P*-interaction=0.037). For melanoma of the skin, males had increased cancer-specific mortality compared to females among heart and/or lung recipients (M:F HR: 5.44, 95% CI: 1.22, 24.19), but no differences in cancer-specific mortality between males and females were seen among kidney and liver recipients. For brain cancer, females had increased cancer-specific mortality compared to males among liver recipients (M:F HR: 0.03, 95% CI: 0.01, 0.25), but there was no association among kidney or heart and/or lung recipients.

Discussion

For most non-sex-specific cancer sites, males have increased cancer-specific mortality compared to females in the general population [3]. One possible explanation for this difference has been stronger immunosurveillance or immunocontainment of cancer among females. Under this model, we hypothesized that females would lose this immunologic advantage in an immunosuppressed cohort of solid organ transplant recipients, manifesting as an attenuation in the M:F HR_{Transplant} compared to the M:F HR_{GenPop}. Indeed, transplant recipients with cancer have higher cancer-specific mortality than patients in the general population for a range of cancers, including colorectal, breast, kidney, and bladder cancers as well as melanoma [11], implying that immunity is important for control of cancer. Notably, however, we did not find a consistent attenuation of the M:F HR_{Transplant} across cancer types even when analyses were restricted to patients diagnosed with localized stage cancers receiving treatment or when stratified by transplanted organ (reflecting the degree of immunosuppression). These results suggest that immunity is not the general explanation for the female advantage in survival seen among cancer patients in the general population.

In healthy populations, females exhibit a stronger innate and adaptive immunity than males due to the make-up and function of immune cells, resulting in increased incidence of autoimmune disorders among females and higher cancer incidence among males [6]. Among transplant recipients, who receive the same amount of immunosuppression regardless of sex,

females are at higher risk of graft failure [15]. Previous research by our group has shown that while the male excess in cancer incidence is attenuated among transplant recipients for many cancer sites, it is not completely null [16].

The only cancer for which we saw an attenuation in the female mortality advantage among transplant recipients was colorectal cancer. In light of the overall null pattern for other cancers, the reasons for the decreased advantage for females diagnosed with colorectal cancer in the transplant population are not clear. Colorectal cancer incidence is modestly increased in transplant recipients [12, 17], and regular screening is recommended [18, 19]. A systematic review of colorectal cancer screening trials found that males experience greater mortality benefits from screening, with a 33% reduction in cancer mortality as compared to a 15% reduction for females [20], perhaps because males have a higher baseline incidence of colorectal cancer and increased mortality after cancer diagnosis [21].

Contrary to our hypothesis, the $M:F HR_{Transplant}$ for cancer of the kidney (including the renal pelvis) was higher than the $M:F HR_{GenPop}$. Here, underlying end-stage kidney disease may play a role. Males have a higher incidence of end-stage kidney disease than females, and this difference increases with age [22]. However, evidence suggests that females spend more time on dialysis before being placed on the transplant waitlist [22] and have higher estimated glomerular filtration rate when listed [23, 24]. Most kidney recipients retain their damaged native kidneys after transplantation of a donor kidney, and most kidney cancers in kidney recipients arise in the native kidneys [25]. Among transplant recipients in our study, 85% of kidney cancers occurred in kidney recipients, and 70% of kidney recipients with kidney cancer were male. In an analysis restricted to kidney recipients, the $M:F_{Transplant} HR$ was 1.33 (95% CI: 1.09, 1.62), similar to our main result.

To examine whether an effect of estrogen on immunity may explain the female survival advantage among cancer patients in the general population, we stratified the analyses by the typical age of menopause [26, 27]. Broadly, estrogen and progesterone are immunoprotective, and androgens are immunosuppressive [28]. Stimulation of estrogen receptor alpha has been shown to reduce both pro-inflammatory and tumor-promoting properties of macrophages [28]. In the age-stratified analysis, the $M:F HR$ s for cancer patients in the general population were often larger at younger ages, in line with the hormone hypothesis. However, we did not see a consistent attenuation across cancer types in the $M:F HR_{Transplant}$ compared to the $M:F HR_{GenPop}$ among patients <50. Anal cancer was the only cancer in this age group for which the $M:F HR_{Transplant}$ was attenuated compared to the $M:F HR_{GenPop}$. These results may suggest that any benefits of sex hormones on survival are not mediated by their effects on immunity. Another possibility is that estrogen does not confer additional benefit in an immunosuppressed setting.

This study used linked data from population-based registries of solid organ transplant recipients and cancer registries in the US. The large sample size allowed us to examine mortality for 13 cancer sites, although the number of cancer patients was more limited for our analysis stratified by age at diagnosis for some of the cancers. The use of population-based cancer registries allowed us to obtain reliable information on cancer diagnoses including stage at diagnosis.

We note several study limitations. We did not restrict the TCM cohort to the same registries included in SEER to maximize the number of cancer patients with a previous transplant. Consequently, the TCM cancer patients in non-SEER states may be different from the general population included in SEER. We could not adjust for details of cancer treatment as registries only collect limited information on the first course of therapy. We also lacked data on menopausal status, including use of hormone replacement therapy, so we could not directly explore the effects of estrogen on cancer mortality. We note that transplant recipients differ from people in the general population in additional ways beyond immune status, notably including the presence of significant medical co-morbidity and complications of transplantation (e.g., severe infections, kidney dysfunction due to toxicity from calcineurin inhibitors). We did not have data on these factors but do not believe that they would have systematically led to sex differences in cancer-specific mortality that could have biased our results. Finally, we did not have data on lifestyle factors for which the prevalence may differ by sex and affect mortality. However, national estimates of current smoking and physical activity are comparable between male and female cancer survivors, with females slightly more likely to smoke and report lower physical activity after a cancer diagnosis than males [29].

Overall, we did not find consistent evidence that the female advantage in cancer mortality is weakened or lost among immunosuppressed transplant recipients. These results suggest that factors other than immunosurveillance or immunocontainment may contribute to the female survival advantage seen among cancer patients in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration, the SRTR (Ajay Israni, Jon Snyder), and the following cancer registries: the states of Alabama (Justin George), Alaska (David O'Brien), Arkansas (Lunda Lehing), California (Cyllene Morris), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Florida (Brad Wohler), Georgia (Rana Bayakly), Hawaii (Brenda Hernandez), Idaho (Bożena Morawski), Illinois (Lori Koch), Iowa (Charles Lynch), Kentucky (Jaclyn McDowell), Louisiana, Michigan (Georgetta Alverson), Montana (Heather Zimmerman), Nebraska (Lifeng Li), Nevada (Ben Claassen), New Jersey (Xiaoling Niu), New Mexico (Angela Meisner), New York (Maria Schymura), North Carolina (Chandrika Rao), North Dakota, Ohio (Emily Bunt), Oklahoma (Raffaella Espinoza), Oregon (Jeff Soule), Pennsylvania (Jim Rubertone), Puerto Rico (Carlos R. Torres), Rhode Island (Junhie Oh), South Carolina (Deborah Hurley), Texas (Leticia Noguera), Utah (Jen Doherty), Virginia (Shuhui Wang), and the Seattle-Puget Sound area of Washington. We also thank analysts at Information Management Services for programming support (David Castenson, Matthew Chaloux, Michael Curry, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

The SRTR is currently operated under contract number 75R60220C00011 by the Hennepin Healthcare Research Institute, Minneapolis, MN. Previously the SRTR was managed under contracts HHSH250201000018C and HHSH234200537009C. The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201800002I), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Idaho (HHSN261201800006I), Illinois (75N91021D00006), Iowa (HHSN261201000032C, N01-PC-35143, HHSN261201800012I), Kentucky (HHSN261201800013I), New Jersey (75N91021D00009), New York (75N91018D00005 [Task Order 75N91018F00001]), Seattle-Puget Sound (HHSN261201800004I, N01

PC-2018-00004), and Utah (HHSN261201800016I). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (5U58DP003875-01), Idaho (1NU58DP007160), Illinois (5NU58DP007162-02-00), Kentucky (1NU58DP007144), Michigan (5U58DP003921-03), Nebraska (NU58DP006278), New Jersey (5NU58DP006279-02-00), New Mexico (HHSN261201800014I, Task Order HHSN26100001), New York (6NU58DP006309), North Carolina (U58DP003933), North Dakota (NU58DP006317-05-01), Ohio (NU58DP006284), Oregon (NU58DP006288), Puerto Rico (NU58DP006318), Texas (5U58DP000824-04), and Utah (NU58DP007131). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, Montana (5 NU58DP006339-05-00), New Jersey, New York (including the Cancer Surveillance Improvement Initiative), Texas, and Fred Hutchinson Cancer Research Center in Seattle, WA.

Funding

This work was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health.

Data Availability statement

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. For more information please visit: <https://dceg.cancer.gov/research/who-we-study/cohorts/transplant-cancer-match>

Abbreviations

95% CI	95% confidence interval
M:F HR	male-to-female hazard ratio
SEER	Surveillance, Epidemiology, and End Results Program
SRTR	Scientific Registry of Transplant Recipients
TCM	Transplant Cancer Match
US	United States

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians* 2023;73(1):17–48. [PubMed: 36633525]
2. Radkiewicz C, Johansson ALV, Dickman PW, et al. Sex differences in cancer risk and survival: A Swedish cohort study. *Eur J Cancer* 2017;84:130–140. [PubMed: 28802709]
3. Cook MB, McGlynn KA, Devesa SS, et al. Sex disparities in cancer mortality and survival. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2011;20(8):1629–1637.
4. Engels EA. Epidemiologic perspectives on immunosuppressed populations and the immunosurveillance and immunocontainment of cancer. *Am J Transplant* 2019;19(12):3223–3232. [PubMed: 31206226]
5. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol* 2008;8(9):737–44. [PubMed: 18728636]
6. Klein SL, Flanagan KL. Sex differences in immune responses. *Nature Reviews Immunology* 2016;16(10):626–638.
7. Dunford A, Weinstock DM, Savova V, et al. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. *Nat Genet* 2017;49(1):10–16. [PubMed: 27869828]

8. Wang S, Cowley LA, Liu X-S. Sex differences in cancer immunotherapy efficacy, biomarkers, and therapeutic strategy. *Molecules* 2019;24(18):3214. [PubMed: 31487832]
9. Schmetzer O, Flörcken A. Sex differences in the drug therapy for oncologic diseases. *Sex and gender differences in pharmacology* 2012:411–442.
10. Radkiewicz C, Edgren G, Johansson ALV, et al. Sex Differences in Urothelial Bladder Cancer Survival. *Clin Genitourin Cancer* 2020;18(1):26–34.e6. [PubMed: 31787542]
11. D’Arcy ME, Coghill AE, Lynch CF, et al. Survival after a cancer diagnosis among solid organ transplant recipients in the United States. *Cancer* 2019;125(6):933–942. [PubMed: 30624768]
12. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011;306(17):1891–901. [PubMed: 22045767]
13. Surveillance, Epidemiology, and End Results Program. Registry Groupings in SEER Data and Statistics. . <https://seer.cancer.gov/registries/terms.html>.
14. Howlader N, Ries LA, Mariotto AB, et al. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst* 2010;102(20):1584–98. [PubMed: 20937991]
15. Momper JD, Misel ML, McKay DB. Sex differences in transplantation. *Transplantation Reviews* 2017;31(3):145–150. [PubMed: 28262425]
16. Jackson SS, Pfeiffer RM, Hsieh MC, et al. Sex differences in cancer incidence among solid organ transplant recipients. *J Natl Cancer Inst* 2023; 10.1093/jnci/djad224.
17. Safaeian M, Robbins HA, Berndt SI, et al. Risk of Colorectal Cancer After Solid Organ Transplantation in the United States. *Am J Transplant* 2016;16(3):960–7. [PubMed: 26731613]
18. Acuna SA, Huang JW, Scott AL, et al. Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines. *Am J Transplant* 2017;17(1):103–114. [PubMed: 27575845]
19. Dharia A, Boulet J, Sridhar VS, Kitchlu A. Cancer Screening in Solid Organ Transplant Recipients: A Focus on Screening Liver, Lung, and Kidney Recipients for Cancers Related to the Transplanted Organ. *Transplantation* 2022;106(1):e64–e65. [PubMed: 33795594]
20. Jodal HC, Helsing LM, Anderson JC, et al. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. *BMJ Open* 2019;9(10):e032773.
21. Clark GRC, Fraser CG, Strachan JA, Steele RJC. Sex variation in colorectal cancer mortality: trends and implications for screening. *European Journal of Public Health* 2023;33(2):331–335. [PubMed: 36847663]
22. Katz-Greenberg G, Shah S. Sex and Gender Differences in Kidney Transplantation. *Semin Nephrol* 2022;42(2):219–229. [PubMed: 35718368]
23. System USRD. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. In. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
24. Melk A, Babitsch B, Borchert-Morlins B, et al. Equally Interchangeable? How Sex and Gender Affect Transplantation. *Transplantation* 2019;103(6):1094–1110. [PubMed: 30747857]
25. Karami S, Yanik EL, Moore LE, et al. Risk of Renal Cell Carcinoma Among Kidney Transplant Recipients in the United States. *Am J Transplant* 2016;16(12):3479–3489. [PubMed: 27160653]
26. Özdemir BC, Dotto G-P. Sex Hormones and Anticancer Immunity. *Clinical Cancer Research* 2019;25(15):4603–4610. [PubMed: 30890551]
27. Rubin JB, Lagas JS, Broestl L, et al. Sex differences in cancer mechanisms. *Biol Sex Differ* 2020;11(1):17. [PubMed: 32295632]
28. Clocchiatti A, Cora E, Zhang Y, Dotto GP. Sexual dimorphism in cancer. *Nat Rev Cancer* 2016;16(5):330–9. [PubMed: 27079803]
29. Cancer Trends Progress Report: Life After Diagnosis. <https://progressreport.cancer.gov/after>.

Novelty and Impact:

Males have increased mortality after a cancer diagnosis compared with females, possibly due to poorer immunosurveillance. If immune differences explain the female survival advantage, it should be attenuated among immunosuppressed individuals. Among immunosuppressed transplant recipients, we found that the female advantage in cancer mortality was attenuated after a diagnosis of colorectal cancer, compared to the general population, but there was no attenuation for 12 other cancer types, suggesting that immunosurveillance does not explain the sex difference in cancer mortality.

Science writer file

Men have higher mortality than women after a cancer diagnosis, and one possible explanation is poorer immunosurveillance. Here, the authors show that the female advantage is not due to immune factors. They tested whether the sex difference is reduced with immunosuppression by evaluating about 17,000 cancer patients who had received a prior solid organ transplant. The study included 13 cancer types, and only in colorectal cancer was the female survival advantage reduced in transplant recipients. In kidney cancer patients, they saw a stronger female survival advantage in transplant recipients.

Table 1.
Characteristics of solid organ transplant recipients and the US general population with cancer

	Cancer patients with a prior transplant ^a		Cancer patients in the general population ^b	
	Male N= 11,535	Female N= 5,513	Male N=702,758	Female N=569,156
	No. (%)	No. (%)	No. (%)	No. (%)
Age at diagnosis, years				
<40	549 (4.8)	392 (7.1)	29,853 (4.3)	48,239 (8.5)
40–49	1,345 (11.7)	720 (13.0)	61,236 (8.7)	59,817 (10.5)
50–59	3,153 (27.3)	1,507 (27.3)	145,346 (20.7)	102,620 (18.0)
60–69	4,331 (37.6)	1,922 (34.9)	199,103 (28.3)	129,500 (22.8)
70–79	1,956 (17.0)	875 (15.9)	174,375 (24.8)	132,311 (23.2)
≥80	201 (1.7)	97 (1.8)	92,845 (13.2)	96,669 (17.0)
Race and ethnicity				
Non-Hispanic White	7,993 (69.3)	3,524 (63.9)	499,935 (71.1)	393,006 (69.1)
Non-Hispanic Black	2,224 (19.5)	1,229 (22.3)	51,422 (7.3)	45,000 (7.9)
Hispanic	946 (8.2)	532 (9.7)	74,131 (10.6)	67,922 (11.9)
Asian American/Pacific Islander	352 (3.0)	228 (4.1)	77,270 (11.0)	63,228 (11.1)
Cancer site				
Lip	277 (2.4)	104 (1.9)	3,968 (0.6)	1,347 (0.2)
Stomach	417 (3.7)	169 (3.1)	31,177 (4.4)	20,466 (3.6)
Colorectum	1,223 (10.8)	837 (15.4)	151,743 (21.6)	141,368 (24.8)
Anus	153 (1.3)	228 (4.2)	4,715 (0.7)	6,861 (1.2)
Liver (including intrahepatic bile duct)	467 (4.1)	131 (2.4)	36,194 (5.2)	14,560 (2.6)
Pancreas	505 (4.4)	234 (4.3)	32,929 (4.7)	32,140 (5.7)
Larynx	296 (2.6)	48 (1.0)	16,645 (2.4)	3,700 (0.7)
Lung	3,174 (27.9)	1,519 (27.9)	156,101 (22.2)	137,970 (24.4)
Melanoma of the skin	1,000 (8.8)	307 (5.6)	76,546 (10.9)	60,780 (10.7)
Kidney (including renal pelvis)	2,850 (25.0)	1,134 (20.8)	56,655 (8.1)	32,855 (5.8)
Urinary bladder	609 (5.4)	190 (3.5)	92,638 (13.2)	29,342 (5.2)
Brain	153 (1.3)	65 (1.2)	20,812 (3.0)	15,595 (2.7)
Thyroid	411 (3.6)	547 (10.0)	20,478 (3.0)	66,699 (11.7)
Stage of disease at diagnosis				
Localized	5,784 (50.1)	2,856 (51.8)	327,122 (46.6)	258,489 (45.4)
Regional	2,292 (19.8)	1,090 (19.8)	174,152 (24.8)	148,407 (26.1)
Distant	2,720 (23.6)	1,240 (22.5)	169,002 (24.1)	134,722 (23.7)
Unknown	739 (6.4)	327 (5.9)	32,482 (4.6)	27,538 (4.8)
Year of diagnosis				
1995–1999	993 (8.6)	424 (7.7)	142,405 (20.3)	111,368 (19.6)
2000–2004	1,838 (15.9)	814 (14.8)	127,410 (18.1)	103,266 (18.1)
2005–2009	2,840 (24.6)	1,318 (23.9)	137,080 (19.5)	112,708 (19.8)

	Cancer patients with a prior transplant ^a		Cancer patients in the general population ^b	
	Male N= 11,535	Female N= 5,513	Male N=702,758	Female N=569,156
	No. (%)	No. (%)	No. (%)	No. (%)
2010–2014	3,644 (31.6)	1,804 (32.7)	143,869 (20.5)	117,947 (20.7)
2015–2019	2,220 (19.3)	1,153 (20.9)	151,994 (21.6)	123,867 (21.8)
Surgery^c				
Yes	7,114 (61.7)	3,571 (64.8)	406,939 (57.9)	340,376 (59.8)
No	3,950 (34.3)	1,739 (31.5)	220,521 (31.4)	170,005 (29.9)
Unknown	471 (4.1)	203 (3.7)	75,298 (10.7)	58,723 (10.3)
Radiotherapy^c				
Yes	2,007 (17.4)	1,015 (18.4)	163,280 (23.2)	135,352 (23.8)
No	8,900 (77.2)	4,225 (76.6)	539,478 (76.8)	433,804 (76.2)
Unknown	628 (5.4)	273 (5.0)		
Chemotherapy^c				
Yes	2,482 (21.5)	1,199 (21.7)	230,131 (32.7)	165,563 (29.1)
No	8,240 (71.4)	3,955 (71.7)	472,627 (67.3)	403,593 (70.9)
Unknown	813 (7.1)	359 (6.5)		

^aData are from the following TCM Study cancer registries that provided information regarding vital status and cause of death: Alaska (years of cancer diagnosis and follow-up: 1996–2017), Alabama (1996–2016), Arkansas (1996–2016), California (1995–2017), Colorado (1995–2016), Connecticut (1995–2017), Florida (1995–2019), Georgia (1995–2017), Hawaii (1995–2017), Illinois (1995–2018), Kentucky (1995–2017), Louisiana (1995–2017), Michigan (1995–2018), Montana (1995–2017), North Carolina (1995–2016), North Dakota (1997–2016), Nebraska (1995–2017), New Jersey (1995–2016), Nevada (1995–2015), New York (1995–2017), Ohio (1996–2015), Oklahoma (1997–2017), Oregon (1996–2016), Pennsylvania (1995–2017), Puerto Rico (1995–2016), Rhode Island (1995–2015), Seattle (1995–2017), Texas (1995–2016), Utah (1995–2017), and Virginia (1995–2016).

^bData are from Surveillance, Epidemiology, and End Results Program (SEER)-12 (years of cancer diagnosis and follow-up: 1995–2019)

^cData come from first course of treatment, which encompasses all types of treatment documented in the treatment plan and given to the patient prior to progression of disease or recurrence of disease.

Table 2.

Cancer-specific mortality rates and cancer-specific male-to-female hazard ratios in cancer patients with a prior transplant and those in the general population

Cancer site	Cancer-specific mortality rate in cancer patients with a prior transplant (per 1,000 py)		Cancer-specific mortality rate in cancer patients in the general population (per 1,000 py)		Cancer-specific M:F HR _{Transplant} (95% CI) ^a	Cancer-specific M:F HR _{GenPop} (95% CI) ^a	Interaction P-value
	Male	Female	Male	Female			
Lip	21.2	10.8	9.4	8.8	1.92 (0.82, 4.47)	1.32 (1.05, 1.67)	0.214
Stomach	352.7	242.0	200.4	166.5	1.02 (0.79, 1.33)	1.07 (1.04, 1.09)	0.880
Colorectal	101.9	121.2	49.3	50.6	0.89 (0.77, 1.03)	1.07 (1.06, 1.08)	0.007
Anus	76.5	70.0	53.7	38.4	1.25 (0.82, 1.91)	1.59 (1.48, 1.70)	0.164
Liver (including intrahepatic bile duct)	355.2	274.2	297.8	311.0	1.17 (0.90, 1.53)	1.06 (1.03, 1.08)	0.827
Pancreas	990.1	927.6	595.0	594.7	1.07 (0.89, 1.28)	1.01 (1.00, 1.03)	0.520
Larynx	95.2	103.7	54.7	57.8	0.78 (0.43, 1.41)	1.04 (0.98, 1.10)	0.976
Lung	501.6	388.4	345.8	251.0	1.20 (1.11, 1.29)	1.19 (1.18, 1.20)	0.683
Melanoma of the skin	56.0	38.4	14.7	8.1	1.11 (0.83, 1.48)	1.41 (1.36, 1.46)	0.632
Urinary bladder	124.0	173.6	29.7	35.7	0.82 (0.63, 1.06)	0.95 (0.93, 0.98)	0.941
Kidney (including renal pelvis)	39.5	25.6	42.5	37.6	1.33 (1.11, 1.60)	1.02 (0.99, 1.04)	0.003
Brain	656.9	433.5	234.8	206.1	1.32 (0.90, 1.94)	1.08 (1.06, 1.11)	0.492
Thyroid	7.8	3.0	7.9	3.0	2.75 (1.10, 6.85)	1.52 (1.42, 1.63)	0.070

^a Adjusted for age (<40 years, 40–79 years in 10-year increments, and 80+ years), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic Asian-American Pacific Islander), stage of cancer (localized, regional, distant, or unknown), year of diagnosis (1995–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2019), and receipt of chemotherapy (yes, no, or unknown), radiation (yes, no, or unknown), and/or surgery (yes, no, or unknown).

Note: Bolding indicates statistical significance at $P < 0.05$.

Table 3. Cancer-specific mortality male-to-female hazard ratios in cancer patients with a prior transplant and those in the general population, by age category

Cancer site	Age <50			Age ≥50		
	M:F HR (95% CI) _{Transplant} ^a	M:F HR (95% CI) _{GenPop} ^a	P-value ^b	M:F HR (95% CI) _{Transplant} ^a	M:F HR (95% CI) _{GenPop} ^a	P-value ^b
Lip	0.62 (0.09, 4.48)	4.61 (1.68, 12.60)	0.180	2.42 (0.87, 6.71)	1.18 (0.92, 1.50)	0.117
Stomach	0.47 (0.13, 1.65)	1.04 (0.98, 1.10)	0.288	1.15 (0.87, 1.51)	1.08 (1.05, 1.10)	0.811
Colorectal	0.98 (0.64, 1.49)	1.11 (1.07, 1.15)	0.147	0.87 (0.75, 1.02)	1.07 (1.05, 1.08)	0.018
Anus	0.67 (0.24, 1.89)	2.02 (1.71, 2.39)	0.024	1.51 (0.95, 2.40)	1.50 (1.38, 1.62)	0.836
Liver (including intrahepatic bile duct)	0.92 (0.41, 2.05)	1.36 (1.25, 1.48)	0.262	1.19 (0.90, 1.59)	1.03 (1.01, 1.06)	0.480
Pancreas	1.45 (0.61, 3.43)	1.14 (1.07, 1.22)	0.958	1.05 (0.87, 1.27)	1.01 (0.99, 1.02)	0.497
Larynx	-- c	1.11 (0.90, 1.37)	-- c	0.82 (0.44, 1.52)	1.03 (0.97, 1.10)	0.895
Lung	1.06 (0.77, 1.46)	1.17 (1.13, 1.22)	0.273	1.21 (1.12, 1.31)	1.20 (1.19, 1.21)	0.546
Melanoma of the skin	1.66 (0.83, 3.31)	1.59 (1.48, 1.72)	0.201	1.02 (0.74, 1.40)	1.34 (1.29, 1.39)	0.380
Urinary bladder	0.74 (0.33, 1.64)	0.96 (0.83, 1.11)	0.434	0.84 (0.64, 1.12)	0.95 (0.93, 0.98)	0.795
Kidney (including renal pelvis)	1.79 (1.14, 2.81)	1.18 (1.09, 1.29)	0.071	1.31 (1.07, 1.61)	1.00 (0.97, 1.03)	0.025
Brain	18.6 (2.06, 169)	1.22 (1.17, 1.29)	0.168	1.25 (0.84, 1.88)	1.00 (0.97, 1.02)	0.124
Thyroid	0.23 (0.01, 6.76)	2.54 (2.09, 3.08)	0.767	4.39 (1.42, 13.6)	1.39 (1.29, 1.50)	0.055

^a Adjusted for age (<40 years, 40–79 years in 10-year increments, and 80+ years), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic Asian-American Pacific Islander), stage of cancer (localized, regional, distant, or unknown), year of diagnosis (1995–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2019), and receipt of chemotherapy (yes, no/unknown), radiation (yes, no/unknown), and/or surgery (yes, no, or unknown).

^b P-value for interaction for the M:F HRs between transplant and general population.

^c The MF HR could not be estimated due to sparse data for this cancer.
Note: Bolding indicates statistical significance at $P<0.05$.