

doi: 10.1093/jnci/djab028 First published online March 11, 2021 Article

# Cancer Stage, Treatment, and Survival Among Transgender Patients in the United States

Sarah S. Jackson , PhD, MPH<sup>1,\*</sup> Xuesong Han , PhD<sup>2</sup> Ziling Mao , MPH<sup>2,3</sup>Leticia Nogueira , PhD, MPH<sup>2</sup> Gita Suneja, MD, MS<sup>4,5</sup> Ahmedin Jemal , DVM, PhD<sup>2</sup> Meredith S. Shiels , PhD<sup>1</sup>

<sup>1</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA; <sup>2</sup>Surveillance and Health Services Research, American Cancer Society, Atlanta, GA, USA; <sup>3</sup>Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA; <sup>4</sup>Radiation Oncology, University of Utah, Salt Lake City, UT, USA and <sup>5</sup>Population Health Sciences, University of Utah, Salt Lake City, UT, USA

\*Correspondence to: Sarah S. Jackson, PhD, MPH, Division of Cancer Epidemiology and Genetics, Infections and Immunoepidemiology Branch, National Cancer Institute, 9609 Medical Center Dr, Rockville, MD 20850, USA (e-mail: sarah.jackson@nih.gov).

#### **Abstract**

Background: Transgender persons face many barriers to health care that may delay cancer diagnosis and treatment, possibly resulting in decreased survival. Yet, data on cancer in this population are limited. We examined cancer stage at diagnosis, treatment, and survival among transgender patients compared with cisgender patients in the National Cancer Database (NCDB). Methods: Gender (male, female, or transgender) was extracted from medical records from patients diagnosed with cancer between 2003 and 2016. Logistic regression estimated odds ratios (ORs) for the associations between gender and stage at diagnosis and treatment receipt. Cox proportional hazards regression estimated hazard ratios (HRs) for associations between gender and all-cause survival. Results: Among 11 776 699 persons with cancer in NCDB, 589 were transgender. Compared with cisgender patients, transgender patients may be more likely to be diagnosed with advanced stage lung cancer (OR = 1.76, 95% confidence interval [CI] = 0.95 to 3.28); be less likely to receive treatment for kidney (OR = 0.19, 95% CI = 0.08 to 0.47) and pancreas (OR = 0.33, 95% CI = 0.11 to 0.95) cancers; and have poorer survival after diagnosis with non-Hodgkin lymphoma (HR = 2.34, 95% CI = 1.51 to 3.63), prostate (HR = 1.91, 95% CI = 1.06 to 3.45), and bladder cancers (HR = 2.86, 95% CI = 1.36 to 6.00). Similar associations were found for other cancer sites, although not statistically significant. Conclusion: Transgender patients may be diagnosed at later stages, be less likely to receive treatment, and have worse survival for many cancer types. Small sample size hampered our ability to detect statistically significant differences for some cancer sites. There is a need for transgender-focused cancer research as the population ages and grows.

The US population that self-identifies as transgender is estimated to be approximately 1.4 million adults (1). Transgender is the umbrella term for a diverse group of individuals whose gender identity differs from their sex assigned at birth (2). Cancer is an understudied topic in transgender health because of the paucity of available data (3). Until recently, research on cancer in this population was limited to case reports or small studies (4). There are several reasons why cancer burden may be higher among transgender individuals than their cisgender counterparts. Transgender persons who retain their natal reproductive organs are at risk for reproductive cancers, and the risks related to long-term use of gender-affirming treatment with high-dose estrogens or testosterone are currently unknown (3,5,6). Because of societal stigma related to gender minority status, transgender people may also be at risk for cancers associated

with elevated levels of smoking and excessive alcohol use in this community (7,8). The prevalence of HIV, hepatitis, and human papillomavirus infections is reportedly higher among transgender persons compared with their cisgender, heterosexual counterparts because of high rates of discrimination, economic marginalization, and unmet health-care needs (9-13). The increased prevalence of these viruses among gender minority adults may result in an increased incidence of AIDS-related cancers, as well as cancers of the liver and anus (3,4,14,15).

Transgender patients face many barriers to cancer care at both the provider and patient level. Cancer screenings may be missed because of the lack of clinician training and transgender-specific screening guidelines (16,17). Transgender patients have also reported discrimination in medical settings (7,18). Because of stigma and discrimination, transgender

individuals are also less likely to be employed and to have health insurance than cisgender patients (4,7). Consequently, there may be delays in cancer diagnoses and treatment, resulting in advanced stage disease at diagnosis and decreased survival among transgender individuals (4). Information on the cancer burden in this community will become increasingly important as the population ages and as best practice recommendations become more transgender inclusive and culturally competent. We sought to examine the association between gender identity and cancer stage at diagnosis, treatment, and survival

#### **Methods**

## **Study Population**

We used data from more than 11 million US patients diagnosed with cancer between 2003 and 2016 from the National Cancer Database (NCDB), a hospital-based registry sponsored by the American Cancer Society and the American College of Surgeons. Sex was recorded in the medical record as "male," "female," and "transsexual" (referred to herein as transgender). This field was updated in 2015 to include the patient's natal sex (eg, "transsexual, natal male") (19). However, because only 3 cancer cases were delineated as such, we were unable to analyze transgender cases separately by natal sex. Patients with "other (hermaphrodite)" were excluded because those with disorders of sex development may have unique cancer risk factors from those of transgender individuals (20). Patients with missing data for sex were also excluded (Supplementary Figure 1, available online).

## **Ascertainment of Cancer Outcomes**

We examined first, primary cancers with 10 or more cases occurring in transgender adults classified with International Classification of Diseases for Oncology, 3rd edition codes (Supplementary Table 1, available online). Individuals with missing information for stage, diagnosis date, or last contact date were excluded (Supplementary Figure 1, available online). Cancer stage at diagnosis was defined as stages 0 (breast and bladder cancers), I, II, III, or IV using the sixth edition of the American Joint Committee on Cancer (AJCC) (21) collaborative stage supplemented with AJCC Tumor, Nodes, and Metastasis pathological and clinical staging to compensate the high missingness in 2003 and 2016 because of AJCC staging coding change. The type of first course of treatment including surgery, radiation, and chemotherapy was recorded in the NCDB.

# **Ascertainment of Covariates**

The NCDB collects information on patient demographics, socioeconomic status, and clinical characteristics. These included age at diagnosis (18-44, 45-54, 55-64, or 65 years or older), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic [all races], or other), year of diagnosis (2004-2006, 2007-2010, or 2011-2014), median income level for the patient's zip code (<\$38 000, \$38 000-\$47 999, \$48 000-\$62 999, or  $\geq$ \$63 000), insurance status (private, 18- to 64-year Medicare-Medicaid, 65year or older Medicare-Medicaid, uninsured, or government or unknown), and type of treating facility (community center, comprehensive community center, teaching or research

institution. National Cancer Institute network cancer center, integrated network, or other or unknown).

#### Statistical Analysis

For each cancer site we used, multivariable logistic regression to evaluate the associations between gender identity (transgender vs cisgender) and cancer stage at diagnosis (0, I, and II vs III and IV) and receipt of cancer treatment (yes vs no). For lymphomas, receipt of treatment was defined as chemotherapy, radiotherapy, or a combination. For all other cancers, treatment was defined as surgery, radiotherapy, chemotherapy, or any combination of these therapies. Those with missing treatment information were categorized as having no treatment. These models were adjusted for age, race and ethnicity, diagnosis year, and stage at diagnosis (in the treatment model only).

We used Cox proportional hazards regression to examine the association between gender identity (transgender vs cisgender) and survival for each cancer site, adjusting for age at diagnosis, race and ethnicity, diagnosis year, stage at diagnosis, and treatment receipt. Follow-up was defined from cancer diagnosis until death from any cause, loss to follow-up, or end of 2017. Cases were limited to those cancers diagnosed before 2014 (2003-2013) to allow for enough follow-up time. The Schoenfeld residuals method was used to test the proportional hazards assumption, which was met for all models.

Additional models for stage, treatment, and survival were run, further adjusted for type of health insurance. A sensitivity analysis was repeated for the treatment models excluding patients who refused treatment. All analyses were conducted in SAS 9.4.

## Results

Among the 11 776 699 patients with cancer diagnosed between 2003 and 2016 in the NCDB, 589 patients were recorded as transgender (Table 1). Compared with cismen and ciswomen, transgender patients tended to be younger and less likely to be non-Hispanic White or to have private health insurance (all P < .001). The proportion of total cancers occurring in the anus, liver, and nonmelanoma skin, as well as Hodgkin and non-Hodgkin lymphoma, was higher among transgender individuals than cisgender individuals, although the proportion of cancers occurring in the prostate was lower in transgender individuals than cismen

None of the associations between transgender identity and stage at diagnosis was statistically significant for any cancer sites (Table 2), although transgender patients may be more likely to be diagnosed at later stages for cancers of the lung (odds ratio [OR] = 1.76, 95% confidence interval [CI] = 0.95 to 3.28) compared with cisgender patients. Transgender patients had lower odds of receiving treatment than cisgender patients for cancers of the kidney (OR = 0.19, 95% CI = 0.08 to 0.47) and pancreas (OR = 0.33, 95% CI = 0.11 to 0.95; Table 2). Gender identity was not associated with receipt of treatment for any of the other cancer sites. In an analysis where patients who refused treatment were excluded, the results did not differ materially from the main results (Supplementary Tables 2-4, available

Transgender patients had twofold or greater increased risk of death compared with cisgender patients for non-Hodgkin lymphoma (hazard ratio [HR] = 2.34,95% CI = 1.51 to 3.63), prostate cancer (HR = 1.91, 95% CI = 1.06 to 3.45), and urinary

Table 1. Characteristics of patients in the National Cancer Database by gender identity, 2003-2016gu

Characteristics	Transgender, No. (%) (n = 589)	Cismen, No. (%) (n = 5 627 603)	P <sup>a</sup>	Ciswomen, No. (%) (n = 6 148 507)	$P^{\mathrm{b}}$
Demographics					
Age at diagnosis, y			<.001		<.001
18-44	129 (21.9)	415 069 (7.4)	(.001	755 202 (12.3)	(,,,,
45-54	148 (25.1)	812 577 (14.4)		1 103 598 (17.9)	
55-64	168 (28.5)	1 619 691 (28.8)		1 481 905 (24.1)	
>65	144 (24.4)	2 780 266 (49.4)		2 807 802 (45.7)	
Race/Ethnicity	( )	,	<.001	( )	<.001
White, non-Hispanic	409 (69.4)	4 439 481 (78.9)		4 792 259 (77.9)	
Black	94 (16.0)	626 021 (11.1)		691 063 (11.2)	
Hispanic	57 (9.7)	310 632 (5.5)		365 393 (5.9)	
Other	19 (3.2)	186 201 (3.3)		238 817 (3.9)	
Missing	10 (1.7)	65 268 (1.2)		60 975 (1.0)	
Year of cancer diagnosis	, ,	, ,	<.001	, ,	.003
2003-2007	165 (28.0)	1 968 922 (35.0)		2 043 803 (33.2)	
2008-2011	203 (34.5)	1 647 431 (29.3)		1 771 614 (28.8)	
2012-2016	221 (37.5)	2 011 250 (35.7)		2 333 090 (37.9)	
Median area income level	, ,	, ,	.07	, ,	.02
<\$38 000	157 (26.7)	1 762,459 (31.3)		1 992 171 (32.4)	
\$38 000-\$47 999	165 (28.0)	1485 186 (26.4)		1 627 660 (26.5)	
\$48 000-\$62 999	137 (23.3)	1 309 690 (23.3)		1 399 673 (22.8)	
≥\$63 000	125 (21.2)	1 006 517 (17.9)		1 067 294 (17.4)	
Missing	<10 (0.8) <sup>e</sup>	63 751 (1.1)		61 709 (1.0)	
Cancer site			<.001		<.001
Esophagus	10 (1.7)	103 318 (1.8)		27 498 (0.4)	
Uterine corpus	10 (1.7)	_ ` '		467 455 (7.6)	
Pharynx	11 (1.9)	90 334 (1.6)		23 180 (0.4)	
Thyroid	12 (2.0)	92 974 (1.7)		304 677 (5)	
Hodgkin lymphoma	13 (2.2)	38 392 (0.7)		31 925 (0.5)	
Brain and other nervous system	14 (2.4)	110 646 (2)		86 478 (1.4)	
Other nonepithelial skin	14 (2.4)	25 354 (0.5)		14 980 (0.2)	
Urinary bladder	15 (2.5)	186 766 (3.3)		67 245 (1.1)	
Pancreas	16 (2.7)	155 598 (2.8)		153 448 (2.5)	
Melanoma of the skin	17 (2.9)	217 743 (3.9)		169 150 (2.8)	
Kidney and renal pelvis	24 (4.1)	268 184 (4.8)		168 479 (2.7)	
Liver and intrahepatic bile duct	26 (4.4)	137 896 (2.5)		53 839 (0.9)	
Rectum	26 (4.4)	202 545 (3.6)		149 206 (2.4)	
Anus, anal canal, and anorectum	28 (4.8)	19 145 (0.3)		32 861 (0.5)	
Breast	35 (5.9)	19 121 (0.3)		1 976 243 (32.1)	
Prostate	36 (6.1)	1 546 832 (27.5)		_	
Colon	39 (6.6)	385 231 (6.8)		414 275 (6.7)	
Non-Hodgkin lymphoma	47 (8)	246 405 (4.4)		215 671 (3.5)	
Lung and bronchus	79 (13.4)	822 817 (14.6)		750 083 (12.2)	
Other and unspecified primary sites <sup>c</sup>	117 (19.9)	958 302 (17)		1 041 814 (16.9)	
Individual insurance status			<.001		<.001
Any private	281 (47.7)	4 004 804 (71.2)		4 463 100 (72.6)	
18-64 Medicare/Medicaid	198 (33.6)	561 566 (10.0)		626 493 (10.2)	
≥65 Medicare/Medicaid	40 (6.8)	652 591 (11.6)		712 300 (11.6)	
Uninsured	53 (9.0)	211 735 (3.8)		198 890 (3.2)	
Government/unknown	17 (2.9)	196 907 (3.5)		147 724 (2.4)	
Type of treating health facility			.002		<.001
Community center	38 (6.5)	460 720 (8.2)		505 417 (8.2)	
Comprehensive community center	186 (31.6)	2 129 547 (37.8)		2 426 115 (39.5)	
Teaching/research institution	165 (28.0)	1 239 517 (22.0)		1 353 454 (22.0)	
NCI network cancer center	90 (15.3)	806 014 (14.3)		738 115 (12.0)	
Integrated network	78 (13.2)	681 314 (12.1)		792 605 (12.9)	
Others/Unknown	32 (5.4)	310 491 (5.5)		332 801 (5.4)	

(continued)

Table 1. (continued)

Characteristics	Transgender, No. (%) (n = 589)	Cismen, No. (%) (n = 5 627 603)	P <sup>a</sup>	Ciswomen, No. (%) (n = 6 148 507)	$P^{b}$
Receipt of treatment <sup>d</sup>			<.001		<.001
Yes	473 (80.3)	4 697 606 (83.5)		5 409 277 (88)	
No	116 (19.7)	929 997 (16.5)		739 230 (12)	

<sup>&</sup>lt;sup>a</sup>Comparing transgender patients with cismale patients. Two-tailed  $\chi^2$  test. NCI = National Cancer Institute.

bladder cancer (HR = 2.86, 95% CI = 1.36 to 6.00; Table 3). Risk of mortality did not appear to differ between transgender and cisgender patients for other cancer sites.

## **Discussion**

The current study includes nearly 600 transgender patients with cancer in a large national database. Transgender patients tended to be diagnosed with more advanced stage lung cancer and were less likely to receive treatment for kidney and pancreas cancers than cisgender patients. Further, transgender patients with non-Hodgkin lymphoma, prostate cancer, and urinary bladder cancer had worse survival compared with cisgender patients. These disparities persisted even after adjusting for health insurance and excluding individuals who refused treatment. No differences in stage at diagnosis, receipt of treatment, or survival were observed for the other cancer sites examined.

Cancer screening among transgender patients is lower than their cisgender counterparts because of several barriers to care (22-25). Many clinicians are unaware of the unique health needs of their transgender patients (16,17). For instance, physicians may perform cancer screening when a patients' gender changes in the medical record (eg, prostate exams for transwomen) or erroneously believe that the risk is lower because of assumptions about sexual behavior and gender identity (eg, cervical cancer screening for transmen) (24,26). Transgender patients also face substantial financial barriers to health care because they are almost 3 times more likely than cisgender individuals to be unemployed and, thus, more likely to be uninsured or underinsured (18,27). Patients have also reported mistreatment in health-care settings, with 23% of transgender people stating that they did not seek health care in the past year because of discrimination and stigma from medical staff (7,18). The absence of transgenderspecific screening guidelines, lack of clinician cultural competence, and patients' fear of discrimination can result in delays in cancer diagnosis and treatment leading to poorer prognosis in this population (7,17).

In transwomen, the prostate is not removed as part of gender-affirming surgery because of possible complications, such as incontinence (28). Previous research suggests prostate cancer is rare among transfeminine patients because of treatment with antiandrogen and estrogen therapy, possibly followed by bilateral orchiectomy (15,29,30). Yet, although the incidence of prostate cancer may be lower in transwomen than cismen, a growing body of research indicates that prostate cancer could be more aggressive among transwomen, which may

explain our finding of increased mortality among transgender patients with prostate cancer (29). Lower levels of serum testosterone may paradoxically increase the risk for aggressive prostate cancer (31,32). Recent research has also highlighted the role of exogenous estrogen therapy in prostate tumorigenesis (29,33,34). Estrogen mediated through estrogen receptor– $\alpha$  may have carcinogenic effects on the prostate alone (34), or it may be that a higher estradiol to dihydrotestosterone ratio may promote stromal cell growth (33). Screening guidelines recommend the same standards for transwomen as cismen (33) even though the use of 5alpha-reductase inhibitors has been shown to decrease serum prostate-specific antigen levels leading to underdetection of early lesions (35). As a result of these findings, it has been suggested that prostate-specific antigen levels of 1 ng/ ml should be used as an upper threshold of normal or an increase from nadir of 0.3 ng/ml or greater for prostate monitoring in transwomen on antiandrogen therapy (28).

Our finding that mortality is elevated among transgender patients with non-Hodgkin lymphoma may be explained by underlying HIV infection. Worldwide, the prevalence of HIV infection is high among gender minority adults. In the United States, it is estimated that 27.7% of transwomen are HIV positive, with the highest prevalence among African American transwomen (56.3%) (10). HIV infection is associated with an elevated risk of AIDS-defining cancers such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer as well as non-AIDS-defining cancers (36-39). HIV is also associated with more aggressive disease and an increased risk of mortality from cancer (40-42). Coghill and colleagues (42) found that HIV infection was associated with a more advanced stage of disease in patients with cancers of the lung, breast, prostate, and bladder and melanoma of the skin and increased mortality in patients with breast and anal cancers.

Little research has been conducted in transgender patients with urinary bladder cancer. An analysis using Surveillance Epidemiology and End Results (SEER) observed a higher proportional incidence of bladder cancer among transgender individuals compared with cisgender women, but not cismen (5). Another SEER analysis examining sex differences in bladder cancer survival found that ciswomen had lower 5-year survival compared with cismen, in part because ciswomen present with later stage at diagnosis and higher-grade lesions (43). This finding may suggest sex hormones play a role in the aggressiveness of this cancer. Testosterone has been found to promote bladder cancer carcinogenesis, whereas estrogens appear to inhibit carcinogenesis but promote tumor progression (44,45). In animal studies, the observed sex difference in bladder cancer carcinogenesis disappeared when male mice were castrated and female mice were treated with testosterone (46). Because we are

<sup>&</sup>lt;sup>b</sup>Comparing transgender patients with cisfemale patients. Two-tailed  $\chi^2$  test.

<sup>&</sup>lt;sup>c</sup>Includes acute lymphocytic leukemia (C91.0); acute myeloid leukemia (C92.0); chronic lymphocytic leukemia (C91.1); larynx (C32.0); multiple myeloma (C90.0); other digestive organs (C26.8-C26.9, C48.8); other leukemia (C42.0, C42.1, C42.4); other and nonspecified primary sites (C96); small intestine (C17); soft tissue (including heart) (C38.0, C47, C49); stomach (C16); testis (C62); tongue (C02); vagina and other genital, female (C52.9, C57.0-C58.9); and vulva (C51).

<sup>&</sup>lt;sup>d</sup>For Hodgkin lymphoma and non-Hodgkin lymphoma, defined as chemotherapy, radiotherapy, or a combination of both. For all other cancer sites, cancer treatment was defined as surgery, radiotherapy, chemotherapy, or any combination of these therapies.

eCells with more than 0 but fewer than 10 individuals are suppressed.

Table 2. Associations between transgender gender identity with stage at cancer diagnosis and receipt of cancer treatment by cancer site among patients in the National Cancer Database, 2003-2016

Cancer site and stage at	Received any cancer				
diagnosis	No. transgender cases	OR (95% CI) <sup>a</sup>	treatment <sup>b</sup>	No. transgender cases	OR (95% CI) <sup>c</sup>
Anus, anal canal, and anorectum					
I and II	11	1.00 (Referent)	No	<10 <sup>e</sup>	1.00 (Referent)
III and IV	14	1.61 (0.73 to 3.56)	Yes	26	0.62 (0.14 to 2.69
Breast					
0, I, and II	24	1.00 (Referent)	No	<10 <sup>e</sup>	1.00 (Referent)
III and IV	11	1.80 (0.87 to 3.70)	Yes	34	0.97 (0.13 to 7.24
Kidney and renal pelvis					
I and II	19	1.00 (Referent)	No	<10 <sup>e</sup>	1.00 (Referent)
III and IV	<10 <sup>e</sup>	0.65 (0.24 to 1.77)	Yes	17	0.19 (0.08 to 0.47
Liver and intrahepatic bile duct					
I and II	14	1.00 (Referent)	No	13	1.00 (Referent)
III and IV	<10 <sup>e</sup>	0.76 (0.33 to 1.77)	Yes	13	0.65 (0.30 to 1.44
Lung and bronchus		,			`
I and II	12	1.00 (Referent)	No	20	1.00 (Referent)
III and IV	63	1.76 (0.95 to 3.28)	Yes	59	0.74 (0.47 to 1.24
Melanoma of the skin		,			,
I and II	11	1.00 (Referent)	No	<10 <sup>e</sup>	1.00 (Referent)
III and IV	<10 <sup>e</sup>	2.11 (0.77 to 5.82)	Yes	15	0.34 (0.07 to 1.76
Non-Hodgkin lymphoma		,			·
I and II	15	1.00 (Referent)	No	12	1.00 (Referent)
III and IV	29	1.59 (0.85 to 2.97)	Yes	35	0.87 (0.44 to 1.69
Pancreas		,			,
I and II	<10 <sup>e</sup>	1.00 (Referent)	No	<10 <sup>e</sup>	1.00 (Referent)
III and IV	10	1.12 (0.41 to 3.08)	Yes	<10 <sup>e</sup>	0.33 (0.11 to 0.95
Prostate <sup>d</sup>		,			,
I and II	25	1.00 (Referent)	No	<10 <sup>e</sup>	1.00 (Referent)
III and IV	10	1.69 (0.81 to 3.55)	Yes	30	0.82 (0.34 to 2.00
Rectum		,			,
I and II	12	1.00 (Referent)	No	0	1.00 (Referent)
III and IV	11	0.80 (0.35 to 1.82)	Yes	26	`f
Urinary bladder		, ,			
0, I, and II	<10 <sup>e</sup>	1.00 (Referent)	No	0	1.00 (Referent)
III and IV	<10 <sup>e</sup>	2.11 (0.76 to 5.89)	Yes	15	`f

aOR calculated with multivariable logistic regression for the association of being transgender (using cisgender as reference group) with stages III and IV vs stage 0 (if applicable), I, and II, adjusted for age at diagnosis (18-44, 45-54, 55-64, or 65 years and older), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other), and year of diagnosis (2004-2006, 2007-2010, or 2011-2014). AJCC = American Joint Committee on Cancer; CI = confidence interval; OR = odds ratio.

unable to identify the natal sex of our transgender urinary bladder cancer cases, we are unable to shed light on the possible hormonal influence on mortality in our study.

Even though this is the first study of its kind to examine cancer presentation, treatment, and survival among transgender individuals, our analysis was hampered by small sample size. The percentage of persons with first, primary cancers who identify as transgender was 0.005%, similar to a study conducted in the North American Association of Central Cancer Registries, which found 0.004% of patients had a transgender gender identity (14). It is difficult to estimate the expected proportion of cancer in this population because the US transgender population has not been fully enumerated, although an estimated 0.6% of US adults identify as transgender (1). Furthermore, the transgender population is younger than the general US population, and those with cancer are not representative of the general population. Because gender identity was not self-reported by the patients themselves, we may have missed some transgender patients. However, with more than 11 million individuals, the number of transgender patients misclassified as cisgender is likely to be too small to change our results. Finally, the absence of data on sex assigned at birth for the transgender patients precluded meaningful comparisons with cismen and ciswomen, respectively.

bCancer treatment is defined as chemotherapy, surgery, and radiotherapy for all sites except lymphoma. Treatment for lymphoma is defined as chemotherapy and radiotherapy.

OR calculated with multivariable logistic regression for the association of being transgender (using cisgender as reference group) with cancer treatment, adjusted for age at diagnosis (18-44, 45-54, 55-64, or 65 years and older), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other), year of diagnosis (2004-2006, 2007-2010, or 2011-2014), and AJCC stage (0-II, III/IV, or unknown).

<sup>&</sup>lt;sup>d</sup>Sex-specific site uses cismen only as reference group.

eCells with more than 0 but fewer than 10 individuals are suppressed.

f" indicates that the cell size was too small to calculate the OR.

Table 3. Associations between transgender gender identity and mortality after cancer diagnosis by cancer site among patients in the National Cancer Database 2003-2013

Cancer site and gender identity	No. of deaths	HR (95% CI) <sup>a</sup>
Anus, anal canal, and anorectum		
Cisgender	16 193	1.00 (Referent)
Transgender	<10 <sup>b</sup>	1.01 (0.52 to 1.94)
Breast		
Cisgender	358 042	1.00 (Referent)
Transgender	<10 <sup>b</sup>	1.23 (0.59 to 2.58)
Kidney and renal pelvis		
Cisgender	127 260	1.00 (Referent)
Transgender	<10 <sup>b</sup>	1.72 (0.82 to 3.61)
Liver and intrahepatic bile duct		
Cisgender	111 818	1.00 (Referent)
Transgender	19	1.06 (0.68 to 1.67)
Lung and bronchus		
Cisgender	1 047 162	1.00 (Referent)
Transgender	46	1.13 (0.85 to 1.51)
Melanoma of the skin		
Cisgender	78 729	1.00 (Referent)
Transgender	<10 <sup>b</sup>	1.06 (0.51 to 2.22)
Non-Hodgkin lymphoma		
Cisgender	165 989	1.00 (Referent)
Transgender	20	2.34 (1.51 to 3.63)
Pancreas		
Cisgender	212 072	1.00 (Referent)
Transgender	12	1.37 (0.78 to 2.42)
Prostate		
Cisgender	261 123	1.00 (Referent)
Transgender	11	1.91 (1.06 to 3.45)
Rectum		
Cisgender	128 998	1.00 (Referent)
Transgender	12	1.32 (0.75 to 2.33)
Urinary bladder		
Cisgender	118 948	1.00 (Referent)
Transgender	<10 <sup>b</sup>	2.86 (1.36 to 6.00)

<sup>&</sup>lt;sup>a</sup>Adjusted for age at diagnosis, (18-44, 45-54, 55-64, or 65 years and older), year of diagnosis (2003-2007, 2008-2011, or 2012-2013), race and ethnicity (non-Hispanic White, Black, Hispanic, or other), AJCC stage (0-II, III/IV, or unknown), and treatment (yes or no). AJCC = American Joint Committee on Cancer; CI = confidence interval: HR = hazard ratio

A thorough examination of cancer disparities among gender minorities relies on complete and representative data on both sex assigned at birth and gender identity (5,47). Groups such as the American Society of Clinical Oncology have called for the routine collection of these variables in cancer registries, electronic medical records, and clinical trials (4,47,48), which will allow for estimates of both cancer risk and more meaningful comparisons between transgender and cisgender patients (5,47). As the population ages and grows, there is a need for cancer research focused among transgender individuals.

## **Funding**

Supported by the American Cancer Society and the Intramural Research Program of the US National Cancer Institute (National Institutes of Health).

#### **Notes**

Role of the funders: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures: Xuesong Han, received funding from AstraZeneca for research outside the submitted work. Gita Suneja is supported by grants K08CA228631 from the National Institutes of Health. The other authors made no disclosures.

Author contributions: SSJ: Conceptualization; Methodology; Writing-original draft. XH: Data curation; Formal analysis; Writing-review and editing. ZM: Data curation; Formal analysis. LN: Writing-review and editing. GS: Writing-review and Writing—review editing. AI: and editing. Conceptualization; Methodology; Supervision; Writing-review and editing.

Acknowledgements: We gratefully acknowledge all cancer registries and their staff for their hard work and diligence in collecting cancer information, without which this research could not have been done.

# **Data Availability**

The data underlying this article were provided by the American Cancer Society and the American College of Surgeons by permission. Data access can be requested directly from the American College of Surgeons: https://www.facs.org/qualityprograms/cancer/ncdb/puf.

# References

- 1. Flores AR, JL H, GJ G, et al. How Many Adults Identify as Transgender in the United States? Los Angeles, CA: The Williams Institute; 2016.
- 2. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Lesbian, gay, bisexual, and transgender health: transgender persons. https://www.cdc.gov/lgbthealth/transgender.htm. Accessed June 3 2020.
- 3. Cancer risk in the transgender community. Lancet Oncol. 2015;16(9):999.
- 4. Institute of Medicine (US) Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Washington, DC: The National Academies Press; 2011.
- 5. Braun H, Nash R, Tangpricha V, et al. Cancer in transgender people: evidence and methodological considerations, Epidemiol Rev. 2017;39(1):93-107.
- 6. de Blok CJM, Wiepjes CM, Nota NM, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands, BMJ, 2019;365:11652.
- 7. Grant JM, Mottet LA, Tanis J, et al. Injustice at Every Turn: A Report of the National Transgender Discrimination Survey. Washington, DC: National Center for Transgender Equality and National Gay and Lesbian Task Force; 2011.
- 8. Institute of Medicine. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. In. Washington, DC: The National Academies Press; 2011.
- 9. Baral SD, Poteat T, Stromdahl S, et al. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis. 2013; 13(3):214-222
- 10. Herbst JH, Jacobs ED, Finlayson TJ, et al. HIV/AIDS Prevention Research Synthesis Team. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav. 2008;12(1):
- 11. Brown B, Poteat T, Marg L, et al. Human papillomavirus-related cancer surveillance, prevention, and screening among transgender men and women: neglected populations at high risk. LGBT Health. 2017;4(5):315-319.
- 12. Mangla N, Mamun R, Weisberg IS. Viral hepatitis screening in transgender patients undergoing gender identity hormonal therapy. Eur J Gastroenterol Hepatol. 2017;29(11):1215-1218.
- 13. Shover CL, DeVost MA, Beymer MR, et al. Using sexual orientation and gender identity to monitor disparities in HIV, sexually transmitted infections, and viral hepatitis. Am J Public Health. 2018;108(S4):S277-S283.

<sup>&</sup>lt;sup>b</sup>Cells with more than 0 but fewer than 10 individuals are suppressed.

- 14. Nash R, Ward KC, Jemal A, et al. Frequency and distribution of primary site among gender minority cancer patients: an analysis of U.S. national surveillance data, Cancer Enidemiol, 2018:54:1-6.
- 15. Silverberg MJ, Nash R, Becerra-Culqui TA, et al. Cohort study of cancer risk among insured transgender people. Ann Epidemiol. 2017;27(8):499-501.
- 16. Shetty G, Sanchez JA, Lancaster JM, et al. Oncology healthcare providers' knowledge, attitudes, and practice behaviors regarding LGBT health. Patient Educ Couns. 2016;99(10):1676-1684.
- 17. Schabath MB, Blackburn CA, Sutter ME, et al. National Survey of Oncologists at National Cancer Institute-designated comprehensive cancer centers: attitudes, knowledge, and practice behaviors about LGBTO patients with cancer. I Clin Oncol. 2019;37(7):547-558.
- 18. James SE, Herman JL, Keisling M, et al. The Report of the 2015 U.S. Transgender Survey. Washington, DC: National Center for Transgender Equality; 2016.
- 19. American College of Surgeons Commission on Cancer. About cancer program categories. https://www.facs.org/quality-programs/cancer/coc/apply/categories. Accessed February 11, 2020.
- 20. Mayer KH, Bradford JB, Makadon HJ, et al. Sexual and gender minority health: what we know and what needs to be done. Am J Public Health. 2008;98(6): 989-995.
- 21. Greene FL, Balch CM, Fleming ID, et al., (eds.). AJCC Cancer Staging Handbook: TNM Classification of Malignant Tumors. New York, NY: Springer Science & Business Media; 2002.
- 22. Tabaac AR, Sutter ME, Wall CSJ, et al. Gender identity disparities in cancer screening behaviors. Am J Prev Med. 2018;54(3):385-393.
- 23. Clark MA, Boehmer U, Rosenthal S, Cancer screening in lesbian and bisexual women and transmen. In: U Boehmer, R Elk, eds. Cancer and the LGBT Community. Switzerland: Springer International Publishing; 2015: 83-98.
- 24. Nelson B. A cancer screening crisis for transgender patients. Cancer Cytopathol. 2019;127(7):421-422.
- 25. Kiran T, Davie S, Singh D, et al. Cancer screening rates among transgender adults: cross-sectional analysis of primary care data. Can Fam Physician. 2019; 65(1):e30-e37.
- 26. Agenor M, Peitzmeier SM, Bernstein IM, et al. Perceptions of cervical cancer risk and screening among transmasculine individuals: patient and provider perspectives, Cult Health Sex, 2016;18(10):1192-1206.
- 27. Gonzales G, Henning-Smith C. Barriers to care among transgender and gender nonconforming adults. Milbank Q. 2017;95(4):726-748.
- 28. Trum HW, Hoebeke P, Gooren LJ. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. Acta Obstet Gynecol Scand. 2015:94(6):563-567.
- 29. Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. Andrologia. 2014:46(10):1156-1160.
- 30. de Nie I, Blok Cjm D, van der Sluis TM, et al. Prostate cancer incidence under androgen deprivation: nationwide cohort study in trans women receiving hormone treatment. J Clin Endocrinol Metab. 2020;105(9):e3293-e3299.
- 31. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol. 2000;163(3):824-827.

- 32. Morgentaler A. Turning conventional wisdom upside-down; low serum testosterone and high-risk prostate cancer. Cancer. 2011;117(17):3885-3888.
- 33. Deebel NA, Morin JP, Autorino R, et al. Prostate cancer in transgender women: incidence, etiopathogenesis, and management challenges. Urology. 2017;110: 166-171.
- 34. Sharif A. Malhotra NR. Acosta AM. et al. The development of prostate adenocarcinoma in a transgender male to female patient; could estrogen therapy have played a role? Prostate. 2017;77(8):824-828.
- 35. Marks LS, Andriole GL, Fitzpatrick JM, et al. The interpretation of serum prostate specific antigen in men receiving 5alpha-reductase inhibitors: a review and clinical recommendations. J Urol. 2006;176(3):868-874.
- 36. Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370(9581):59-67.
- 37. Hernández-Ramírez RU, Shiels MS, Dubrow R, et al. Cancer risk in HIVinfected people in the USA from 1996 to 2012: a population-based, registrylinkage study. Lancet HIV. 2017;4(11):e495-e504.
- Silverberg MJ, Lau B, Achenbach CJ, et al.; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS, Cumulative incidence of cancer among persons with HIV in North America: a cohort study. Ann Intern Med. 2015;163(7): 507-518.
- 39. Shiels MS. Cole SR. Kirk GD. et al. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009; 52(5):611-622
- 40. Coghill AE, Pfeiffer RM, Shiels MS, et al. Excess mortality among HIV-infected individuals with cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017;26(7):1027-1033.
- 41. Coghill AE, Shiels MS, Suneja G, et al. Elevated cancer-specific mortality among HIV-infected patients in the United States. J Clin Oncol. 2015;33(21):
- 42. Coghill AE, Han X, Suneja G, et al. Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base. Cancer. 2019;125(16):2868-2876.
- 43. Cook MB. McGlynn KA. Devesa SS, et al. Sex disparities in cancer mortality and survival, Cancer Epidemiol Biomarkers Prev. 2011;20(8):1629-1637
- 44. Zhang Y. Understanding the gender disparity in bladder cancer risk: the impact of sex hormones and liver on bladder susceptibility to carcinogens. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2013;31(4):287-304.
- 45. Lucca I, Fajkovic H, Klatte T. Sex steroids and gender differences in nonmuscle invasive bladder cancer. Curr Opin Urol. 2014;24(5):500-505
- 46. Bertram JS, Craig AW. Specific induction of bladder cancer in mice by butyl-(4-hydroxybutyl)-nitrosamine and the effects of hormonal modifications on the sex difference in response. Eur J Cancer. 1972;8(6):587-594.
- 47. Reisner SL, Conron JK, Baker K, et al. "Counting" transgender and gendernonconforming adults in health research: recommendations from the gender identity in US Surveillance Group. Transgend Stud Q. 2015;2(1):34-57.
- 48. Griggs J, Maingi S, Blinder V, et al. American Society of Clinical Oncology position statement: strategies for reducing cancer health disparities among sexual and gender minority populations. J Clin Oncol. 2017;35(19):2203-2208.