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Cancer Stage at Diagnosis in HIV-infected People and Transplant Recipients

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Abstract

Background—It is unknown whether immunosuppression results in more aggressive, advanced stage cancers. As cancer stage is influenced both by tumor biology and medical surveillance, we assessed cancer stage in HIV-infected individuals and solid organ transplant recipients, two immunosuppressed groups with differences in healthcare utilization.

Methods—We used data on all cases of 15 cancer types, diagnosed during 1996–2010 in two studies that linked U.S. cancer registries to HIV and transplant registries. Odds ratios (ORs) for advanced (vs. local) disease were estimated comparing HIV and transplant populations to immunocompetent people in polytomous logistic regression models, adjusted for age, sex, race, registry and year.

Results—A total of 8,411 of 4.5 million cancer cases occurred in HIV-infected people, and 7,322 of 6.4 million cancer cases occurred in transplant recipients. Compared to immunocompetent people with cancer, HIV-infected people were more likely to be diagnosed with distant stage lung (OR=1.13), female breast (OR=1.99), and prostate cancers (OR=1.57), while transplant recipients had fewer distant stage lung (OR=0.54), female breast (OR=0.75) and prostate cancers (OR=0.72). Both immunosuppressed populations had a shift toward advanced stage melanoma (ORs: HIV=1.97; transplant=1.82) and bladder cancer (ORs: HIV=1.42; transplant=1.54).

Conclusions—Bladder cancer and melanoma were more likely to be diagnosed at non-local stage in both HIV-infected people and transplant recipients, suggesting a role of

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immunosuppression in their progression. Additionally, we observed a shift for some common cancers toward later stages in HIV-infected individuals and toward earlier stages in transplant recipients, consistent with differential access to medical care or surveillance.

Keywords

cancer; stage; transplant; HIV

Individuals with suppressed immune systems are at increased risk for developing a number of cancers, particularly those associated with viral infections. Solid organ transplant recipients and people infected with human immunodeficiency virus (HIV) are two populations with immunosuppression, predominantly related to deficits in T-cell function, and have elevated cancer risks (1). However, it is unknown whether immunosuppression also increases tumor aggressiveness, so that malignancies progress particularly quickly to advanced disease and death. The stage of cancer at the time of diagnosis reflects whether the tumor is localized, has spread to regional tissues or metastasized to more distant sites. Thus, assessing cancer stage in these populations may provide insight into the effect of immunosuppression on cancer progression.

Prior research on cancer stage in HIV and transplant populations has been limited. One study, which compared cancers from an international transplant registry to cases from the U.S. general population, found that transplant recipients presented at later stages (2). Studies of HIV-infected people have demonstrated advanced stages at diagnosis for colorectal cancer (3;4) and lung cancer (5), but others had discrepant findings (6;7). No prior study has assessed cancer stage for multiple cancer sites among both HIV-infected individuals and transplant recipients.

Though both the HIV-infected and transplant recipient populations experience deficits in cell-mediated immune function, the characteristics of these populations differ. HIV-infected people are more likely to be uninsured (8), affected by poverty (9), and more likely to exhibit social behaviors, such as drug use, that interfere with utilization of health services, including cancer screening. In contrast, health insurance is a requirement for organ transplantation, and transplant recipients undergo frequent monitoring of immunosuppressive medications and graft function. The parallel comparison of cancer stage in these two immune suppressed populations is important, because stage at diagnosis is influenced both by the tumor biology and the point during the course of cancer development when the tumor is first detected. People who receive less healthcare are more likely to be diagnosed with later stage disease, particularly for screen-detectable cancers (10), while people receiving increased surveillance are more likely to be diagnosed with earlier stage disease. Thus, a similar shift towards advanced stage in both populations would be best explained by an effect of immunosuppression on malignancy biology. Tumor grade (i.e., degree of differentiation manifested by tumor cells) is another marker of tumor aggressiveness that may be less impacted by the timing of cancer diagnosis; however, grade is not systematically ascertained for all tumor sites.

In the current study, we compared the stages of cancers diagnosed in HIV-infected people and transplant recipients with the stages for other cancer patients (i.e., “immunocompetent”

patients), using data from two large registry linkage studies. We also evaluated the distribution of tumor grade for select cancer sites. Additionally, among individuals with cancer within each population, we assessed whether indicators reflecting the degree of immunosuppression were associated with advanced stage.

Methods

Cancers were ascertained from the National Cancer Institute's HIV/AIDS Cancer Match (HACM) (www.hivmatch.cancer.gov) and Transplant Cancer Match (TCM) Studies (www.transplantmatch.cancer.gov). Briefly, the HACM Study is a linkage of U.S. HIV and cancer registries (1980–2010), and the TCM Study is a linkage of the U.S. Scientific Registry of Transplant Recipients (SRTR) and cancer registries (1987–2010). Automated matching software was used to link HIV and cancer registries, and the SRTR and cancer registries, based on social security, name, date of birth and sex. Matches identified by the software were confirmed through clerical review. Fourteen regions from each study were included in this analysis. From cancer registries, we identified all cases in the general population of the most common solid tumors (i.e., oral cavity/pharynx, stomach, colorectum, anus, liver, pancreas, lung, melanoma, female breast, cervix, uterus, prostate, bladder, kidney and thyroid), and linkage with HIV registries and the SRTR identified cases that occurred in HIV-infected people or among transplant recipients, respectively. Cancer diagnoses were classified using a previously described classification scheme (11). We restricted to cancers diagnosed during 1996–2010, the time period following introduction of highly active antiretroviral therapy to treat HIV.

Stage at cancer diagnosis (i.e., *in situ*, localized, regional, distant) was categorized using Surveillance, Epidemiology, and End Results (SEER) summary stage (i.e., a combination, based on diagnosis year, of SEER summary stage 1977 and 2000 and derived SEER summary stage 2000). All cancer sites were limited to invasive disease, except for bladder cancer, female breast cancer and melanoma, where *in situ* cases were also considered. We also assessed cancer grade (i.e., well differentiated, moderately differentiated, poorly differentiated and undifferentiated) for a subset of cancers where grade information was available on >70% of cases (i.e., oral cavity/pharynx, stomach, colorectum, uterus, prostate, and bladder cancers). New York and Michigan registries were excluded from the grade analysis due to a larger fraction of missing information. Liver cancers occurring among liver transplant recipients were excluded to avoid counting cancers in the native liver that were present prior to transplantation. Male breast cancers were excluded.

Statistical Analysis

To provide context for our results, we estimated standardized incidence ratios (SIRs) for each cancer, comparing observed cancer cases in HIV-infected people or transplant recipients with expected cases, calculated by applying general population cancer rates from the cancer registries, standardized by age, sex, race, calendar year and registry to the HIV and transplant populations. SIRs represent the relative risk of each cancer in the HIV or transplant population, compared to the general population.

Next, we assessed the associations of HIV and transplantation with cancer stage in separate analyses that included all cases captured by the cancer registries of the HACM and TCM Studies, respectively. We utilized polytomous logistic regression models to assess the association between HIV (yes/no) or transplant status (yes/no) with stage at diagnosis (local as reference category). Regional and distant stages were collapsed for cancers with <10 distant stage cases. All models were adjusted for age, sex, race (white, black and other), calendar year and registry. Proportional odds logistic regression models were used to estimate p-values for trend across stages. These models were also used to assess grade as the outcome (well-differentiated as the reference category). Grade categories with <10 cases were collapsed with adjacent categories.

For our stage analysis, we interpreted our results based on the consistency of our findings across both HIV and transplant populations, focusing on p-values for trend across stages to assess statistically significant shifts in stage at diagnosis. When stage was more advanced only among HIV-infected people, and/or stage was less advanced only among transplant recipients, we interpreted the results to indicate that differences in surveillance or screening were the likely explanation. We interpreted the evidence as supporting a role of immunosuppression in cancer progression when stage was more advanced in both populations. Finally, we assessed the association between indicators of immunosuppression (i.e., AIDS status and time since transplant) with stage at diagnosis (regional/distant vs. local) using logistic regression, adjusting for age and sex. All analyses were carried out with SAS version 9.3 (Cary, NC).

Results

We included a total of 4,471,704 and 6,435,000 cancer cases from the HACM and TCM Studies, respectively (Table 1). Of these cases, 8,411 (0.19%) were HIV-infected at the time of cancer diagnosis and 7,322 (0.11%) were transplant recipients. Compared to cancer cases without HIV, HIV-infected cases were more likely to be male, black, and 30–49 years old. Cancer cases with a transplant were more likely to be male, black, and aged 50–69 years than cancer cases who had not had a transplant. These differences generally reflect demographic characteristics of the U.S. HIV and transplant populations. Of the cancers included, lung, anal and cervical cancers were the most common cancers in people with HIV, while lung, prostate and kidney cancers were the most common in transplant recipients.

Compared to the general population, the risk of several cancers was significantly elevated (i.e., oral cavity/pharynx, anus and lung) or decreased (i.e., uterine corpus, female breast, and prostate) in both HIV-infected people and transplant recipients (Figure 1; Supplemental Table 1). In contrast, the risks of stomach, colorectal, pancreatic, bladder, kidney, and thyroid cancers and melanoma were increased only in transplant recipients, and the risks of liver and cervical cancers were increased only in HIV-infected people. HIV-infected people had decreased risks of colorectal, thyroid and bladder cancers.

For several cancers, we observed trends toward advanced stage disease only in HIV-infected people, and/or trends toward local stage disease in transplant recipients, compared to

immunocompetent patients (i.e., those without HIV or a transplant, respectively; Table 2), likely indicating a role for differences in surveillance or screening. For lung cancer, HIV-infected people were somewhat more likely to present with distant stage cancer (odds ratio [OR]=1.13, 95%CI 0.98–1.29, p-trend=0.08), and transplant recipients were less likely to present with distant stage cancer (OR=0.54, 95%CI 0.48–0.61, p-trend<0.001). A similar pattern was seen for female breast cancer (HIV: OR=1.99, 95%CI 1.40–2.83, p-trend=0.008; transplant: OR=0.75; 95%CI 0.47–1.19, p-trend<0.001). For prostate cancer, HIV-infected individuals were more likely to present with distant stage disease (OR=1.57, 95%CI 1.10–2.25), but less likely to have regional stage disease (p-trend=0.21); transplant recipients were less likely to present with distant stage prostate cancer (OR=0.72, 95%CI 0.51–1.04, p-trend<0.001). Additionally, compared with immunocompetent patients, HIV-infected individuals had a shift toward distant stage cervical cancers (p-trend=0.01), and transplant recipients had a shift toward local stage kidney (p-trend<0.001) and oral cavity/pharynx cancers (p-trend<0.001).

In contrast, a role for immunosuppression was suggested for melanoma and bladder cancer, because both HIV-infected people and transplant recipients were more likely to be diagnosed with advanced stage disease (i.e., regional or distant stage disease) than immunocompetent people (Table 2). For melanoma, HIV-infected individuals were more likely to be diagnosed with distant stage disease (OR: 2.43; 95%CI 1.45–4.06; p-trend<0.001); and transplant recipients were more likely to be diagnosed with regional stage disease (OR=2.01; 95%CI 1.53–2.65). Though the OR for distant stage melanoma among transplant recipients was not statistically significant, a trend toward more advanced stage disease was present (p-trend=0.04). HIV-infected individuals were more likely to be diagnosed with regional/distant stage bladder cancer (OR=1.42; 95%CI 0.88–2.30; p-trend=0.001), and transplant recipients were more likely to be diagnosed with distant stage bladder cancer (OR=1.80; 95%CI 1.16–2.77; p-trend=<0.0001).

For anal cancer, there was a trend toward local stage for both groups (both p-trends<0.05). No associations were observed between either HIV infection or transplant and stage for cancers of the stomach, colorectum, liver, pancreas, uterus or thyroid (Table 2).

In an analysis restricted to HIV-infected cancer cases, no significant associations were observed between an AIDS diagnosis and regional/distant cancer stage for any cancer site (Supplemental Table 2). In an analysis restricted to cancer cases among transplant recipients, tumors diagnosed early after transplant were more likely to be local stage for female breast cancer (p-trend=0.04), and distant/regional stage for melanoma (p-trend=0.01; Supplemental Table 3). Compared to recipients diagnosed with melanoma 10+ years after transplant, a strongly increased likelihood of regional/distant disease was observed in recipients diagnosed <1 year (OR=2.67; 95%CI 0.75–9.47) and 1–4 years (OR=3.92; 95%CI 1.32–11.7) after transplant.

As shown in Table 3, both HIV-infected people and transplant recipients were more likely to be diagnosed with higher grade bladder cancers than immunocompetent people (undifferentiated vs. well differentiated: HIV: OR=2.48; 95%CI 1.43–4.32; transplant: OR=1.74; 95%CI 1.15–2.65). In contrast, both HIV and transplantation were associated with

a shift toward more well differentiated oral cavity/pharynx cancers (p-trends<0.05), and prostate cancer (p-trends<0.05).

Discussion

HIV-infected people and solid organ transplant recipients have an elevated risk of cancer (1), but it has been unclear whether immunosuppression also affects the clinical behavior of cancer and accelerates progression. Here we have shown that several cancer sites are shifted toward more advanced disease only among HIV-infected individuals and/or toward less advanced disease only among transplant recipients (i.e., oral cavity/pharynx, lung, female breast, cervix, prostate, and kidney), which is probably most consistent with differences between these populations in medical care or surveillance. In contrast, only bladder cancer and melanoma were more likely to be diagnosed at regional/distant stage in both the HIV and transplant populations, potentially indicating a role for immunosuppression.

HIV-infected individuals and solid organ transplant recipients have been studied to understand the role of immunity in cancer development. Immunosuppression is induced in HIV-infected people when HIV infects and destroys CD4+ T helper cells and other cell types, and is induced in transplant recipients through the administration of medications designed to suppress the cell-mediated immune system and prevent rejection of the transplanted organ. The striking similarity in the spectrum of cancer in these two populations speaks to the importance of defects in T-cell immunity in the etiology of many cancer sites. Immunosuppression is particularly relevant for cancers caused by viral infections (1), as an intact immune system is needed to control oncogenic infections and virally infected pre-cancerous cells.

Despite similarities in immunosuppression, these populations differ in other characteristics. For example, HIV-infected individuals are disproportionately affected by poverty (9), which results in decreased access or utilization of health care, while transplant recipients are followed closely after transplantation, resulting in heightened medical surveillance. Further, in the U.S., HIV-infected people are less likely to have health insurance; one study of HIV-infected individuals in care reported that 28.4% were uninsured, compared to 2.6% of liver transplant recipients in another study (8;12).

Differences in the frequency and comprehensiveness of medical surveillance likely provide the basis for some differences in cancer stage that we observed between these populations. For example, transplant recipients had more local stage prostate and female breast cancers, while HIV-infected people had more distant stage prostate and female breast cancers. As prostate-specific antigen (PSA) testing and mammography lead to early cancer detection, stage shifts could be driven by differential screening (13;14). Similarly, HIV-infected women were more likely to be diagnosed with distant stage cervical cancer, which could represent a failure in cervical Pap smear screening. Though the Centers for Disease Control and Prevention recommends semi-annual Pap testing in the year after HIV diagnosis followed by annual testing for HIV-infected women, many women fail to receive screening or do not follow up after an abnormal Pap test (15;16). In a similar way, the down-staging of lung and kidney cancers in transplant recipients could be due to incidental detection through

radiological imaging during medical follow-up. Our suggestive finding of a later stage at lung cancer diagnosis in HIV-infected individuals could indicate delayed diagnosis. These results highlight the need for HIV clinicians to be alert to the possible presence of lung cancer and send HIV-infected patients for appropriate testing if they present with lung cancer symptoms.

These findings are thus consistent with health disparities among HIV-infected people, who are also less likely to receive appropriate cancer treatment (17) and more likely to die from their cancer diagnoses (18). Targeted efforts should be made to ensure that HIV-infected individuals receive comprehensive medical care that includes cancer prevention counseling and appropriate cancer screening. Screening in HIV-infected people may explain our findings for anal cancer, which was diagnosed at earlier stages in HIV-infected people, because anal Pap testing has been advocated for HIV-infected men who have sex with men (19). In additional analyses (not shown), we observed a shift toward earlier stage disease among HIV-infected men (p-trend<0.0001), but not women (p-trend=0.41), which may reflect this pattern in screening. It is unclear whether anal cancer screening could explain the downward stage shift in transplant recipients.

Our results showed a shift towards advanced stage disease for bladder cancer and melanoma in both HIV-infected people and transplant recipients. Though melanoma and bladder cancer risks are only elevated in the transplant population, later stages may indicate that an intact immune system plays a role in controlling the spread of these malignancies. Immunotherapies are used to treat melanoma, including T-cell agonists and drugs that target immune checkpoints (20). Further supporting the importance of immunity, among transplant recipients we observed that non-local cancers were most frequent in the first several years after transplantation. Transplant recipients experience the most intense immunosuppression during this period, and these results are consistent with prior analyses showing that the melanoma risk is greatest in the years immediately following transplantation (21).

Immunosuppression likely also contributes to bladder cancer metastasis (22). Bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, is a standard treatment for intermediate-risk and high-risk non-muscle invasive bladder cancers (23). BCG establishes a local infection in the bladder, inducing a strong immune response, which has been shown to help prevent recurrence and tumor progression (24).

Our analyses of cancer grade provided a complementary perspective for some cancers. Grade is a metric that assesses how closely a tumor resembles the tissue of origin, and lack of differentiation is associated with higher mortality. Grade is less affected than stage by the timing of diagnosis along the continuum of cancer development. However, grade may be more subjective than cancer stage (25), and it is not uniformly collected. Bladder cancers diagnosed in both the HIV-infected and transplant populations were more poorly differentiated, providing further evidence for a biological role of immunosuppression in the clinical features of bladder cancer. Likewise, grade was more likely to be well differentiated for prostate cancer in transplant recipients, paralleling our findings showing a favorable shift in cancer stage. Finally, both HIV-infected people and transplant recipients were more likely

to have well differentiated cancers of the oral cavity/pharynx, perhaps indicating less aggressive tumors in immunosuppressed populations.

The main strength of this study is the availability of large and representative samples of cancer cases from the HIV-infected and transplant recipient populations in the U.S. This allowed us to systematically evaluate the stage distribution in these populations for the first time across 15 cancer sites. Given the shared mechanism of immunosuppression, but differences in access to medical care and cancer surveillance between these two populations, we were able to make inferences about the role of immunosuppression vs. detection in cancer stage. Our study was nonetheless limited by the information collected by population-based registries. Therefore, we were unable to consider important factors, such as cigarette smoking, medical care, cancer screening, and molecular tumor characteristics that may also be related to progression and prognosis. Further, it is likely that there is some misclassification of the HIV and transplant status of some cancer cases due to the imperfect sensitivity of the linkages; however, we do not believe that these differences were differential by stage or grade, and thus they should not have biased the results. Finally, due to multiple cancers studied, it is possible that some of our results are false positives due to chance.

In conclusion, we have documented that bladder cancers and melanoma are more likely to be diagnosed at an advanced stage in both HIV-infected people and transplant recipients, indicating a potential role of immunity in the progression of both malignancies. In addition, we observed a shift for some common cancers toward later stages in HIV-infected people and toward earlier stages in transplant recipients, consistent with differences in medical surveillance and cancer screening. The advanced stage of cancers in HIV-infected people indicates a need for more comprehensive cancer prevention and early detection strategies for this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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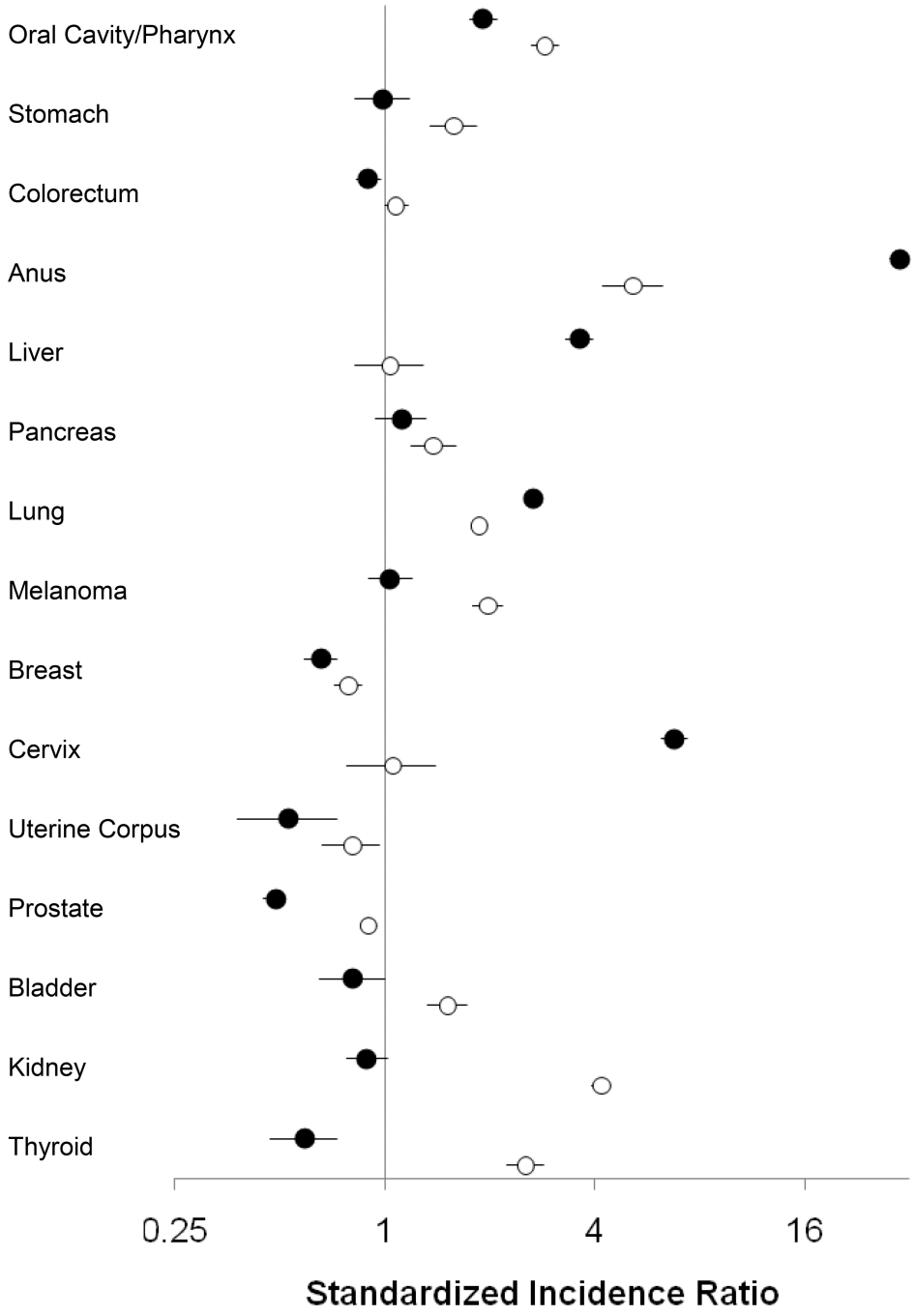

Figure 1. Relative risks of cancer in people with HIV and in transplant recipients compared to the general population

Standardized incidence ratios (SIRs) and 95% confidence intervals comparing cancer risk in people with HIV (closed circles) and in transplant recipients (open circles) to the general population. Estimates are for invasive cancers. Circles indicate point estimates and lines indicate 95% confidence intervals. Results are shown on a logarithmic scale.

Table 1

Characteristics of cancer cases in the HIV/AIDS Cancer Match Study and Transplant Cancer Match Study.

	HIV-infected		Transplant Recipient	
	Yes, %	No, %	Yes, %	No, %
Total	8,411	4,471,704	7,322	6,435,000
Sex				
Male	73.2	49.3	65.5	49.4
Female	26.8	50.7	34.6	50.7
Race				
White	47.0	85.0	78.4	84.2
Black	51.7	11.4	15.3	10.8
Other	1.3	3.7	6.3	5.1
Age, years				
<30	2.7	1.6	0.9	1.4
30–49	53.0	13.4	15.8	13.4
50–69	41.7	44.2	67.8	45.0
70+	2.6	40.8	15.6	40.2
Cancer site				
Oral cavity/pharynx	6.2	2.7	6.6	2.7
Stomach	1.5	1.9	2.2	2.0
Colorectal	8.2	13.5	9.1	13.2
Anus	20.9	0.4	2.0	0.5
Liver	5.8	1.2	1.1	1.4
Pancreas	1.8	2.5	2.5	2.7
Lung	24.4	16.1	19.9	15.6
Melanoma	2.9	6.0	7.4	6.0
Female breast	5.1	20.6	9.0	20.4
Cervix	9.5	2.5	1.3	2.1
Uterus	0.5	3.3	1.5	3.5
Prostate	8.2	18.3	16.9	18.3
Bladder	1.5	5.4	5.0	5.4
Kidney	2.7	3.5	12.0	3.6
Thyroid	1.1	2.2	3.7	2.6

Table 2

Associations of HIV and transplant status with cancer stage of cancer diagnosis.

		HIV				Transplant			
Cancer	**Stage**	**No**	**Yes**	**OR***	**95%CI**	**No**	**Yes**	**OR***	**95%CI**
Oral cavity/pharynx	Local	39,531	151	1.00		58,091	225	1.00	
	Regional	54,863	199	0.67	(0.54–0.83)	78,267	149	0.46	(0.37–0.57)
	Distant	12,088	79	1.05	(0.79–1.38)	21,251	43	0.49	(0.35–0.68)
	P-trend			0.26				<0.001	
Stomach	Local	18,607	24	1.00		30,241	40	1.00	
	Regional	26,999	35	0.82	(0.48–1.38)	39,930	45	0.79	(0.51–1.21)
	Distant	25,268	48	1.03	(0.63–1.70)	39,935	64	1.06	(0.71–1.58)
	P-trend			0.69				0.54	
Colorectum	Local	199,639	186	1.00		304,259	264	1.00	
	Regional	216,666	172	0.85	(0.69–1.04)	299,198	200	0.78	(0.65–0.94)
	Distant	97,072	114	0.91	(0.72–1.15)	147,139	135	0.99	(0.80–1.21)
	P-trend			0.33				0.31	
Anus†	Local	7,536	545	1.00		12,364	57	1.00	
	Regional	4,146	264	0.79	(0.67–0.93)	9,772	29	0.62	(0.39–0.97)
	Distant	1,403	51	0.52	(0.38–0.71)				
	P-trend			<0.001				0.04	
Liver	Local	19,113	160	1.00		34,749	33	1.00	
	Regional	9,970	101	1.05	(0.81–1.35)	19,902	16	0.82	(0.45–1.50)
	Distant	11,020	104	1.12	(0.87–1.44)	17,261	18	1.06	(0.59–1.90)
	P-trend			0.41				0.90	
Pancreas	Local	9,829	9	1.00		15,631	15	1.00	
	Regional	34,031	33	0.79	(0.38–1.65)	51,259	54	0.94	(0.53–1.67)
	Distant	53,176	83	1.10	(0.55–2.20)	86,482	97	0.97	(0.56–1.67)
	P-trend			0.18				0.97	
Lung	Local	132,713	255	1.00		184,301	382	1.00	
	Regional	178,853	483	1.03	(0.89–1.20)	242,954	348	0.63	(0.54–0.72)
	Distant	325,390	1061	1.13	(0.98–1.29)	487,039	639	0.54	(0.48–0.61)

		HIV				Transplant			
Cancer	**Stage**	**No**	**Yes**	**OR***	**95%CI**	**No**	**Yes**	**OR***	**95%CI**
	P-trend			0.08				<0.001	
Melanoma	*In situ*	84,291	46	0.77	(0.54–1.08)	110,904	156	1.19	(0.97–1.47)
	Local	132,561	120	1.00		210,519	265	1.00	
	Regional	14,260	27	1.77	(1.16–2.70)	23,424	64	2.01	(1.53–2.65)
	Distant	6,976	17	2.43	(1.45–4.06)	11,266	21	1.43	(0.92–2.24)
	P-trend			<0.001				0.04	
Female breast	*In situ*	164,267	71	0.88	(0.66–1.16)	209,468	176	1.83	(1.51–2.22)
	Local	449,336	157	1.00		668,032	298	1.00	
	Regional	224,641	133	1.08	(0.86–1.36)	336,732	155	0.94	(0.77–1.14)
	Distant	35,700	39	1.99	(1.40–2.83)	56,006	19	0.75	(0.47–1.19)
	P-trend			0.008				<0.001	
Cervix†	Local	28,212	244	1.00		39,180	28	1.00	
	Regional	18,197	155	1.13	(0.92–1.39)	34,816	15	0.64	(0.34–1.22)
	Distant	5,362	52	1.57	(1.16–2.14)				
	P-trend			0.01				0.18	
Uterus	Local	97,895	20	1.00		152,137	81	1.00	
	Regional/Distant	34,935	12	1.42	(0.69–2.94)	56,546	19	0.69	(0.42–1.15)
	P-value			0.35				0.16	
Prostate	Local	621,978	533	1.00		915,473	1,075	1.00	
	Regional	74,982	56	0.66	(0.50–0.87)	113,547	66	0.44	(0.35–0.57)
	Distant	29,799	33	1.57	(1.10–2.25)	47,248	31	0.72	(0.51–1.04)
	P-trend			0.21				<0.001	
Bladder**	*In situ*	95,411	39	0.64	(0.42–0.98)	142,194	139	0.75	(0.59–0.95)
	Local	101,793	52	1.00		146,559	145	1.00	
	Regional	25,135	25	1.42	(0.88–2.30)	25,627	41	1.42	(1.00–2.01)
	Distant					11,662	24	1.80	(1.16–2.77)
	P-trend			0.001				<0.0001	
Kidney	Local	89,011	143	1.00		140,539	681	1.00	
	Regional	25,562	25	0.80	(0.52–1.22)	38,661	80	0.49	(0.39–0.62)

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		HIV				Transplant			
Cancer	**Stage**	**No**	**Yes**	**OR***	**95%CI**	**No**	**Yes**	**OR***	**95%CI**
	Distant	24,855	42	1.25	(0.88–1.76)	37,719	77	0.48	(0.38–0.61)
	P-trend			0.61				<0.001	
Thyroid	Local	66,347	49	1.00		110,177	184	1.00	
	Regional/Distant	27,388	34	1.47	(0.94–2.30)	47,742	76	0.86	(0.66–1.13)
	P-value			0.09				0.29	

*Adjusted for registry, race, calendar year, sex and age.

†Regional/distant stages collapsed for the transplant analysis.

**Regional/distant stages collapsed for the HIV analysis.

Stage information was unknown/missing for 4.9–25.4% of cases (HACM Study) and for 3.1–21.4% (TCM Study).

OR: odds ratio, CI: confidence interval

Table 3

Associations of HIV and transplant status with tumor grade.

		HIV				Transplant			
		No	Yes			No	Yes		
Cancer	**Grade (i.e., differentiation)**			**OR[1]**	**95%CI**			**OR[1]**	**95%CI**
Oral cavity/pharynx	Well	13,879	61	1.0		17,114	51	1.0	
	Moderate	35,895	153	0.77	(0.57–1.04)	44,362	129	0.95	(0.68–1.31)
	Poor*	25,259	98	0.68	(0.49–0.94)	35,952	64	0.54	(0.38–0.79)
	Undifferentiated*	3,060	12	0.60	(0.32–1.11)				
	P-trend			0.01				0.0002	
Stomach	Well/moderate	19,712	22	1.0		23,313	30	1.0	
	Poor/undifferentiated	39,557	67	0.79	(0.49–1.28)	48,224	64	0.90	(0.58–1.39)
	P-value			0.34				0.63	
Colorectum	Well	47,599	46	1.0		54,096	49	1.0	
	Moderate	291,791	246	0.86	(0.63–1.18)	348,324	229	0.72	(0.53–0.98)
	Poor/undifferentiated	85,025	89	1.18	(0.82–1.68)	102,604	99	1.07	(0.76–1.50)
	P-trend			0.13				0.13	
Prostate	Well	34,340	22	1.0		28,795	28	1.0	
	Moderate	412,871	311	0.71	(0.45–1.09)	469,904	536	0.83	(0.56–1.22)
	Poor/undifferentiated	188,966	228	0.99	(0.63–1.56)	289,398	272	0.61	(0.41–0.92)
	P-trend			0.004				<0.0001	
Uterus	Well	44,728	14	1.0		58,050	28	1.0	
	Moderate	62,621	13	1.55	(0.72–3.34)	43,730	13	0.70	(0.36–1.35)
	Poor/undifferentiated					34,855	12	0.92	(0.46–1.85)
	P-trend			0.27				0.67	
Bladder	Well†	102,226	44	1.0		41,425	40	1.0	
	Moderate†					74,092	61	0.91	(0.61–1.36)
	Poor	58,719	28	1.34	(0.83–2.16)	65,256	90	1.74	(1.19–2.53)
	Undifferentiated	19,434	19	2.48	(1.43–4.32)	33,863	56	1.74	(1.15–2.65)
	P-trend			0.002				<0.0001	

[1] Adjusted for registry, race, calendar year, sex and age. Grade information was unknown/missing for 8.7–26.4% of cases (HACM Study) and for 7.0–25.4% (TCM Study).

[*] Poorly/undifferentiated tumors combined in transplant analysis.

[†] Well/moderately-differentiated tumors combined in HIV analysis.

OR: odds ratio, CI: confidence interval