Incidence and risk factors for HPV-associated cancers in women with end-stage renal disease

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ABSTRACT

Human papillomavirus (HPV) causes the majority of cervical, anal/rectal, and oropharyngeal cancers in women. End-stage renal disease (ESRD) is also associated with an increased risk of malignancy, but the incidence of and risk factors for HPV-associated cancers in US dialysis patients are not defined. We queried the US Renal Data System for women with HPV-associated cancers and assessed for incidence of cancer diagnosis and association of risk factors. From 2005 to 2011, a total of 1032 female patients with ESRD had 1040 HPV-associated cancer diagnoses. Patients had a mean age of 65 years, were mostly white (63%), and on hemodialysis (92%). Cervical cancer (54%) was the most common, followed by anal/rectal (34%), and oropharyngeal (12%). The incidence of HPV-associated cancers in patients with ESRD increased yearly, with up to a 16-fold increased incidence compared with the general population. Major risk factors associated with the development of any HPV-associated cancer included smoking (adjusted relative risk=1.89), alcohol use (1.87), HIV (2.21), and herpes infection (2.02). Smoking, HIV, and herpes infection were prominent risk factors for cervical cancer. The incidence of HPV-associated cancers in women with ESRD is rising annually and is overall higher than in women of the general population. Tobacco use is a universal risk factor. For cervical cancer, the presence of HIV and herpes are important comorbidities. Recognizing risk factors associated with these cancers may improve diagnosis and facilitate survival. The role of HPV vaccination in at-risk dialysis patients remains to be defined but warrants further study.

Significance of this study

What is already known about this subject?

- Human papillomavirus (HPV)-associated cancers frequently have an insidious onset and early diagnosis helps improve prognosis and survival.
- Patients with end-stage renal disease (ESRD) are at increased risk of multiple malignancies.
- There has not yet been a nationwide investigation of disease burden and risk factors for HPV-associated cancers in women with ESRD.

What are the new findings?

- We found that the incidence of HPV-associated cancer in women with ESRD is higher than in the general population and increasing yearly.
- Tobacco use is a universal risk factor for all the HPV-associated cancers.
- For cervical cancer, HIV and herpes simplex are major independent risk factors.
- Alcohol use is heavily correlated with head and neck cancer, and inflammatory bowel disease with anal and rectal cancer.

How might these results change the focus of research or clinical practice?

- The present study provides evidence of a rising incidence of HPV-associated cancer in women with ESRD and reveals major risk factors for cancer diagnosis, which may guide improved secondary prevention.

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the USA.[1] HPV infection is also a well-documented cause of oropharyngeal and urogenital cancer. In women, over 90% of cervical, anal, and rectal cancer cases, and over 60% of oropharyngeal cancers are attributed to HPV.[2]

End-stage renal disease (ESRD) is associated with an increased risk of malignancy, including renal carcinoma, bladder carcinoma, breast cancer, non-Hodgkin's lymphoma, and colorectal cancer.[3–7] Further, we have shown that dialysis patients with HIV are at greater risk for developing malignancy than patients with HIV from the general population.[8] On this basis, we theorized that the risk of HPV-associated malignancy would also be increased in patients with ESRD. Moreover, we elected to limit our study population to women, due to the predominance of cervical cancer in this group, and its known association with HPV infection. To address the above questions, we queried the US Renal Data System (USRDS) for

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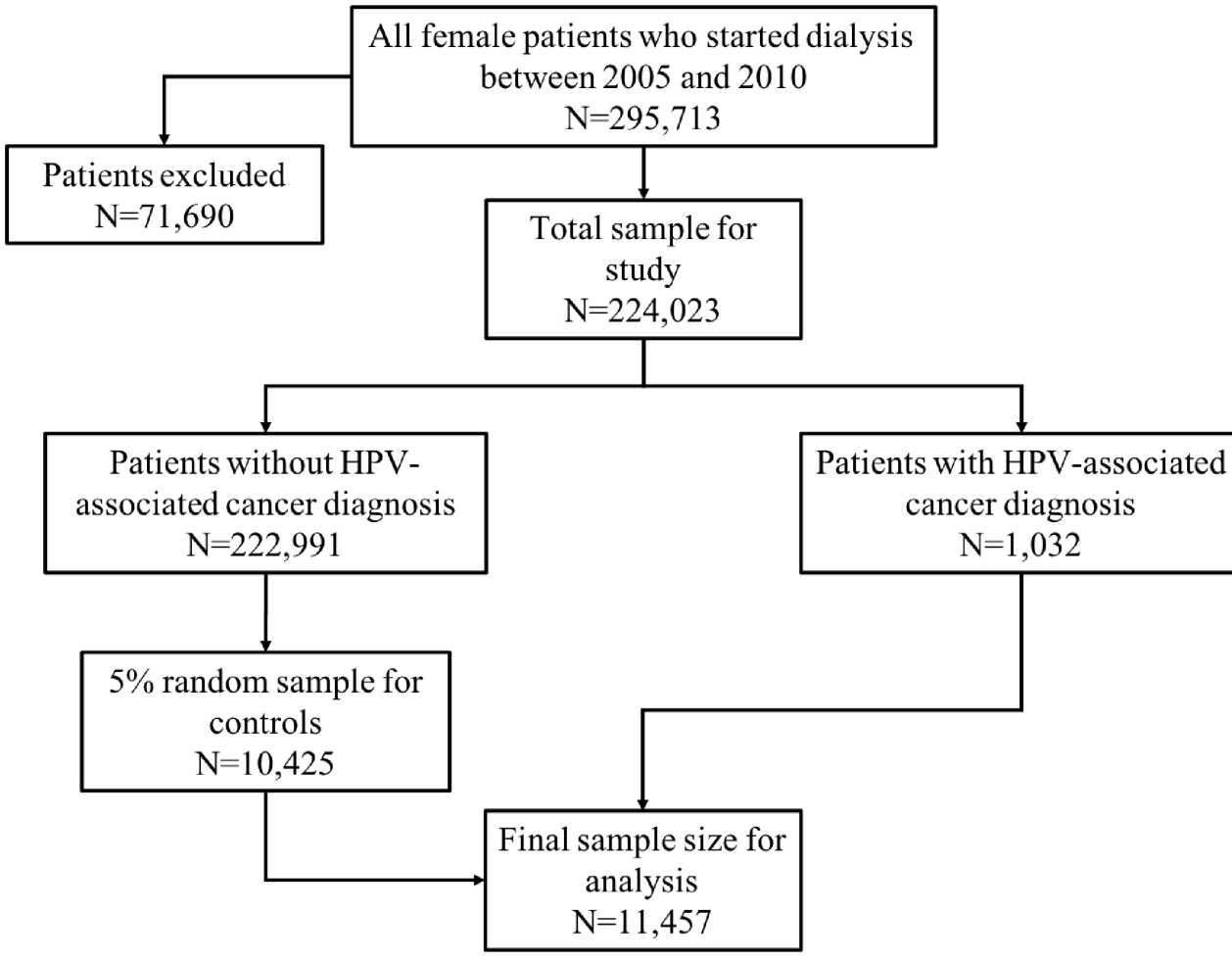

Figure 1 Flow chart showing the derivation of the sample size for the study cohort. Patients were excluded for age less than 18 y, missing race, missing ethnicity, and having died at entry into the US Renal Data System (USRDS). HPV, human papillomavirus.

women with HPV-associated cancers and assessed the risk factors for their development.

METHODS

Study cohort

A retrospective cohort study design was used to examine the incidence of HPV-associated cancer diagnoses (cervical, head/neck, and anal/rectal cancer) in women on dialysis, and the association of these cancer diagnoses with demographic and clinical risk factors, using data from the USRDS. The USRDS is a large federal data set containing demographic data and physician/supplier claims on all Medicare-funded patients with ESRD in the USA.

All female patients with ESRD in the USRDS who started dialysis between 2005 and 2010 were included in the study. Exclusions for age less than 18 years, missing race, missing ethnicity, and having died at entry into the USRDS were made. Derivation of the sample size for the study cohort is shown in figure 1. Patients with an HPV-associated cancer diagnosis were identified by querying hospital claims files using International Classification of Diseases Ninth Revision (ICD-9) codes (online supplementary table 1). The incidence of all HPV-associated cancer diagnoses was based on person-years of risk. Patients were classified based on the appearance of a risk factor from the initiation of dialysis to the date of an HPV-associated cancer diagnosis. Due to the large number of subjects without an HPV-related cancer diagnosis (n=222,991), a 5% random sample of control subjects was used for statistical analysis. Control subjects used in the analysis (n=10,425) were not statistically different in the distribution of age (p=0.3794), race (p=0.2445), ethnicity (p=0.6598), access type (p=0.2182), or dialysis type (p=0.2634). The total analysis sample size was 11,457.

Risk factors associated with HPV-associated cancer

Demographic and selected clinical data were taken from Centers for Medicare & Medicaid Services (CMS) form 2728 (included in the USRDS data set) and included age at the start of dialysis, race, ethnicity, mode of dialysis, and access type. Form 2728 is required on every patient entering dialysis and is submitted to Medicare by the respective dialysis center.

Eighteen additional clinical diagnoses, selected for their recognized role as risk factors for HPV-associated cancers in the general population,[9–12] were identified from hospital claims files using ICD-9 codes. These included: (1) tobacco or alcohol use; (2) 10 STIs encompassing HIV, syphilis,

gonorrhea, viral hepatitis (A, B, or C, 'hepatitis'), herpes simplex ('herpes'), chlamydia, HPV infection, genital warts, viral warts, and additional STIs collectively classified in the data set as 'other' STIs; (3) 5 comorbidities associated with immunosuppression, including history of prior solid organ or bone marrow transplant ('transplant'), rheumatoid arthritis, systemic lupus erythematosus ('lupus'), Crohn's disease, and ulcerative colitis; and (4) 1 condition known to promote urogenital cancer risk, lichen sclerosus.[13]

Statistical analysis

All statistical analyses were performed using SAS V.9.4 and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics for demographic and clinical risk factors or diagnosis variables were determined overall, by each HPV-associated cancer, and by any HPV-associated cancer. χ^2 or t-tests were used to examine preliminary differences between those with and without cancer.

To examine the association of risk factors on each HPV-associated cancer diagnosis and on any HPV-associated cancer overall, a series of generalized linear models (GLIM) were used. Each GLIM assumed a Poisson distribution of the outcome measure, logistic regression models, and used the natural log of the number of person-years at risk as an offset parameter to estimate the relative risk (RR) for cancer diagnosis. Person-years was defined as the number of years from the incident date of dialysis to the date of the first HPV-related cancer diagnosis for those with the diagnosis or to the last known follow-up date (last claim date or date of death) for controls. Using the natural log of person-years at risk as an offset parameter in a GLIM model allows for the estimation to account for the person-years at risk. For each cancer outcome measure (cervical, anal/rectal, head/neck, any HPV-associated cancer) each risk factor was examined in a simple model and the crude RR was estimated along with the 95% CI. All risk factors were then entered into a comprehensive full GLIM for each cancer outcome and a backward model building strategy was used to arrive at the comprehensive final model. Starting with the full model, the least significant demographic or clinical risk factor or diagnosis variable was removed from the model. The Akaike's information criterion (AIC) and −2log likelihood (−2LL) test were used to determine whether the reduced model fit was as good as the previous model. A lower AIC and non-statistically significant −2LL test indicated that the reduced model was as good as the previous model. If the reduced model was not as good as the previous model, the variable was re-entered in the model and the next least significant variable was examined for removal. The final model included any demographic or clinical diagnosis that was statistically significant and/or needed in the model to improve model fit. The adjusted RR (aRR) and corresponding 95% CI are presented for the final model.

RESULTS

Characteristics of the study population

There were 295,713 women with ESRD identified from the study period, of whom 224,023 offered a complete data set for analysis. Within this cohort, 1032 patients had 1040 HPV-associated cancer diagnoses. Overall, the study population had a mean age of 65±14.7 years, were mostly white (63%), non-Hispanic (88%), on hemodialysis (92%), and began dialysis with a vascular catheter (72%) (table 1). As a reference, the presence of 18 comorbidities from the overall cohort is shown in table 1. Small numbers of subjects precluded analysis for 10 comorbid conditions.

The control group consisting of a 5% random sample of the patients without an HPV-associated cancer diagnosis that was used for all comparisons in the statistical analyses was not different in the distribution of age, race, ethnicity, access type, or dialysis type from the 95% of control subjects not used in the analysis.

Descriptive statistics

Tables 1 and 2 present the descriptive statistics for patients with HPV-associated cancers. From the total cohort, and as seen in table 2, cervical cancer (n=560, 54%) was the most common, followed by anal and rectal (n=355, 34%), and head and neck (n=125, 12%). The results from patients with any HPV-associated cancer and the 3 site-specific cancers are presented below.

Any HPV-associated cancer

When compared with controls, patients diagnosed with any HPV-associated cancer (table 1) tended to be younger at cancer diagnosis, black, less likely to have Hispanic ethnicity, more likely to be on hemodialysis, and more likely to have started dialysis with a vascular catheter. Comorbidities more common in HPV-associated cancer included tobacco use, a diagnosis of hepatitis, a history of transplant, lupus, HIV, alcohol use, and any diagnosis of herpes infection. Ten other comorbidities are shown in table 1, but small numbers of patients precluded further analysis.

From 2005 to 2011, and when compared with the general population, the incidence of HPV-associated cancers in patients with ESRD increased and has shown an annual rise in risk (figure 2A). Thus, at every time point, patients with ESRD have over a sixfold to 16-fold increased incidence of cancer.

Cervical, anal and rectal, and head and neck cancer

Table 2 presents the incidence, demographics, and associated comorbidities for patients with a diagnosis of cervical, anal and rectal, and head and neck cancer. When compared with controls, patients with a diagnosis of cervical cancer tended to be younger, black, and start dialysis with a catheter. In contrast, patients with anal and rectal cancer were older than controls, but there were no other demographic differences. There were no demographic differences between patients with head and neck cancer when compared with controls. For all 3 cancer types, some analyses could not be performed due to small numbers of patients.

Tobacco use was more common in all 3 cancer groups when compared with controls. In patients with cervical cancer, hepatitis, lupus, HIV, and a herpes diagnosis were more common. Alcohol use was more common in the head and neck group, but otherwise small numbers precluded further assessment of most other comorbidities for all 3 cancer groups.

The incidence of cervical cancer was examined from 2005 to 2011 and is shown in figure 2B. When compared with the general population, the incidence of cervical cancer in

Table 1 Descriptive statistics for demographics, dialysis parameters, and comorbidities for any HPV-associated cancer

			Any HPV-related cancer		
Variable	**Level**	**Overall**	**Yes n=1032 (9.0%)**	**No 10,425 (91.0%)**	**P value**
Age, mean (SD)		65.1 (14.7)	63.2 (14.6)	65.3 (14.7)	<0.0001
Race, n (%)	Black	3717 (32.4)	369 (35.8)	3348 (32.1)	0.0385
	Other	560 (4.9)	42 (4.1)	518 (5.0)	
	White	7180 (62.7)	621 (60.2)	6559 (62.9)	
Ethnicity, n (%)	Hispanic	1308 (11.4)	95 (9.2)	1213 (11.6)	0.0192
	Non-Hispanic	10,149 (88.6)	937 (90.8)	9212 (88.4)	
Dialysis type, n (%)	HD	10,545 (92.0)	973 (94.3)	9572 (91.8)	0.0142
	Unknown	268 (2.3)	14 (1.4)	254 (2.4)	
	PD	644 (5.6)	45 (4.4)	599 (5.8)	
Access type, n (%)	Catheter	8267 (72.2)	782 (75.8)	7485 (71.8)	0.0369
	Graft	530 (4.6)	44 (4.3)	486 (4.7)	
	Other/UNK	1523 (13.3)	125 (12.1)	1398 (13.4)	
	AVF	1137 (9.9)	81 (7.9)	1056 (10.1)	
Comorbidities, n (%)					
Tobacco use	1211 (10.6)	188 (18.2)	1023 (9.8)	<0.0001	
Hepatitis	320 (2.8)	43 (4.2)	277 (2.7)	0.0050	
Transplant	275 (2.4)	37 (3.6)	238 (2.3)	0.0091	
Lupus	310 (2.7)	36 (3.5)	274 (2.6)	0.1043	
HIV	118 (1.0)	31 (3.0)	87 (0.8)	<0.0001	
Alcohol use	111 (1.0)	24 (2.3)	87 (0.8)	<0.0001	
Herpes	50 (0.4)	13 (1.3)	37 (0.4)	<0.0001	
Rheumatoid arthritis	191 (1.7)	12 (1.2)	179 (1.7)	0.1847	
Crohn's disease	50 (0.4)	<11	43 (0.4)		
Ulcerative colitis	36 (0.3)	<11	29 (0.3)		
Genital warts	<11	<11	<11		
Syphilis	<11	<11	<11		
Chlamydia	<11	<11	<11		
HPV	<11	<11	<11		
Viral warts	<11	<11	<11		
Lichen sclerosus	<11	<11	<11		
Gonorrhea	<11	<11	<11		
Other STD	<11	<11	<11		

AVF, arteriovenous fistula; HD, hemodialysis; HPV, human papillomavirus; PD, peritoneal dialysis; SD, standard deviation; STD, sexually transmitted disease; UNK, unknown.

Table 2 Descriptive statistics for demographics, dialysis parameters, and comorbidities for cervical, anal and rectal, and head and neck cancer

		Cervical cancer (54%)			Anal and rectal cancer (34%)			Head and neck cancer (12%)		
Variable	Level	Yes n=560	No n=10,897	P value	Yes n=355	No n=11,102	P value	Yes n=125	No n=11,332	P value
Age, mean (SD)		59.3 (15.6)	65.4 (14.6)	<0.0001	68.3 (11.9)	65 (14.8)	<0.0001	65.6 (12.1)	65.1 (14.8)	0.6664
Race, n (%)	Black	214 (38.2)	3503 (32.2)	0.0054	119 (33.5)	3598 (32.4)	0.8829	–	–	0.8983
	Other	19 (3.4)	541 (5.0)		18 (5.1)	542 (4.9)		<11	–	
	White	327 (58.4)	6853 (62.9)		218 (61.4)	6962 (62.7)		–	–	
Ethnicity, n (%)	Hispanic	54 (9.6)	1254 (11.5)	0.1759	36 (10.1)	1272 (11.5)	0.4426	<11	–	–
	Non-Hispanic	506 (90.4)	9643 (88.5)		319 (89.9)	9830 (88.5)		–	–	
Dialysis type, n (%)	HD	–	–	–	–	–	0.1247	–	–	–
	Unknown	<11	–		<11	–		<11	–	
	PD	–	–		–	–		<11	–	
Access type, n (%)	Catheter	436 (77.9)	7831 (71.9)	0.0109	259 (73.0)	8008 (72.1)	0.8982	–	–	0.4993
	Graft	21 (3.8)	509 (4.7)		17 (4.8)	513 (4.6)		<11	–	
	Other/UNK	66 (11.8)	1457 (13.4)		48 (13.5)	1475 (13.3)		–	–	
	AVF	37 (6.6)	1100 (10.1)		31 (8.7)	1106 (10.0)		13 (10.4)	1124 (9.9)	
Comorbidities, n (%)										
Tobacco use		106 (18.9)	1105 (10.1)	<0.0001	54 (15.2)	1157 (10.4)	0.0039	30 (24.0)	1181 (10.4)	<0.0001
Hepatitis		32 (5.7)	288 (2.6)	<0.0001	<11	311 (2.8)		<11	316 (2.8)	
Lupus		25 (4.5)	285 (2.6)	0.0085	<11	301 (2.7)		<11	308 (2.7)	
Transplant		20 (3.6)	255 (2.3)	0.0634	<11	267 (2.4)		<11	266 (2.4)	
Rheumatoid arthritis		<11	183 (1.7)		<11	189 (1.7)		<11	189 (1.7)	
HIV		27 (4.8)	91 (0.8)	<0.0001	<11	113 (1.0)		<11	117 (1.0)	
Alcohol use		<11	103 (1.0)		<11	108 (1.0)		13 (10.4)	98 (0.9)	<0.0001
Herpes		11 (2.0)	39 (0.4)	<0.0001	<11	49 (0.4)		<11	49 (0.4)	
Crohn's disease		<11	50 (0.5)		<11	44 (0.4)		<11	49 (0.4)	
Ulcerative colitis		<11	34 (0.3)		<11	31 (0.3)		<11	36 (0.3)	
Genital warts		<11	<11		<11	<11		<11	<11	
Syphilis		<11	<11		<11	<11		<11	<11	
Chlamydia		<11	<11		<11	<11		<11	<11	
HPV		<11	<11		<11	<11		<11	<11	
Viral warts		<11	<11		<11	<11		<11	<11	
Lichen sclerosus		<11	<11		<11	<11		<11	<11	
Gonorrhea		<11	<11		<11	<11		<11	<11	
Other STD		<11	<11		<11	<11		<11	<11	

Hemodialysis (HD), Peritoneal dialysis (PD), Arteriovenous fistula (AVF), Unknown (UNK), Standard deviation (SD), Sexually transmitted disease (STD)
HPV, human papillomavirus; STD, sexually transmitted disease.

patients with ESRD was increased and has shown an annual rise. Thus, at every time point, patients with ESRD have over a sixfold to 16-fold increased incidence of the disease.

Factors associated with HPV-associated cancer

The results of simple, full, and final GLIMs are provided in online supplementary tables 2–4. The aRRs for any HPV-associated cancer and the 3 site-specific cancers from the final model are shown in figure 3.

For any HPV-associated cancer (figure 3A), the aRR was increased with each increasing year of age (1.01), tobacco use (1.89), alcohol use (1.87), HIV (2.21), herpes (2.02), a history of transplant (1.71), starting dialysis with a catheter (1.59), and ulcerative colitis (2.67). Other race versus white, and Hispanic ethnicity were protective. The aRR for cervical cancer (figure 3B) was increased with tobacco use, HIV, and herpes. Younger age, other versus white race, and Hispanic ethnicity were protective. An increased aRR for anal and rectal cancer was associated with increased age, tobacco use, Crohn's disease, and ulcerative colitis (figure 3C). Finally, for head and neck cancer (figure 3D), tobacco use, alcohol use, and history of transplant showed an increased aRR, while Hispanic ethnicity was protective.

DISCUSSION

In this study, we found that the incidence of HPV-associated malignancies is substantially higher in female dialysis patients when compared with the general population, and that cervical cancer accounts for the majority of cases. Further, the incidence of HPV-associated cancer in women with ESRD has increased every year between 2005 and 2011, whereas the annual rates in the general population have been flat. These observations raise important questions about the susceptibility of the dialysis population to these diseases. In this regard, the results of our study show that major risk factors associated with the development of an HPV-associated cancer include smoking, alcohol use, HIV, and herpes infection, with smoking, HIV, and herpes infection prominent risk factors specifically for cervical cancer. These data are of particular importance given the availability of an effective vaccine against HPV and may raise questions about the role of vaccination in dialysis patients.

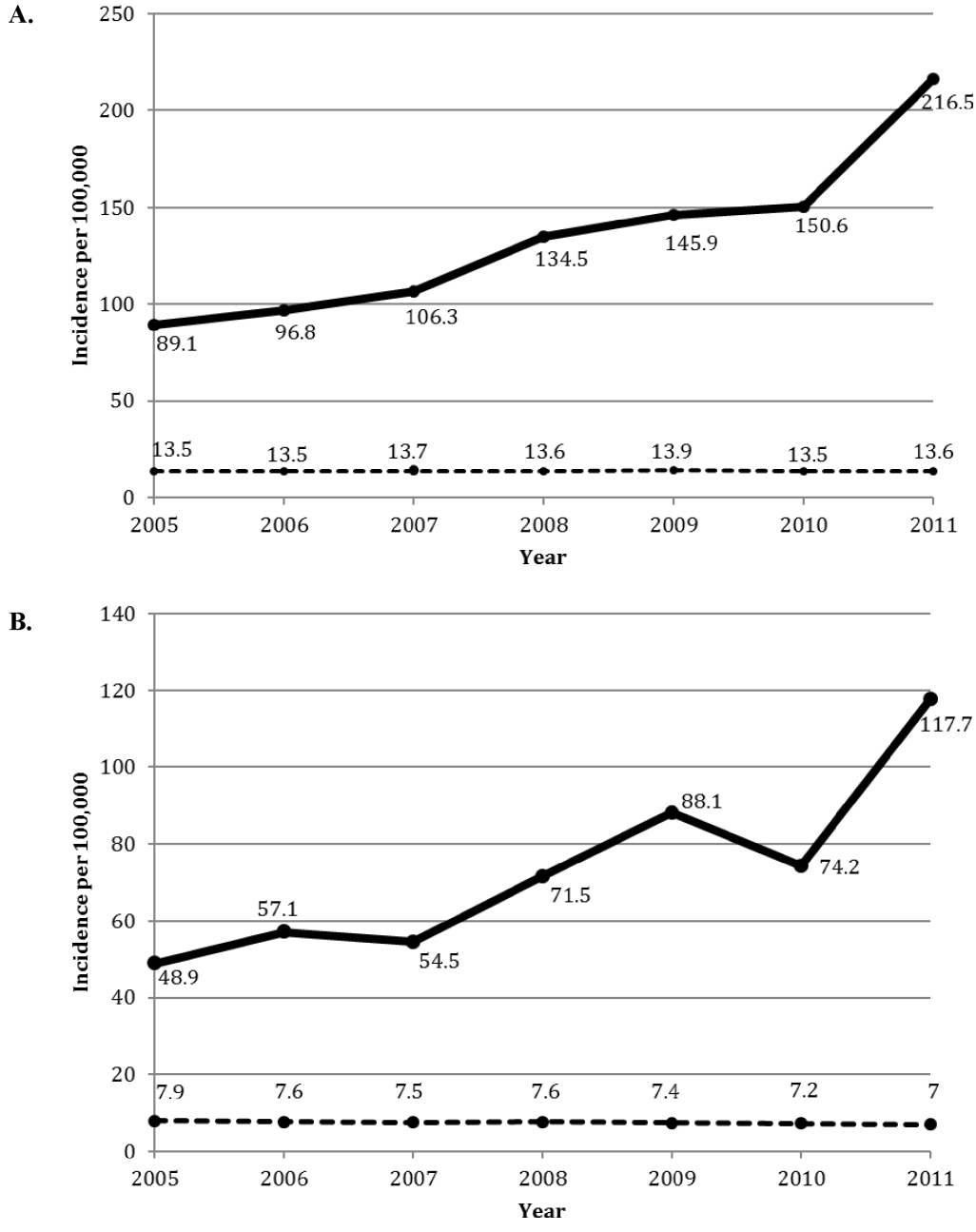

Figure 2 Comparison of the annual incidence of human papillomavirus (HPV)-associated cancer (A) and cervical cancer (B) between patients with end-stage renal disease (ESRD) (solid line) and the general population (dashed line). For both cancer groups, patients with ESRD show a higher incidence of disease and an increasing annual incidence.

In the present work, the incidence of HPV-associated cancer, particularly cervical cancer, in women on dialysis in 2011 was nearly 16-fold greater than the general population.[14 15] In a study assessing HPV-associated cancer in Denmark, 62 HPV-associated tumors were identified from over 12,000 dialysis patients. The women from the Danish ESRD patient population had ~5-fold risk of developing an HPV-associated cancer compared with the general population.[16] Our data investigated a large US dialysis population and are in general agreement with this study. Differences in the observed risk for HPV-associated cancers may be in part due to differences in demographics, and the higher rate of HPV-associated cancers observed in the Danish control patients when compared with the US cohort (for 2010, 40.8 vs 13.5 per 100,000 person-years, respectively).[16]

The present study is the first to examine potential risk factors for HPV-associated cancer in US women on dialysis. The final model showed that the risk associated with the development of any HPV-associated cancer was greatest for ulcerative colitis (aRR=2.67), HIV (2.21), herpes infection (2.02), smoking (1.89), alcohol use (1.87), and a history of bone marrow or solid organ transplant (1.71). The strong association with ulcerative colitis is likely due to the high risk associated with anal and rectal cancer (5.11). Ulcerative colitis was not associated with either cervical or head and neck cancer. Smoking was a common association for each

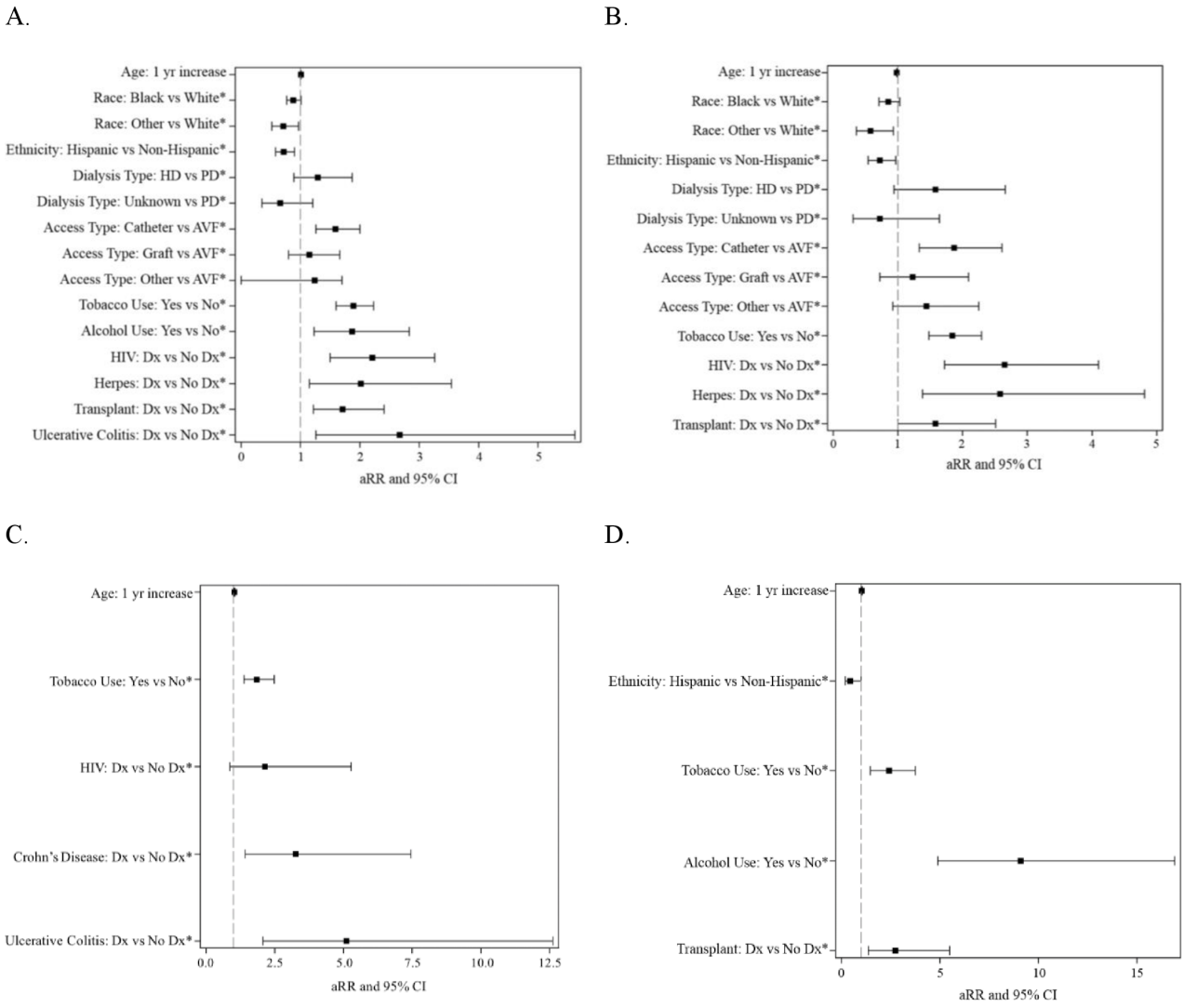

Figure 3 Forest plots of the adjusted relative risk (aRR) and 95% CI for risk factors for a diagnosis of human papillomavirus (HPV)-associated cancer. (A) Any HPV-associated cancer. (B) Cervical cancer. (C) Anal and rectal cancer. (D) Head and neck cancer. AVF, arteriovenous fistula; HD, hemodialysis, PD, peritoneal dialysis.

site-specific tumor and highest in head and neck cancer (2.42). This is consistent with what is observed with the general population.[17]

In our work, cervical cancer accounted for over 50% of the HPV-associated cancers. Risk factors associated with the diagnosis included HIV (2.65), herpes infection (2.58), starting dialysis with a vascular catheter (1.87), smoking (1.84), and a history of bone marrow or solid organ transplant (1.58). Like HPV, both HIV and herpes infections may be sexually transmitted, suggesting a common thread. Moreover, in HPV-positive women in the general population, herpes simplex 2 was found to increase the risk of developing cervical cancer, even after controlling for self-reported sexual risk factors.[10] The finding of catheter access type as an independent risk factor for cervical cancer may be a surrogate marker for lower socioeconomic status and/or reduced access to healthcare. In this regard, patients who have had more follow-up with a nephrologist prior to initiation of dialysis have a higher likelihood of beginning dialysis with an arteriovenous fistula rather than a vascular catheter.[18] Finally, we would postulate that the general carcinogenic effect of smoking and the presence of immunosuppression may explain the increased susceptibility to cervical cancer for smokers and transplant patients, respectively.

In the present study, the most significant risk factor for head and neck cancer was alcohol use (9.09). In the general population, heavy alcohol use is associated with 5 times the risk of oral and pharyngeal cancer in both sexes.[12] Another significant risk factor for head/neck cancer in women with ESRD was transplant history, likely due to immunosuppression impairing tumor surveillance. This finding warrants further investigation as a possible indication for additional screening, as head and neck cancers that occur after transplant have worse prognoses than those that occur in patients who do not have a history of transplant.[19]

We showed that the main risk factors associated with an anal and rectal cancer diagnosis were ulcerative colitis and Crohn's disease (5.11 and 3.26, respectively). The exact risk that inflammatory bowel disease confers to the

development of anal and rectal cancers in the present study may be underestimated, as we could not differentiate inflammatory bowel disease based on anatomical location.[9] Further, previous studies in the general population have found that Crohn's disease, but not ulcerative colitis, is a risk factor for anal cancer.[20–22] In contrast, our study showed that ulcerative colitis was associated with over 5 times the risk of anal and rectal cancer development, most likely due to the increased risk in the development of rectal cancer.[23]

The results of this work show tobacco use to be the single risk factor in common for all HPV-associated cancers in women with ESRD. These patients would be expected to share susceptibility to the carcinogenic effects of tobacco use, similar to the general population. In this regard, there is a positive relationship between smoking and higher HPV viral loads, increased HPV prevalence, incidence, and persistence after infection, as well as impaired immune responses.[24]

In the present studies, some demographic and clinical factors were associated with either an increased risk of HPV-associated cancer or were found to be protective. In this regard, for any HPV-related tumor, anal and rectal cancer, and head and neck cancer, there was a small increase in risk for each additional year of age. For cervical cancer, older age was associated with a decreased risk (0.98). The explanation for this observation is unclear, but we would speculate that current screening tools for cervical cancer, and increased awareness of the disease, may have led to diagnosis at an earlier age. There was also an increased risk for any HPV-associated cancer, cervical cancer, and head and neck cancer in other races when compared with white, possibly reflecting differences in socioeconomic and/or access to healthcare between white and other races.

In our study, Hispanic ethnicity was protective for any HPV-associated cancer, cervical, and head and neck cancer, but was not a significant variable for anal and rectal cancer. It is unclear why Hispanic ethnicity may confer protection from these tumors, but we would speculate that there may be cultural differences that may favorably affect patient education, access to medical care, or compliance with medical advice. This speculation is consistent with trends for all women in the USA, for whom non-Hispanic ethnicity corresponded to a twofold risk of HPV-associated oropharyngeal cancer compared with Hispanics.[14] This finding concurs with the 'Hispanic paradox', which has historically observed better health outcomes and increased survival among Hispanics, despite higher exposure to risk factors for mortality, including tobacco, alcohol, and lower socioeconomic status. Explanations for this correlation remain inconclusive and controversial.[25]

Our work has shown an increased risk of HPV-associated cancers in women on dialysis. In this regard, it is well established that patients with ESRD have a higher risk of cancer overall, most likely due to immune dysregulation and uremia-induced inflammation associated with poor kidney function.[26] Moreover, women with ESRD have a significantly higher risk of developing HPV-associated cancers than their male or non-ESRD counterparts.[16] Further, HPV-associated cancers tend to be asymptomatic and be insidious in onset.[27] Thus, recognition of high-risk groups may lead to earlier diagnosis and improved outcomes.

The present studies relied on queries of the USRDS data set, and thus have several limitations. First, all diagnoses lacked actual medical documentation (neither laboratory nor diagnostic testing results were available) but instead were inferred from billing codes submitted to Medicare or taken from CMS form 2728. However, to improve diagnostic reliability, more than 1 ICD-9 code was used to define a specific cancer diagnosis whenever possible.[28] Second, the patients reported in our study were from inpatient encounters in which HPV-associated cancer diagnoses were coded. We could not account for patients in whom the diagnosis was made as an outpatient, not identified in the inpatient setting, for whom there were coding errors, nor any discrepancy between positive billing codes and pathology-confirmed diagnosis. Third, this study was unable to directly query for several factors recognized to affect HPV cancer risk, such as age at first sexual encounter, number of full-term pregnancies, long-term oral contraceptive use, as well as factors that increase cancer risk overall, such as family history, socioeconomic status, and lifestyle variables.[29] Fourth, the queried malignancies are known to be heavily associated with HPV infection, but the analysis is unable to confirm HPV infection as the definitive causative agent. Additionally, we did not have access to vaccination status of the patients and thus cannot account for its effects on the data. Finally, for statistical analysis, the cancer OR could have been used to compare the risk factors based on how the control group was selected. Despite these limitations, this study used the largest available database on US women with ESRD, offering strength in the size and comprehensive nature of the data set.

In summary, we have shown that from 2005 to 2011, women with ESRD in the USA have a higher incidence of HPV-associated cancer than the published rates for the general population and that the annual incidence is rising. Tobacco use appears as a universal risk factor for all HPV-associated cancers, and for cervical cancer, the presence of HIV and/or herpes are important comorbidities. Alcohol use is important in head and neck cancer, and inflammatory bowel disease contributes to anal and rectal cancer. Recognizing risk factors associated with these cancers may allow earlier diagnosis, improved management strategies, and facilitate survival. The role of HPV vaccination in at-risk dialysis patients remains to be defined. Given the apparent burden of disease, future investigation into the impact of HPV vaccination on HPV-associated cancers in women with ESRD, including its role in secondary prevention, is warranted.

Contributors The lead author (JH), senior author (SLB), and authors REC and NSN conceived the study and developed the study design, along with additional critical contributions from JLW, VS, LY, and MFK. JLW performed data extraction and statistical analysis. JH drafted the manuscript. JLW, REC, VS, LY, MFK, AM, WBB, NSN, and SLB contributed to data analysis and interpretation, as well as reviewed and revised the final manuscript and figures. All authors have approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval was not required for this study. The data reported here have been supplied by the US Renal Data System (USRDS).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The USRDS is a deidentified patient database that includes demographic characteristics, dialysis claims, transplant history, payer source, hospitalization, physician/supplier claims (including ICD-9 and CPT diagnosis codes) and vital statistics on all patients with ESRD in the USA. Demographic information was available in the USRDS patient information data set, and comorbidities were defined by inpatient ICD-9 billing codes submitted to Medicare. The latest version of the form CMS-2728, implemented in 2005, was used to obtain information about age at the start of dialysis, race, ethnicity, mode of dialysis, and vascular access type on first dialysis.

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