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Prevalence of high-risk human papilloma virus among women with hepatitis C virus before liver transplantation

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Abstract

Background—We sought to assess the prevalence and risk factors for high-risk human papillomavirus (HPV) infection among female liver transplant (LT) candidates. Traditional health screening before LT listing has included Pap smear and is typically carried out by the patient's local provider. The prevalence of high-risk HPV in this population has not been studied.

Methods—With Institutional Review Board approval, 62 LT candidates received a liquid-based Pap smear with high-risk HPV testing as part of their pre-transplant evaluation by a single provider. Clinical variables included age, ethnicity, insurance status, prior Pap smear, and HPV results, HPV risk factors including age of first intercourse, number of lifetime partners, last sexual activity, smoking, birth control pill use, history of sexually transmitted infections, human immunodeficiency virus status, immunosuppressive medication, medical diagnoses, prescribed medications, and history of hepatitis A, B, C, or D.

Results—The 62 women had a median age of 56 years, and 39% had high-risk behavior known to be associated with HPV. Ten of 62 patients (16.1%) had high-risk HPV at baseline screening, 5 of whom had atypical cytology. All of the patients who were positive for high-risk HPV had an etiology of hepatitis C virus (HCV) as the underlying cause of liver disease, with the majority (90%) having no history of high-risk behavior for HPV. In contrast, all patients with high-risk behavior who were HCV negative were HPV negative. Fisher's exact test demonstrated a statistically significant relationship between HPV and HCV; odds ratio = 24.4, 95% confidence interval, *P*-value = 0.0013. None of the other potential risk factors were associated with HPV in this cohort.

Conclusions—In this study, we provide evidence of a strong association between HCV and HPV in LT candidates, which has not been previously reported. HPV positivity was observed in non-sexually active women, suggesting a reactivation of dormant HPV. An association between hepatitis C and high-risk HPV could involve impairment of T-cell function by hepatitis C. These data support close surveillance in women's health screening for LT candidates. Further studies to characterize immune responses in these patients will be in order.

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Keywords

immunosuppression; liver disease; liver transplantation; human papilloma virus; hepatitis C virus; cancer prevention; women's health screening; genital neoplasm; HPV; HCV

Human papillomavirus (HPV) is detected in >90% of cervical cancers. A causal relationship between HPV and lower genital tract neoplasms has been established. In 2010, there were 12,200 estimated new cases of cervical cancer in the United States and 4210 estimated deaths (1, 2). Annual incidence of newly diagnosed HPV is an estimated 6.2 million cases worldwide, with approximately 500,000 new cases of cervical cancer and 274,000 related deaths.

Oncogenic or high-risk HPV infection has been identified as an underlying cause of cervical cancer (3) and the World Health Organization has designated HPV infection as necessary for cervical cancer development (4). High-risk HPV types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 (5). Persistent infection with oncogenic or high-risk types of HPV is strongly associated with the development of cervical cancer (6).

The immune system plays a major role in persistence of HPV infections, and the oncogenic potential of HPV may be enhanced by immunosuppression (7). Immunocompetent women infected with HPV usually eradicate virus within 24 months, regardless of viral oncogenicity (8). Reactivation of latent DNA viruses, such as Epstein-Barr virus, cytomegalovirus, herpes simplex, and hepatitis B, and of RNA viruses, such as hepatitis C virus (HCV) and human T-lymphotropic virus 1, has been documented in immunocompromised hosts and organ transplant recipients (9). Similarly, HPV reactivation can occur and lead to malignancies without proper surveillance in long-term transplant survivors.

Organ transplant recipients have a high risk of developing other malignancies, because of lifelong immunosuppressive therapy. These patients are susceptible to cancers that have been linked to viral infections, such as non-Hodgkin lymphoma and Hodgkin lymphoma (to Epstein–Barr virus), Kaposi sarcoma (to human herpesvirus-8), adult T-cell leukemia (to human T-lymphotropic virus 1) (10), hepatocellular carcinoma (to hepatitis B virus and HCV), and anogenital cancers, which include cervical, vaginal, perianal, and vulvar malignancies (to HPV) (11).

We conducted a retrospective chart review of 266 female livertransplant (LT) recipients, ages 18–70 years, followed in our center. Sixteen patients (6%) were documented to have had a pre-transplant Pap smear, and of these only 1 was tested for HPV. To address this deficiency in clinical practice, a protocol was introduced that offers gynecology exam and HPV screening to women, ages 18–70, referred for transplant evaluation. All women with abnormal Pap smears and/or positive HPV test receive follow-up care according to the American Society for Colposcopy and Cervical Pathology treatment guidelines.

Patients and methods

Institutional Review Board approval was obtained before study enrollment. Women with history of liver transplantation were excluded from the study, as they were already on immunosuppressive medication. All women referred for LT evaluation were asked to participate and provide informed consent.

Study subjects received a baseline Pap smear, HPV screening, and education about cervical cancer screening as part of their pre-transplant evaluation. Demographic and clinical information obtained at the time of the initial visit included HPV risk factors, age of first

sexual encounter, number of lifetime partners, most recent sexual activity, tobacco history, oral contraception use, detailed history of sexually transmitted infections, human immunodeficiency virus (HIV) status, medical diagnoses, etiology of underlying liver disease, and all prescribed medications, including immunosuppressive agents.

Descriptive data were summarized with means, medians, standard deviations, frequency, and percentages. Fisher's exact test was used to determine the statistical significance of the relationship between HPV and etiology of liver disease. Statistical analyses were conducted using SPSS version 13 (SSPS Inc., Chicago, Illinois, USA).

Results

In total, 62 women were screened for cervical/vaginal high-risk HPV before liver transplantation. Median age was 56 years (27–69). Hispanics represented 54.9% of the cohort. HCV was the underlying cause of liver disease in 54.8% of subjects. Other causes of liver disease are summarized in Table 1.

Over half of the group (53.8%) reported no history of smoking, 6 subjects (9.6%) reported a history of injection drug use, and a third of the cohort (32.7%) reported a history of >1 alcoholic drink per day. Three women had HIV infection, and another 7 subjects (11.6%) reported history of other sexually transmitted infections. Twenty-five percent of subjects reported ≥5 sexual partners in their lifetime. Current sexual activity versus abstinence of 10 years or longer was reported among 38.5% and 61.5% of women, respectively.

Fifty-eight subjects (93.5%) had normal Pap cytology while 5 women (6.5%) had atypical squamous cells of undetermined significance. HPV screening identified 10 subjects (16.1%), ages 46–61 years, with high-risk HPV. All women with high-risk HPV had chronic HCV (Table 2), and 90% of these reported no risk factors for HPV ($P = 0.0013$) (Table 3).

Discussion

Limited research is available on HPV incidence or prevalence in liver transplantation patients before and after transplant. In this cohort of 62 pre-transplant female subjects, 10 had high-risk HPV at baseline screening and 5 had atypical cytology. All of the patients who were positive for high-risk HPV had an etiology of HCV as the underlying cause of liver disease, and 90% reported no identifiable risk factors for HPV.

There is compelling evidence of HPV-related infections and malignancies among renal transplant recipients and the HIV+ population. Serraino et al. (12) examined the risk of cancer following immunosuppression in solid organ transplant recipients and in HIV+ individuals in Southern Europe. The transplant group consisted of 1829 kidney transplants, 682 heart transplants, 42 lung transplants, and 322 LTs. After 5 years, 3.1% in the HIV+ group and 4.4% of transplant recipients had developed cancer. The cumulative probabilities of cancer at 15 years in the HIV and transplant cohorts, were 13.3% and 14.7%, respectively (12).

A meta-analysis of cancer incidence among patients with HIV/AIDS and immunosuppressed transplant recipients found a substantially higher rate of HPV-related cancers in the transplant group. However, infection-related cancers, such as those related to HPV, were more prevalent in immunosuppressed patients, independent of the source of immune deficiency (13).

Roka et al. (14) conducted a clinical trial to determine the prevalence of anal HPV in solid organ transplant patients. The study included 43 kidney and 17 LT patients. A 10-fold

increased relative risk for the development of anal cancer in transplanted patients, and a strong association between persistent high-risk HPV with anogenital neoplasia, including cervical, anal, vulvar, penile, and vaginal cancers, have been reported in the literature. HPV was detected in 23% (14/60) of patients, with 15% having high-risk HPV, 13.4% having low-risk HPV, and 5% having both types. The prevalence of HPV was higher in LT than in kidney transplant patients (29.4% vs. 20.9%), although this was not statistically significant. HPV infection was found in 23% of patients before immunosuppression. Although this study provided needed information about this population, it is unclear whether the outcomes were different because of the type of organ being transplanted or the regimen (14).

Data from our study of pre-transplant subjects demonstrate several important findings. Hispanics represented 54.9% of the cohort, with a median age of 56. Datta et al. (15) looked at high-risk HPV prevalence by demographic characteristics, and Hispanics had 20% prevalence of high-risk HPV, non-Hispanics 24%, and unknown ethnicity revealed 21%, with only 6% within the ages of 50–65. Baseline general population prevalence data for HPV infection in the United States revealed that women aged 20–24 years had the highest prevalence of HPV at 44.8%, with a steady decline with age (16).

Sixteen percent of patients were found to have high-risk HPV infection before transplantation. All high-risk HPV-positive patients had HCV as the underlying cause of their liver disease. Ninety percent of these patients had no known risk factor for HPV. Although the sample size is small, it is intriguing that patients with high-risk HPV reported no history of recent sexual activity or identifiable risk factors for HPV, and had concomitant HCV infection. The absence of sexual activity for > 5 years excludes the possibility of new infection.

We know that HPV can become a persistent chronic infection through an efficient immune evasion mechanism. Because HPV infects and replicates in keratinocytes, which are distant from immune centers and have a short life span, it evades the innate immune response and delays the activation of the adaptive immune response. In addition, like most DNA viruses, HPV has evolved mechanisms to inhibit antiviral interferon (IFN) synthesis and signaling. High-risk HPVs down-regulate IFN-α-inducible gene expression, and HPV oncoproteins interfere with IFN signaling (17).

However, almost all natural history studies show that genital HPV infection is common in young sexually active women, and most infections “clear” effectively. Failure of the immune response to clear or control the infection results in viral persistence. Individuals with impaired immunity have increased probability of progression to high-grade cervical intraepithelial neoplasia (CIN 2/3) and invasive carcinoma. This vulnerability is evidenced by the increased incidence and progression of HPV infections in HIV+ patients (18).

Cirrhosis has been characterized as the most common acquired immunodeficiency syndrome worldwide (19). It is associated with several immune system abnormalities, specifically, decreased monocyte function, characterized by a deficiency in adherence and phagocytosis, altered natural killer activity, and lectin-induced proliferation of T lymphocytes.

Finally, an increased concentration of serum immunoglobulin in patients with liver cirrhosis may indicate an altered balance between T-lymphocyte helper (Th) responses implicated in cytotoxicity (Th1) and those implicated in the synthesis of specific antibodies (Th2) (20). Therefore, we hypothesize that the immunodeficiency associated with HCV cirrhosis may contribute to persistence of infection and increase the risk for incident high-grade intraepithelial lesions in this group of women with high-risk HPV infection.

These findings have important practice implications with regard to preventive care for this population. Cervical cancer screening guidelines in the general population have recently been revised and recommend screening for women beginning at age 21 regardless of the age sexual activity was initiated. These guidelines do not address special populations who may need more intensive or alternative screening. These include women (i) with a history of cervical cancer, (ii) who were exposed *in utero* to diethylstilbestrol (DES), and (iii) who are immunocompromised (e.g., infection with HIV) (21). Women who are immunocompromised from end-stage liver disease should be included in this category. The time interval has not yet been established for screening women who are immunocompromised.

Renal transplant is the most frequently performed organ transplant. Although minimal data are available regarding cervical screening in liver disease, there are recommendations for renal transplantation recipients. The American Society of Transplantation and the European Best Practice guidelines advise annual cervical screening and pelvic exam in women who are renal transplant recipients (22).

It is acceptable to follow general population guidelines and not begin screening before age 21. The majority of adult patients who require liver transplantation are over the age of 30 (23). However, it is reasonable to apply renal transplant guidelines to women who are immunocompromised secondary to liver disease. Immunosuppression is one of the most significant risk factors for the development of high-grade anogenital lesions and cervical cancer. These persons are at risk for persistent and multiple types of HPV infections (24).

Further data are needed to describe the population, risk factors, and prevalence of high-risk HPV among women enrolled in transplantation programs. Controlled prospective studies should be conducted to determine risks for development of cervical cancer in this population. As liver transplantation becomes more successful and patients live longer, clinicians must understand the risks of secondary cancer development and the need for early detection and prevention by improving surveillance before and after transplant.

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Table 1

Population characteristics ($N = 62$)

Variable	Number	Percentage
Age, years (Mean = 54, Median = 56)		
27–37	6	9.7
38–48	6	9.7
49–59	28	45.2
60–69	22	35.4
Etiology of liver disease		
HCV	34	54.8
AIH	10	16.1
NASH	4	6.5
ETOH	3	4.8
Other	11	17.8
Ethnicity		
Hispanic	34	54.9
Caucasian	17	27.4
Black	9	14.5
Asian	2	3.2

HCV, hepatitis C virus; AIH, autoimmune hepatitis; NASH, non-alcoholic steatohepatitis; ETOH, ethanol.

Table 2

Association of females with human papilloma virus (HPV) and hepatitis C virus (HCV)

	HPV+	HPV−	Total
HCV+	10	24	34
HCV−	0	28	28
Total	10	52	62

OR = 24.4, 95% CI of OR is (1.4, 438.7); *P*-value = 0.0013 (based on Fisher's exact test).

OR, odds ratio; CI, confidence interval.

Table 3

Risk factors for woman with human papilomavirus (HPV) infection

Variables	HPV+ (*n* = 10)	HPV− (*n* = 52)	*P*-value
Smoking			0.62
Never	7 (70%)	28 (53.8%)	
Quit >10 y	2 (20%)	14 (27%)	
Quit <10 y	1 (10%)	10 (19.2%)	
Sexual partners			0.42
<5 lifetime	9 (90%)	39 (75%)	
>5 lifetime	1 (10%)	13 (25%)	
IVDA			1.00
Never	9 (90%)	47 (90.4%)	
History	1 (10%)	5 (9.6%)	
ETOH abuse			0.26
No history	9 (90%)	35 (67.3%)	
History	1 (10%)	17 (32.7%)	
Sexual activity			0.73
>10 y	7 (70%)	32 (61.5%)	
Currently active	3 (10%)	20 (38.5%)	
STI			1.00
No history	9 (90%)	46 (88.4%)	
History	1 (10%)	6 (11.6%)	
HIV			0.51
Negative	9 (90%)	49 (94.2%)	
Positive	1 (10%)	3 (5.8%)	

y, years ago; IVDA, intravenous drug abuse, ETOH, ethanol; STI, sexually transmitted infection; HIV, human immunodeficiency virus.