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COMPREHENSIVE REVIEW

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Human papillomavirus-related cancer risk for solid organ transplant recipients during adult life and early prevention strategies during childhood and adolescence

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Abstract

Malignancies are among the top three causes of patient death in pediatric and adult kidney transplant (KT) recipients. Solid organ transplant (SOT) recipients, including KT individuals, experience more cancer compared with the general population, including human papillomavirus (HPV)-related anogenital and oropharyngeal cancers. This article describes the epidemiology, pathophysiology and natural history of the HPV infection in both the general population and in SOT recipients, as well as its role in the development of HPV-related pre-cancerous lesions and cancers. Emphasis is given to the primary prevention strategy, HPV vaccination in SOT recipients, and its particularities compared with the general population. Secondary prevention strategies in SOT recipients are discussed and compared with the general population, highlighting cervical cancer screening needs within SOT populations. The article emphasizes how these primary and secondary HPV prevention strategies applied during childhood and adolescence by the pediatric transplant professionals, can lower the burden of HPV-related cancers for SOT recipients in subsequent years, during their adult life.

KEYWORDS
human papillomavirus, malignancy, screening, solid organ transplant, vaccination

1 | INTRODUCTION

Malignancies are among the top three causes of patient death in pediatric and adult kidney transplant (KT) recipients according to the North American Pediatric Renal Trials and Collaborative Studies 2014 Annual Report and the U.S. Renal Data System 2020 Annual Data Report. Transplant professionals know their patients walk a tightrope, being potential victims of either underimmunosuppression that leads to rejection on one side, or overimmunosuppression that leads to infections and malignancies on the other side.[1] Indeed, solid organ transplant (SOT) recipients experience more cancer compared with the general population. For example, KT recipients experience a 14-fold increased risk of cervical cancer, a 50-fold increased risk of vulvar cancer, and a 100-fold increased risk for anal cancers.[2,3] In addition, male SOT recipients have an increased risk for penile cancers.[4] Population-based cohort studies of SOT recipients have shown an increased risk of HPV-associated cancers: standardized incidence ratios have been shown to be 2.13 (95%CI 1.37–3.30), 4.85 (95%CI 1.36–17.3), and 3.23 (95%CI 2.40–4.35) for cervical, anal, and oropharyngeal cancers, respectively, relative to

Abbreviations: CKD, chronic kidney disease; HIV, human immunodeficiency virus; HPV, human papillomavirus; KT, kidney transplant; SOT, solid organ transplant.

the general population in large metanalyses.[5] The common denominator for these types of cancers is human papillomavirus (HPV).[6]

Given that adult SOT patients are at increased risk for malignancies, including HPV-associated cancers, and that the treatment for these diseases can negatively impact the graft viability, one needs to ask the question: how do we proceed about the most effective prevention, starting as early as possible in life? This article will delineate the most efficient primary and secondary prevention strategies that, applied during childhood and adolescence, have been proven to mitigate the risk for HPV-related cancers for SOT recipients later, during their adult life.

2 | HPV: DESCRIPTION, EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND NATURAL HISTORY

HPV is a small DNA virus with tissue tropism for squamous epithelial cells which are common to sites of HPV-associated cancers. HPV is the most common sexually transmitted infection and 12 types, belonging to the α genus (including HPV 16, −18, −31, −33, −35, −39, −45, −51, −52, −56, −58, and −59), are responsible for >95% of HPV associated cancers. HPV has been causally associated with cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers in >91%, 75%, 69%, 63%, 91%, and 70%, respectively (https://www.cdc.gov/cancer/hpv/statistics/cases.htm). Among these, cervical carcinoma should be emphasized, as it is the second most common cancer and cause of cancer death in women worldwide and it is linked to HPV in more than 91% of cases. Of the oncogenic types, HPV 16 confers the highest risk for development of invasive cervical carcinoma.[7] In addition, HPV 16 is also responsible for the majority of the oropharyngeal and anal cancers.[8,9] HPV 16 and to a much lesser extent HPV 18 are responsible for the majority of the anogenital cancers.[6] While non-oncogenic HPV types are not associated with cancer, non-oncogenic HPV types 6 and 11 are nevertheless associated with genital warts as well as respiratory papillomatosis, which may lead to severe and refractory disease in the face of immunosuppression.[10,11] In natural history studies of HPV infection of the cervix, most women are thought to become infected with at least one HPV type within the first 2 years after the onset of sexual activity.[12] The HPV infection may result in either total clearance or latency.[12] Many early infections at the cervix clear and/or become non-detectable within 2 years of initial detection.[12] Some progress to cervical intraepithelial neoplasia (graded by severity as 1, 2, and 3), which over time can progress to HPV-associated invasive cancerous lesions.[12] What is not known is the proportion of cervical cancer that is related to a newly acquired infection later in life, versus a reactivation of an infection acquired earlier in life.[13] Due to immunosuppression, SOT recipients are at risk at multiple points in its epidemiological trajectory, including poor cell-mediated viral clearance that can lead to increased infection rates, as well as persistent infections, accelerated reactivation due to immunosuppression, and accelerated progression of precancerous disease to cancer.[14–18]

In contrast, the natural history of HPV infection in the anus and oropharynx is not as well understood. Like cervical dysplasia, anal cancer has cytologic precursors. The terminology used to describe the precancerous lesions of the anus is similar to that of cervical disease and is designated as anal intraepithelial neoplasia grades 1, 2, and 3; however, the pathophysiology remains unclear.[19] Certain groups remain at higher risk for the development of anal squamous cell dysplasia, including those who are immunosuppressed due to medications or human immunodeficiency virus (HIV). Specifically, the cross-sectional prevalence of HPV in the anus in KT recipients was found to be 17% (15/86 available samples), 1% had detectable HPV 16 DNA and 2% had evidence of high-grade squamous cell dysplasia on anal cytology examination (as well as being positive for a high-risk HPV type).[20] Studies investigating the HPV prevalence in the anus among large numbers of transplant patients are still lacking. The prevalence of oral HPV in the general population has been reported to be 11.5% in men and 3.2% in women in national surveys in the United States.[21] The prevalence of high-risk HPV types was also increased in men relative to women with HPV 16 being the most frequently detected type. When considering the SOT population, cohorts examining the prevalence of HPV among KT recipients and simultaneously recruited healthy controls have found a slightly increased risk of oral HPV DNA detection and detection of high-risk HPV types. This trend was still seen when investigators controlled for the number of lifetime sex partners.[22]

Prevention strategies in public health target interventions to promote and protect the health of the general population. Over the last two decades, the development and implementation of the HPV vaccine have allowed a primary intervention to be implemented to prevent HPV-related cancers. Secondary prevention involving the detection of early cancer has changed as we better understand the epidemiology of cancer within the transplanted population. While these are effective interventions, the use of the vaccine and following cancer screening recommendations for those immunosuppressed SOT recipients has been less than optimal.

3 | PRIMARY PREVENTION (VACCINATION) IN THE GENERAL POPULATION AND IN SOT RECIPIENTS

HPV vaccines have been shown to be highly efficacious in preventing persistent oncogenic HPV infection, the development of precancerous lesions, and the development of HPV-related cancers.[23] Specifically, recent studies have demonstrated a true reduction in abnormal cervical cytology, cervical precancers, cervical cancers, and anal cancers with the use of HPV vaccine,[24–26] as well as early evidence of possible oropharyngeal cancer prevention.[27] There are currently three types of vaccines available: the quadrivalent (HPV types 6, 11, 16, 18), licensed in 2006 for women and in 2009 for men; the bivalent (HPV types 16 & 18), licensed for women in 2009; in the United States, currently

only the 9-valent (HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58) is available and was approved for both women and men in 2014.[28]

3.1 | Dosing

Dosing for SOT populations differs slightly from the general population guidelines. The main difference between healthy individuals and SOT patients is the following: healthy individuals less than 15 need only two doses of the vaccine, while a SOT recipient should always receive three, regardless of age.[29] In addition, while the vaccine is not routinely offered after age 26, it can be considered in SOT recipients[12] (Table 1).

3.2 | Timing

Importantly, HPV vaccine trials have been shown to prevent HPV infection in immunocompetent individuals when the vaccine was given prior to viral exposure.[30] This is because the vaccine is effective in preventing infection, but will not clear any previously acquired or prevalent infections.[31] Therefore, because HPV is sexually transmitted and often acquired soon after the onset of sexual activity,[32] vaccination should ideally occur before sexual debut. In the United States, the proportion of males who reported having sexual intercourse before age 13 years varied from 5% to 25% across metropolitan sites; hence, the need to vaccinate at a young age in order to capture most teenagers before becoming sexually active.[33] Reported sexual experiences of adolescents, as well as robust immune responses of young adolescents, were guiding forces for the Advisory Committee on Immunization Practices recommendation of administering the HPV vaccine at 11–12 years of age.[31] However, it can be administered as early as 9 years of age (American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, and American Cancer Society consensus guidelines).

Vaccination-produced antibody titers are higher than those after natural infection, as in one study only 54%–69% of women with incident HPV 16 or 18 infections had antibodies.[34] In healthy populations, the seroconversion rates are 95%–100% after vaccination.[35,36] However, in SOT recipients, while the HPV vaccines are efficacious, antibody titer production appears to be reduced relative to the non-transplant population. The first study of the immunogenicity of the HPV vaccine in SOT recipients was done in a cohort of 47 adults with SOT (females and males) and there were lower rates of seroconversion (defined as meeting the manufacturer's cut-off criteria): 63.2%, 68.4%, 63.2%, and 52.6% for HPV 6, 11, 16, and 18, respectively.[37] Although the study did not use a control group, it is well known that in healthy populations, the seroconversion rates are 95%–100% after vaccination; therefore, SOT recipients clearly had a much weaker response.[35,36] Somewhat similarly, in pediatric transplant recipients, a study of a cohort of 57 patients (females only) aged 9–21 with KT, seropositivity rates were significantly lower (62.5%, 50.0%, 75.0%, and 50.0% for HPV 6, 11, 16, and 18, respectively), compared to patients with chronic kidney disease (CKD) or on dialysis.[38] Our multicenter study conducted through the Pediatric Nephrology Research Consortium included 72 patients (girls and boys) aged 10–16 with KT and reported lower seroconversion rates in this population compared to patients with CKD.[39] Indeed, while patients with CKD had seroconversion rates of 100%, 100%, 100%, and 94.4% for HPV 6, 11, 16, and 18, respectively, the KT recipients were significantly lower in terms of seroconverting, only at 72.4%, 69.0%, 89.7%, and 62.1%, respectively.[39] Therefore, it appears it is best to vaccinate, if possible, prior to transplantation, during the last stages of CKD or while patients are on dialysis. In the case that HPV vaccination has not occurred prior to transplantation, it is still recommended to be done after transplantation; however, starting no earlier than 3- to 6-month post-transplantation, in order to ensure the best possible immune response.[40]

In regards to long-term maintenance of immunity after vaccination for healthy women, data are available from a follow-up European study measuring the immunogenicity of bivalent HPV vaccine, which found that seropositivity rates 10 years after vaccination remained relatively high: 100% for HPV-16 and 99.2% for HPV-18; immunity was predicted to remain above natural infection levels for at least 30 years.[41] In contrast, an Australian study recently looked at males and females vaccinated post-SOT and found that seropositivity after vaccination dropped from 100% immediately post-vaccination

TABLE 1 HPV vaccine dosing guidelines

Age	Healthy population	Solid organ transplant recipients (SOT)
9–15	Two doses of HPV vaccine at 0 and 6–12 months	Three doses of HPV vaccine at 0, 1–2, and 6 months
15–26	Three doses of HPV vaccine at 0, 1–2, and 6 months	Three doses of HPV vaccine at 0, 1–2, and 6 months
26–45	Not routinely offered	Should be considered in shared clinical decision-making with patient[a]

[a]Evidence suggests that although HPV vaccination is safe for adults aged 26 through 45 years, population benefit would be minimal; however, SOT recipients who are not adequately vaccinated may be at risk for new HPV infection and therefore might benefit from vaccination in this age range.

to 94.6% for HPV-16 and from 91.2% to 78.4% for HPV-18 5 years later.[42] This has raised the question of the utility of revaccination in SOT recipients. Indeed, revaccination in immunocompetent individuals has resulted in an increase in antibody titers or anamnestic responses from B-cell memory.[43] However, this has not been studied in individuals who are immunosuppressed, and it should be also noted that the exact neutralizing antibody titer needed to prevent infection is unknown; therefore, the need for revaccination in SOT recipients has not been so far demonstrated.

3.3 | The suboptimal HPV immunization rates in SOT recipients and potential ways to address this problem

Although SOT recipients are at increased risk for HPV-related malignancies, unfortunately they appear to also be at high risk for either not getting vaccinated, or getting vaccinated later than the recommended time, despite the guidelines.[44] HPV vaccine acceptance by patients and their parents/guardians has always been problematic even in the general population[45,46] and probably more so in specific groups, such as SOT patients, where data are scant.[44] However, recent studies provided further evidence that patients who are likely to need a KT in the future respond best to the HPV vaccine pre-transplantation, while with CKD or on dialysis.[38,39] As the majority of causes of end-stage renal disease in pediatrics are congenital diseases in which the kidney function slowly deteriorates over time, pediatric nephrologists often have the advantage of being able to better plan a KT (whether pre-emptive or not) considering multiple aspects, including vaccinations, compared to their Internal Medicine Nephrology colleagues.[44] Therefore, the results of the recent studies should help pediatric nephrologists, transplant physicians, and pediatricians in their work with patients and families to pursue and complete the administration of HPV vaccine ideally prior to transplant whenever possible but also post-transplant in cases where it was not given prior to SOT.

As noted in one study, SOT recipients are vaccinated later than the recommended time, despite the guidelines.[39] This is likely due to less immediate concerns about sexual activity when patients are ill and awaiting transplantation, as has been shown in other patients with severe chronic illnesses.[39,47] However, in children with CKD and on dialysis, contrary to what was believed in the past, recent cohort studies have shown that growth and sexual maturation are only slightly delayed compared to healthy subjects.[48] Although there is lack of specific data, given the circumstances of normal or close to normal sexual development, it is plausible that adolescents with CKD or on dialysis are not far behind their peers in terms of their onset of sexual activity; therefore, it is important that they receive the HPV vaccine no later than the recommended age.[39] Routine childhood vaccines in KT candidates and recipients are more likely to be administered by primary care providers, while other vaccines, such as ones that lie outside of routine schedules (including HPV vaccination), are more likely to be administered by transplant providers.[44] Therefore, it is important for both primary care and transplant providers to be aware of the most recent guidelines for childhood immunizations for SOT recipients, including KT recipients. In addition, it is important to keep close communication between all providers in order to ensure an ongoing fully immunized status for pediatric KT candidates and recipients.

3.4 | Other primary prevention strategies

As primary prevention measures are considered, one also must think about behaviors and behavioral counseling in the prevention of HPV infections. While consistent condom use has not always been associated with reduced HPV infection risk,[49] the number of lifetime partners is clearly a risk factor for cervical, anal, as well as oropharyngeal HPV-related cancers.[50,51] However, consistent and correct condom use and limiting numbers of sex partners are not only likely to reduce HPV infections but will also help protect against other sexually transmitted infections, including HIV, that may enhance progression of any HPV-associated cancer.[52] Collaboration between pediatric transplant nephrologists and adolescent medicine specialists (or a primary provider who feels comfortable addressing the needs of adolescents) becomes very important in this context, highlighting the utility of addressing safe-sex practices and psycho-social issues through a multidisciplinary approach in our pediatric transplant transition clinics.

4 | SECONDARY PREVENTION

4.1 | Cervical cancer and cervical intraepithelial neoplasia (CIN) screening

Cervical cancer screening via cervical cytology (Pap smear) has been very successful, given that prior to the onset of the actual invasive cervical cancer there is a long preliminary preinvasive stage consisting of cervical intraepithelial neoplasia, which can generally be successfully treated.[53] Several professional societies, including the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force, have come together with joint guidelines[40] (Table 2). It should be noted that limited data exist to support the development of SOT cervical cancer screening guidelines and most guidelines have been modeled after HIV-infected women, which is supported from evidence of both retrospective and prospective studies.[54] In addition, cervical cancer screening guidelines for healthy women, as well as for SOT recipients, are country-specific; therefore, there are some differences between countries.[55]

Cervical cytology screening for women immunosuppressed and 21 years and younger differs from general screening guidelines. SOT recipients, if sexually active, should begin cervical screening within 1 year of sexual debut regardless of age, even when less than 21.[40]

TABLE 2 Secondary prevention of cervical cancer

Age	Healthy women	Solid organ transplant recipients (SOT)[a]
<21	Screening not required	If sexually active, begin screening within 1 year of sexual debut
21–30	Cervical cytology (Pap smear) every 3 years	Cytology every year (once negative x 3, extend screening to every 3 years)
30–65	Co-testing (HPV + Pap smear) every 5 years	Baseline co-testing (HPV + Pap smear) If negative continue every 3 years.
>65	Screening not required	Continue screening throughout life

[a]Cervical cytology testing should be performed every 6 months for the first year after SOT, or after treatment of rejection using lymphocyte-depleting agents; if the results are normal, the interval can be increased to annually.

(Table 2). Above age 21, screening should begin in SOT recipients, even if not sexually active and generally continues throughout a lifetime.[54] Recommendations also include that the cervical cytology test be performed every 6 months for the first year after transplant, after which, if the results are normal, the screening interval can be increased to annually.[40] It is reasonable to also reinstate screening every 6 months for 1 year following treatment for rejection, particularly if lymphocyte-depleting agents are used.[40] Recognizing that most pediatric transplant providers are less comfortable and lack the added time to address confidential issues with adolescents, it is imperative that a member of the transplant team address this issue and if unable to perform screening, make necessary referrals for cervical screening (as well as sexually transmitted infection screening) when needed.

But what about other HPV-related cancers? Are screening strategies available and is it really being done? Of the non-cervical HPV-associated cancers, anal and oropharyngeal cancers have been increasing in incidence over the past decade.[56] Among these two cancer types, HPV types 16 and 18 account for 87% of anal cancers and 84.9% of oropharyngeal cancers.[57] There is currently no standard screening for HPV-related anal or oropharyngeal cancers, at least not in the pediatric age group, although anal cytology has been proposed and its utility is currently being evaluated for adults who are high risk for HPV-associated malignancies, including SOT recipients.[58] The lack of screening further emphasizes the need for primary prevention strategies of HPV vaccination and behavioral counseling in reducing HPV-related cancers.

5 | CONCLUSIONS

To best protect SOT patients from HPV-related malignancies, as pediatric transplant professionals, we should strongly recommend our patients to initiate the HPV vaccine series pre-transplant, as long as they are at least 9 years of age. Should the transplant occur during the series, vaccination should be completed post-transplant. If unvaccinated post-transplant, providers should consider the vaccine even after age 26. Further research is needed to evaluate the effectiveness of the HPV primary series when given prior to transplant in preventing HPV and HPV-related disease and the potential need for booster doses post-transplant. In addition, the immunogenicity and safety of the HPV vaccine when given before age nine will need to be tested first of all in the general population and subsequently in SOT candidates. If proven effective and safe, the possibility of giving the HPV vaccine to SOT candidates before age nine could open a door for many patients, who otherwise would get transplanted before that age and therefore would miss the opportunity to mount a good antibody response. As for secondary prevention, although proven screening for HPV-related cancers is limited only to cervix at this time, following guidelines requires that we, pediatric transplant professionals, at the minimum obtain a sexual history from our adolescent and young adult patients in order to ensure timely referral for initiation of cervical screening. This is important, as SOT patients will need to start cervical cancer screening earlier compared to healthy women, be screened more frequently per guidelines and continue screening for life.

AUTHOR CONTRIBUTIONS

C. Nailescu was responsible for the literature review and manuscript writing. M.L. Shew was responsible for the article's concept, structure and for corrections. A.C. Ermel contributed to the writing of the subchapter "HPV: description, epidemiology, pathophysiology and natural history", as well as to manuscript corrections.

CONFLICT OF INTEREST

The authors declare absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

No new data is presented, therefore no statement.

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