Considerations for Child Cancer Survivors and Immunocompromised Children to Prevent Secondary HPV-associated Cancers

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Abstract

Survivors of childhood cancer and other immunocompromised children are at high risk for the development of secondary Human Papillomavirus (HPV)-associated cancers. In this overview, the authors examine the epidemiology of vaccine efficacy, the natural history of HPV infections, and accelerated HPV-associated cancer development in these populations. The authors highlight the opportunities for preventive care and future research directives.

Introduction

The high efficacy of the HPV vaccine in immunocompetent populations has translated into a resounding public health success in reducing HPV infection[1-4] and cervical precancers.[3,5-7] However, in recent studies, vaccination against HPV in HIV positive (HIV+) persons does not appear to result in the same clinical protection from infection and diseases as in HIV negative (HIV-) persons.[8-12] These concerning data led us to reflect on as yet unanswered questions about the natural history of HPV infection (latency and reactivation) in both immunocompetent and immunosuppressed populations[13-15] and how these issues impact the predicted effectiveness of HPV vaccination in specific immunosuppressed subpopulations beyond HIV+ persons. In particular, this narrative will focus on survivors of childhood cancer (those with and without bone marrow transplants) and solid organ transplant recipients. Consideration of non-HIV+, immunocompromised children and adolescents who are being immunized to protect from future HPV infection and diseases must be thoughtfully addressed. This is especially true as there are concurrent changes to the standards of cervical cancer screening and the management of young and middle-aged women that are in place based on the presumption of homogeneity of risks and outcomes in HPV natural history.

Observations

Epidemiology and pathophysiology of primary HPV infections and their reactivation

First, we must consider that, in addition to the differences between HIV- and HIV+ populations in their response to HPV infections and preventive HPV vaccinations, the HPV vaccine trials in HIV+ populations may not be reflective of or translatable to all immunocompromised populations. Many of those participating in these clinical trials acquired HIV through sexual transmission,[9] an important fact when considering the risk if HPV

acquisition – also a sexually transmitted infection. Prospective studies on the natural history of

HPV suggest that the first HPV acquisition takes place in women aged 15-19 years, with the

peak prevalence of HPV at 20 -29 years of age.[16] Thus if HIV+ is behaviorally acquired, the

likelihood that a HIV+ person also has a prior history of HPV infection is high, making

conclusions drawn from HPV vaccination studies more challenging to interpret. As

demonstrated in longitudinal studies, clinical trials of HIV+ individuals are at risk for

reactivation of latent HPV infections acquired earlier.[17,18] And yet, consistent with

immunocompetent populations, HIV+ participants in HPV vaccine trials demonstrated that

younger age at vaccination against HPV strongly correlated with higher antibody titers (HPV 16

OR= -1.2 per 1 year increase in age).[19]

Second, in animal model studies of cottontail rabbit papillomavirus, immunosuppression

facilitated the reactivation of latent papillomavirus infections, prevented papilloma regression,

and led to an elevation of the viral DNA copy number at sites of previous disease.[20] Thus, not

only is it important to consider the translatability of this animal model for human papillomavirus

reactivation, especially among people who have been treated for cancer or received organ

transplants, but when this group of individuals actually receives the vaccine in relationship to

their age, clinicians must also consider their onset of sexual activity and the timing of their

immunosuppressive therapy. With this in mind, we will focus on the differences in the natural

history of HPV infection and its associated-cancer development in cancer survivors and

transplant patients (Figure 1).

Epidemiology of HPV reactivation and disease progression in immunosuppressed cohort: cancer survivors

Cancer treatment itself is genotoxic and places patients at future risk for secondary cancers. Immunosuppression and inadequate humoral response from the cancer treatments may linger long-term, creating a milieu for accelerated cancer development and progression with HPV, either due to its reactivation or to acquiring a new primary infection (Figure 1B). Reactivation of other DNA viruses, such as Herpes Simplex Virus and Epstein-Barr virus, has been well documented.[21,22] Biological and epidemiological evidence of HPV latency in humans has also been observed.[15,23-26] After allogeneic stem cell transplantation (allo-SCT), long-term survivors are at increased risk for HPV-associated cancers.[27] Studies have demonstrated an increased risk of cervical dysplasia in long-term survivors of allo-SCT compared to time periods before their transplant.[28,29] Another complexity is 40-60% of allo-SCT patients develop graft versus host disease (GVHD).[30] GVHD immunosuppressive therapy can be intensive and prolonged and likely augments the risk for HPV reactivation as seen in case studies.[31-33] What is unclear is whether the GVHD itself, which can be inflammatory, promotes HPV reactivation similar to studies on chlamydia and HPV redetection after clearance,[34] or the treatment of GVHD, which can be immunosuppressive, drives this augmented risk. Regardless of which, all of these risk factors (Figure 1B, red arrows) can accelerate the transition from infection to dysplasia, from latency to reactivation, and from dysplasia to HPV-associated cancers in patients treated for cancer.

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Epidemiology of HPV reactivation and disease progression in immunosuppressed cohort: solid organ transplant patients

Beyond cancer treatment, further evidence of HPV latency and risk exists in solid organ transplant (SOT) recipients (Figure 1C). People who have had SOT, similar to allo-SCT, are living longer. With their improved longevity comes a new health risk – people with SOT have HPV-associated cancers at higher rates than healthy persons.[35-37] In 2011, Engles, et al. examined the risk of secondary cancers for organ transplant patients using standardized incidence ratios (SIRs). Cervical cancer, which is preventable by screening to detect and treat nonreportable precancers, had an SIR of only 1.03; however, cancer of the vulva, which is also HPV-associated but does not have an algorithm for screening and management, had an SIR of 7.6.[38] In a study of women with renal transplants, there was a higher prevalence of oral HPV and genital HPV compared to immunocompetent women, despite studies that suggest women with renal transplants were similar or even more conservative in their recent sexual behavior.[39-41] Similar patterns of increased risk of HPV-associated cancers in both the SOT recipients and HIV+ population, overlaid with the risk among cancer survivors and bone marrow transplant recipients, suggest that immune deficiency may be most responsible for this increased risk.[14,42] Like cancer patients, transplant patients are at risk of accelerated disease develop and progression, as well as poor clearance and latent infection reactivation, which lead to greater risk of HPV-associated cancers (Figure 1C, green arrows).

Epidemiology of HPV reactivation and disease progression in immunosuppressed cohort: patients with autoimmune disorders and pregnant patients

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The impact of other immunosuppressive conditions, such as Lupus, Crohn's disease, or Rheumatoid Arthritis, on cervical abnormalities and cancer was examined in a 2013 review. The authors found that patients with end-stage renal disease were at higher risk for cervical cancer, and patients with autoimmune diseases (particularly those on medication for treatment) had an increased risk of precancerous lesions.[43] Data also suggest that even episodic periods of immunosuppression in otherwise healthy women may also contribute to reactivation. One example of this is HR-HPV infection and cytological abnormalities are detected more often in pregnant women.[44,45] In a study of 274 pregnant women matched on age to 1060 nonpregnant women, HR-HPV was detected in 38.2% of the pregnant women compared to 14.2% in the nonpregnant women. In their multivariate analysis, pregnancy increased the odds of an HPV infection more than 3-fold (OR=3.5).[46]

Understanding the differences between immunocompromised populations, with regard to reactivation of latent HPV infections, risk of new HPV acquisition, and speed of cancer development and progression, will be key to the development of best screening practices for them. If, in fact, non-HIV+ immunocompromised persons are at a higher risk for reactivation of latent viruses compared to immunocompetent persons, and equivalently or even at greater risk compared to HIV+ populations, then vaccination and screening at an ideal time and in an ideal manner will be essential for prevention of secondary, HPV-associated cancers. We discuss these prevention strategies below (see Figure 1 for preventions strategies in italics).

Efficacy of the vaccine in immunosuppressed cohorts

It must be emphasized that the presumed main function of vaccine-induced HPV antibodies is to prevent HPV entry into cells. The antibody titers gained by HPV vaccination in HIV+ populations are only slightly diminished compared to the high levels seen in HIV-

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populations, and this suggests that vaccination should be an effective prevention modality for both groups.[9,10,19] However, in natural history studies of HIV+ women, newly detected HPV infections can be found even in the absence of current sexual activity, and this risk is proportionate to decreasing CD4+ T-cell count and increasing HIV viral load.[47] These HPV detections deemed "incident" may in fact not be new infections but instead the reactivation of a latent or quiescent HPV infection that had been controlled previously through T-cell mediated immune responses.[18] These data suggest that, in people with an increased risk of prior HPV exposure, most new detection and disease onset may indeed not be from a true new infection, where the humoral response has failed; rather, it may be detection of a newly reactivated infection that cannot be suppressed through HPV vaccination, as antibodies derived from HPV vaccination do not function in clearing or eradicating previous established infections. When the quadrivalent HPV vaccine was administered to HIV+ children aged 7 to 12, seroconversion rates were greater than 96%[48]; therefore the immunization is leading to the type-specific antibodies that are detectable and quantifiable. A recent study in Lupus patients found that the HPV vaccine was safe and immunogenic,[49] extending seroconversion data to non-HIV+ populations that experience periods of immunosuppression. Determining how to apply these natural history findings to other immunosuppressed subpopulations, like SCT and SOT patients, and their implications on approaches to and timing of vaccination as a primary HPV prevention strategy, will require thoughtful attention.

In immunocompetent populations, the HPV vaccine is highly cost-effective when administered before sexual debut, but that decreases with increased age.[50] The cost-effectiveness of the HPV vaccine in non HIV+ immunocompromised populations has not been determined; however, a cost-effectiveness study of the HPV vaccine was conducted at HIV and other STI

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testing clnics in men who have sex with men (MSM). The authors stated that offering vaccination to HIV+ MSM up to the age of 40 years is likely to be cost-effective.[51] With that in mind, the cost-effectiveness of the HPV vaccine in male or female immunosuppressed populations likely should be even more cost-effective, relative to the general population, due to their increased burden of disease and their healthcare costs.

The 2017 position paper of the International Papillomavirus Society recommends a 3 dose regimen to all immunocompromised people, preferably before they become immunocompromised.[52] Additional data published in the last year has examined HPV vaccine responses in immunosuppressed patients, and the findings support the 2017 position paper. A Phase 1 quadrivalent HPV vaccine trial was conducted in allo-SCT patients 1.2 (median) years posttransplant. In this study, antibody responses were demonstrated in 78.3% of patients receiving immunosuppression and in 95.2% patients not receiving immunosuppression.[53] Seroconversion to the quadrivalent HPV vaccine was also recently examined in adolescents before and after kidney transplantation. Those vaccinated after transplantation had lower seroconversion rates than those with chronic kidney disease, regardless of whether they received dialysis or not, suggesting that their immunosuppression directly impacted their ability to seroconvert.[54]

These findings lead to this question: Do children, who have had a SCT or received a transplanted organ and subsequently are fully revaccinated, merit more frequent clinical follow-up for HPV diseases than the general population? Those with SCT have bone marrow that has been fully repopulated with new cells. This naïve bone marrow requires a repeat of a patient's childhood and adolescent vaccination series to reestablish their protective humoral response. Revaccinated SCT may have a noninferior humoral response, especially if the

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immunosuppression is tapered to be minimal; however, the need for chronic

immunosuppression, or intermittent high dose suppressive therapy, likely would result in a more

muted protection.

Problems and ideas for future research: when and how to we vaccinate?

Most alarmingly, survivors of pediatric and young adult cancers (PYAC) have an excess

relative risk for HPV-associated malignancies,[55] yet have a low HPV vaccine initiation rate.[56] In

an active clinical trial, 679 adolescent and young adult cancer survivors had an HPV vaccine

initiation rate of 22% for 13-17 year olds and 26% for 18-26 year olds.[57] This is surprising as the

vaccine has been recommended for PYAC survivors by the Children's Oncology Group's Long-

Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult cancer

since 2008.[57,58] One study observed that survivors of PYAC had later sexual debuts, but still

over 90% report sexual activity.[59] Some studies have reported risky sexual behaviors, such as

not using condoms due to perceived infertility from their cancer treatments.[60] When compared

to sibling controls, PYAC survivors engaged in risky sexual behavior at the same rate as their

siblings,[61] yet were less likely to have received a Pap smear within the last 3 years.[62] If PYAC

survivors only see their oncologist, and are less likely to see primary healthcare practitioners or

gynecologists, could this be a reason for the low vaccine and screening rates? Are there

opportunities to increase vaccination and screening in the oncologist's office?

For allo-SCT, the 2015 guidelines from the International Consensus Project on Clinical

Practice in Chronic GVHD provide a 'should generally be offered' HPV immunization

recommendation to young women 12-26 years after the transplantation, if they have not already

received any or all vaccine doses.[63] This recommendation falls well short of stating all allo-SCT

patients should be vaccinated after the transplant, despite their transplanted bone marrow being

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vaccine naïve. When considering which vaccines to include, it is not clear if the vaccine schedule includes the HPV vaccine in the same way other vaccines are recommended 3 to 24 months posttransplant, such as Hepatitis B or pneumococcal conjugate.[64] With changing guidelines, is there any indication that allo-SCT patients still would need 3 doses versus the recommended 2 in the younger patients? A current phase IV clinical trial[65] is underway for safety and efficacy of HPV vaccination 6 to 12 months post allo-SCT with a 3 dose schedule. This study's findings will likely guide better recommendations based on stronger evidence.

Children with an SOT may be at even greater risk for inadequate primary HPV protection due to waning HPV vaccine efficacy because they will require lifelong immunosuppressive medications to avoid organ rejection. These medications may also lead to reactivation of a latent HPV infection. There are several guidelines for management of solid organ transplant patients specific to HPV, but much of the natural history behind these management guidelines is still unknown. HPV vaccine administered 5 months after transplant yielded an overall seroresponse to any HPV type at 62% for the quadrivalent vaccine.[66] Guidelines from the American Society of Transplantation state that vaccination of eligible patients is preferred prior to transplantation, based on the hypothesis that an antibody response to vaccination would be more robust.[67] Could this recommendation be extended to those younger than age 9 and those older than age 26? The corollary question -- how protective is the humoral response as one starts to receive immunosuppressive or dialysis prior to transplant? -- is another unknown. In a recent review, attention is drawn to the need for research in the post transplant period. The authors suggest research studies to better understand the immune response in post transplant patients in order to find optimal periods in which to recommend the vaccine. Coupled with the decrease in vaccine

uptake in the general population, which reduces herd immunity protection, they urge the prioritization of immunizations, including HPV, in transplant patients.[68]

With this background in mind, it is important to ask ourselves to consider different approaches to accelerate prophylactic HPV vaccination among transplant populations. Are there opportunities for the specialist to become the vaccinator in order to increase HPV vaccination rates when children are waiting for transplants? Strategies for vaccination of patients pretransplantation, and a possible need for future revaccination, should be further examined.

Finally, returning to patients who were treated for cancer during their childhood, when examining reasons for low vaccine uptake in these young women, physician recommendation and familial HPV communication were found to be associated with an increased likelihood of vaccine initiation.[69] Another study in PYAD survivors found that younger age at cancer diagnosis (under 15 years old), and a shorter interval from diagnosis to vaccine eligibility, were more likely to start the vaccination series.[70] This may be reflective of primary healthcare practitioners following regular vaccination guidelines or primary healthcare practitioners who are unfamiliar with specific vaccination recommendations for these patients. Other considerations, such as vaccine storage in nonprimary care clinic sites, must also be addressed if oncologists or transplant physicians would initiate a vaccination program.

Problems and ideas for future research: when and how do we screen for HPV-related diseases?

Recognizing that primary and secondary prevention strategies are both integral parts of cancer prevention, we must consider how and when to screen all immunocompromised patients for HPV infections and disease (Figure 1, italics). Recent guidelines suggest that screening for cervical cancer in SOT and SCT patients should mirror the screening of women with HIV.[67,71] However, SCT patients also have a recommendation that a new diagnosis of GVHD should lead

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to more intensive screening that mirrors reinitiation of screening, beginning with repeated yearly exams.[71] Other populations at risk for immunosuppression could benefit from information gained in allo-SCT and SOT recipients, such as those with Lupus or Fanconi Anemia. They may manifest with similar risk for HPV, or require more specific recommendations, in regards to vaccination and screening. The outcomes from variations in screening algorithms will need to be examined in clinical trials and within the context of vaccination status and serologic titers.[72] Observational data from international screening programs that utilize HPV testing can also be analyzed to understand positivity rates and disease over time, and ultimately better guidance on future screening. However, developing an algorithm for screening and management of cancer, SCT, and SOT patients needs to based on the acknowledgement that these patients may inherently have cellular DNA damage and chronic or episodic immune system activation and immunosuppression, all of which could place these patients at greater risk for inferior HPV vaccination protection, accelerated reactivation of a latent HPV infection, poorer clearance of a HPV infection, and rapid progression from infection to dysplasia to cancer.

Discussion

We must understand if there are subpopulations of children and adolescents who may not be completely protected against HPV by vaccination, a primary prevention strategy for the general population that should be universally endorsed. We also must determine if HPV infection, latency, and reactivation are more likely to occur in subpopulations of high-risk children and adolescents, and determine ways to migitate that risk before infection and during disease progression. Future research efforts should focus on each of these groups -- survivors of allo-SCT, all childhood cancers, and SOT -- to better understand the HPV vaccine efficacy in each group, their targeted screening and intervention, their risk of HPV-associated diseases, and

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the possible utility of HPV vaccine boosters. These research efforts will permit a transition from acknowledging the potential inherent risk within these groups to the quantifiable determination of their true risk and the effective migitating actions that will reduce that risk. Current guidance from the Advisory Committee on Immunization Practices on HPV vaccination for adults with preexisting risks provides "shared decision making" instead of clear guidance for populations with underlying risks.[73] Ambiguity in recommendations can lead to both missed vaccination opportunities with the added burden of a lack of insurance coverage. There is great potential in large pediatric national registries, such as the Center for International Blood and Marrow Transplantation, the North American Pediatric Renal Trials and Collaborative Trials, or Improving Renal Outcomes Collaborative, to determine best practices. The single current strategy that we know will protect survivors of childhood cancer in preventing secondary HPV-associated cancers is to achieve a high vaccination rate in the general population; with high vaccination rates, immunosuppressed persons will gain benefit through herd immunity at a minimum. All physicians and healthcare providers should support on-time, routine vaccination of young adolescents and put vaccination of higher risk groups, such as those who are immunosuppressed, front of mind in their day to day practice.

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Figure Legends

Figure 1. The natural history of HPV infection, clearance, latency, dysplasia, and cancers and prevention strategies (in italics) for HPV-associated cancers. A. The natural history and prevention strategies for the general population. B. The differences in natural history (red arrows) and prevention strategies in cancer patients. C. The differences in natural history (green arrows) and prevention strategies in transplant patients.
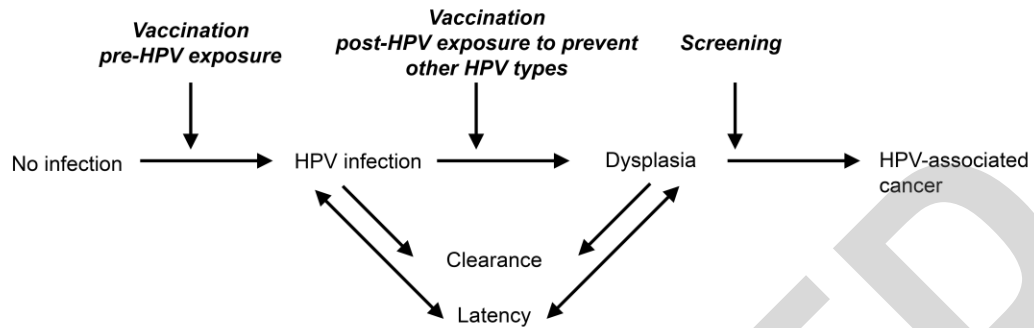
The Supplement Visual Abstract associated with this article will be available at
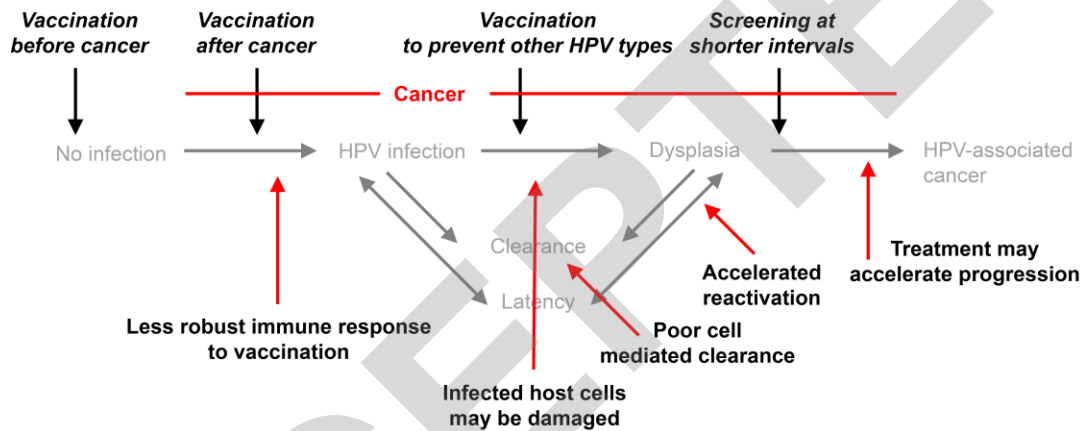
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Figure 1

A Natural history and *prevention strategies* for the general population

B Natural history and *prevention strategies* for cancer patients

C Natural history and *prevention strategies* for transplant patients