Association of Human Papillomavirus Vaccine With the Development of Keratinocyte Carcinomas

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IMPORANCE Keratinocyte carcinomas (KCs), consisting of squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs), are the most common human malignant neoplasms. Several risk factors have been implicated in KC development. For some SCCs, particularly those in immunocompromised patients, human papillomavirus (HPV) may be an important factor.

OBJECTIVE To determine whether quadrivalent HPV vaccination would affect the development of KCSs in immunocompetent patients with a history of multiple KCSs.

DESIGN, SETTING, AND PARTICIPANTS Two patients with a history of multiple KCSs—a man in his 70s (patient 1) and a woman in her 80s (patient 2)—were treated in a private dermatology practice. Each patient received 3 doses of the quadrivalent HPV vaccine at 0, 2, and 6 months in 2013, and both patients underwent full-body skin examinations at least every 3 months. Biopsy-proven skin cancers were recorded for 16 months (for patient 1) or 13 months (for patient 2) after the first dose of vaccine and then compared with the number of biopsy-proven skin cancers recorded over a similar period before the first dose of vaccine. The period of observation was from October 18, 2011, to June 21, 2014.

MAIN OUTCOMES AND MEASURES The numbers of new SCCs and BCCs after the first dose of the quadrivalent HPV vaccine.

RESULTS Patient 1 had a mean of 12.0 new SCCs and 2.25 new BCCs per year before vaccination. After vaccination, he developed 4.44 SCCs and 0 BCCs per year, a 62.5% reduction in SCCs and a 100% reduction in BCCs. Patient 2 had a mean of 5.5 new SCCs and 0.9 new BCCs per year before vaccination. After vaccination, she developed 1.8 SCCs and 0 BCCs per year, a 66.5% reduction in SCCs and a 100% reduction in BCCs. The quadrivalent HPV vaccine was well tolerated by both patients and had no adverse effects.

CONCLUSIONS AND RELEVANCE A reduction of SCCs and BCCs was observed in 2 patients after administration of the quadrivalent HPV vaccine. These findings highlight the possibility that cutaneous SCC development, and perhaps BCC development, may be driven in part by HPV in immunocompetent patients. Human papillomavirus vaccination may represent an efficacious, cost-effective, readily available, and well-tolerated strategy for preventing KCSs.

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Keratinocyte carcinomas (KCs), comprising squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs), represent the most common human malignant neoplasms. For these cancers, cure rates are high, but incidence is rising and the associated direct and indirect costs in the United States alone are staggering—estimated at $2.4 billion even back in 2004. Keratinocyte carcinomas are a chief cause of morbidity after solid organ transplant. Among patients who underwent transplantation, SCC is the most common cancer, with 65- to 250-fold increased incidence in patients treated with calcineurin inhibitors and azathioprine. In these patients and others, multiple skin cancers are not uncommon. Human papillomavirus (HPV) infection, particularly with β-HPV, has been suggested to play a role in the development of SCCs in immunocompromised patients and may partly explain the development of SCCs in patients treated with BRAF inhibitors.

Despite the high morbidity and high cost associated with treatment of KCs, chemopreventive strategies are limited and consist primarily of sunscreen and sun avoidance, nicotinamide, photodynamic therapy, acitretin, and sirolimus. In 2 immunocompetent patients with a history of multiple KCs without known HPV infection, we found that quadrivalent HPV vaccination was associated with a reduction in the development of new KCs. Our observations suggest that HPV vaccination could be an efficacious chemopreventive strategy for patients with a history of multiple KCs.

Report of Cases

Patient 1 was a man in his 70s, and patient 2 was a woman in her 80s. Patients were considered immunocompetent on the basis of an absence of immunodeficiency, history of opportunistic infection, autoimmune disease, systemic malignancy, or treatment with immunomodulatory medications. Both patients—treated in a private dermatology practice—received 3 doses of the quadrivalent HPV (qHPV; Gardasil) vaccine at 0, 2, and 6 months and full-body skin examinations at least every 3 months for 16 months (patient 1) and for 13 months (patient 2). The number of biopsy-proven skin cancers was recorded for at least 12 months after the first dose of the qHPV vaccine was administered, and that number was compared with the number documented over an equivalent period before the first qHPV dose. Biopsy-proven skin cancers were treated with surgery. During the observation period after the first dose of the vaccine, the patients were not treated with oral nicotinamide, topical fluorouracil cream, or topical imiquimod cream. Actinic keratoses were treated with cryotherapy. There were no obvious changes in either patient's immune status.

Prior to vaccination, patient 1 had a mean of 12.0 new SCCs (87.5% SCC in situ, 6.25% well-differentiated SCC, and 6.25% SCC, keratoacanthoma-type) and 2.25 new BCCs per year. After vaccination, patient 1 developed a mean of 4.4 SCCs (100% SCC in situ) and 0 BCCs per year. This result represents a 62.5% reduction in SCCs and a 100% reduction in BCCs within the observation time of 16 months before and 16 months after the first dose of the qHPV vaccine (Figure). Prior to vaccination, patient 2 had a total of 5.5 new SCCs (100% SCC in situ) and 0.9 new BCCs per year. After vaccination, the patient developed 1.8 SCCs (100% well-differentiated SCCs) and 0 BCCs per year, representing a 66.6% reduction in SCCs and a 100% reduction in BCCs during the observation time of 13 months before and 13 months after the first dose of the qHPV vaccine (Figure). Neither patient had cutaneous warts or oral papillomas. There was no change in UV exposure during the period of observation. The vaccine was well tolerated without adverse reactions.

Discussion

To our knowledge, this is the first report of qHPV vaccination as chemoprevention for KCs. Because HPV has been implicated in SCCs in immunocompromised patients, we offered the...
vaccine to these patients because of potential HPV cross-reactivity. Vaccination resulted in a reduction in both SCC and BCC development in patients without known HPV infection. The skin-tropic β-HPV types that have been associated with SCCs and actinic keratoses include HPV-5 and HPV-8 mostly but also types 12, 14, 15, 24, 25, 36, and 43. This qHPV vaccine is protective against the α-HPV types 6, 11, 16, and 18, which cause most cases of genital warts and contribute to the development of anogenital carcinomas. These HPV subtypes are not associated with cutaneous malignant neoplasms; however, the reduction in SCCs and BCCs after vaccination was substantial in our 2 patients. Our observations suggest the possibility that SCC, and perhaps BCC, development may be driven by HPV or mechanisms shared with HPV. Although HPV has been identified as a risk factor for SCCs in immunocompromised patients, its association with SCCs in immunocompetent patients and BCCs in any patient population is less clear. Our observations identify a possible correlation between both types of KSs and HPV in immunocompetent patients, particularly elderly patients who have had significant sun exposure.

Evidence linking HPV to KSs is accumulating. The presence of HPV in warts, actinic keratoses, and cutaneous SCCs in immunocompromised patients, especially immunocompromised patients after solid organ transplant, has been well documented. Recently, studies have shown that HPV may be a risk factor for the development of SCCs in some immunocompetent patients, particularly in patients who have a tendency to develop sunburns and are seropositive for multiple HPV types.

The principal risk factor for skin cancer development is UV radiation. UV light directly damages DNA, causing the formation of mutagenic pyrimidine dimers and disrupting DNA repair mechanisms. Studies have shown a higher prevalence of HPV DNA in sun-exposed skin rather than in non-sun-exposed skin, suggesting possible synergism between UV light and HPV. In one study, transgenic mice expressing the HPV viral oncogenes E6 and E7 in the basal layer of the epidermis were irradiated with UV light. These transgenic mice developed actinic keratoses and cutaneous SCCs, while their wild-type counterparts that did not express E6 and E7 oncogenes did not. Clearly, HPV has the ability, in some settings, to initiate and accelerate the early stages of skin tumorigenesis by acting as a cocarcinogen. Human papillomavirus oncoproteins may do this directly by disrupting DNA repair or apoptotic mechanisms and causing cells to become more vulnerable to UV radiation-induced damage. In addition, UV light may cause a transient immunosuppressive effect in skin, permitting HPV to escape the immune system.

Reports that HPV may be involved in the development of BCC are rare, and their results are conflicting. Thus, the observed effect on BCCs was unexpected. Molecular mimicry or a nonspecific immune response is a potential explanation supported by several reports, in which recalcitrant oral papillomas and chronic cutaneous warts resolved completely after qHPV vaccination. Another possible explanation is that vaccination results in the production of cytotoxic T cells and cross-protective immunoglobulins.

An effective strategy to reduce the development of KSs in patients with a history of multiple cutaneous tumors is an urgent but unmet medical need. The potential for HPV vaccination to prevent the development of KSs in high-risk patients is an extremely appealing notion. Clinical trials are necessary to assess the safety and efficacy of HPV vaccination as a chemopreventive strategy in both immunocompetent and immunocompromised patients. Translational studies designed to better understand the pathogenesis of HPV-induced tumors and their responsiveness to HPV vaccination in diverse patient populations will provide additional insight for future studies.

Conclusions

Human papillomavirus vaccination resulted in a reduction of SCCs and BCCs in 2 immunocompetent patients with a history of multiple skin cancers. Our observation provides evidence that SCC and BCC development may be driven, at least in part, by HPV in some immunocompetent patients. If our preliminary observations in these 2 patients are supported by large, well-designed clinical trials, HPV vaccination may become an efficacious, cost-effective, and readily available strategy for the prevention of KSs.