Treasure Hunt for Human Papillomaviruses in Nonmelanoma Skin Cancers

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The article by Shamanin et al. (1) in this issue of the Journal reports the detection of a wide spectrum of human papillomaviruses (HPVs) in nonmelanoma skin cancers from both immunosuppressed and nonimmunosuppressed subjects. The high prevalence of HPV DNA detected in squamous cell carcinomas (65%) and basal cell carcinomas (60%) of immunosuppressed patients and the moderate prevalence in lesions from nonimmunosuppressed patients (31% and 36%, respectively) suggest a potential role for HPV infection in the etiology of these lesions. Although Shamanin et al. do not address the role of these HPVs in the lesions in either epidemiologic or molecular terms, they do set the stage for the next phase of investigations.

The take-home message from the study by Shamanin et al. (1) and from a recent study by ter Schegget’s group (2) is that a wide diversity of HPV types can be detected in cutaneous neoplastic lesions of the skin, particularly in those from immunosuppressed individuals. The one important caveat in these studies is that HPV detection by enhanced polymerase chain reaction (PCR) detection methods is not necessarily equivalent to infection with HPV. Shamanin et al. have developed a very complex method for the molecular amplification and characterization of HPVs in the skin lesions. Even when one is familiar with HPV PCR methodology, it is hard to follow the complicated strategy employed in which multiple primer pairs, reamplification, and nested PCR were used (1,3). The authors, however, provide convincing data that they, in fact, have detected a large group of new HPV DNA types. This proof is in the sequences.

HPVs are typed or classified according to their genome sequence, since standard methods used in virology (i.e., culture and/or serology) have not proved efficacious for HPVs (4). The identification of a broad spectrum of HPVs is dependent on the PCR primer system used. Thus, using a comprehensive PCR system (1,3), Shamanin et al. purposely searched for a group of new viruses. The final detection of an HPV was based on the sequence of the PCR product. This is clearly the strength of the study. The challenge for molecular virologists, however, will be to develop a simpler PCR strategy for the detection of cutaneous HPVs. Development of such a strategy will now be facilitated by a growing database of cutaneous HPV sequences, which should allow the design of consensus primers for PCR. For example, the availability of consensus primers that amplify a broad spectrum of HPV types in the genital tract has been instrumental in revolutionizing the molecular epidemiology of cervical HPV infection and solidifying the role that these viruses play in cervical cancer (for review, see (5-7)). Prior to use in epidemiologic studies, however, the PCR system will need to be validated (8).

Many of the skin lesions described by Shamanin et al. (1), such as keratoacanthomas, resemble warty, hyperplastic lesions, and pathologists reviewing such cases frequently observe cytologic changes resembling the cytopathic effects of HPV (koilocytosis-like). Many squamous intraepithelial lesions in the skin and in other sites, such as the laryngeal mucosa, resemble those described in the genital tract. Basal cell carcinoma is generally distinctly different from squamous cell carcinoma;
however, pathologists recognize that basaloid lesions frequently have increased amounts of keratinization, and they have used the term "basso-squamous" to describe them. Although keratinizing lesions of skin more often resemble warty lesions known to be associated with HPV, the prevalence of HPV infection was similar among the basaloid and the squamous lesions in the study by Shamanin et al. (1). This finding has an analogy with lesions in the genital tract, where carcinomas in situ, whether of the keratinizing type or of the nonkeratinizing basaloid type, contain similar HPV types despite histopathologic differences.

The leading paradigm of HPV-associated cancer is that between cervical HPV infection and the subsequent development of cervical intraepithelial neoplasia (CIN) and cancer. Infection precedes the development of premalignant lesions, and HPV can be detected in the majority of cervical cancer tissue (reviewed in [9]). Moreover, a specific subset of mucosal HPV types can be found in cervical cancer and high-grade CIN lesions (7,10,11). In contrast, the spectrum of HPV types amplified from the skin cancers is difficult to interpret. In addition, the virus types detected in the immunosuppressed and in the nonimmunosuppressed populations were distinctly different, and neither type was similar to the HPV types reported in the cancers arising in epidermodysplasia verruciformis (12). Furthermore, the observed spectrum of HPV types was different from the epidermodysplasia verruciformis-associated HPV types detected in cutaneous cancers from a different group of renal transplant patients (2). Unexpectedly, many of the virus types (oncogenic and nononcogenic) detected in the genital tract were seen in these skin lesions.

The majority of skin lesions studied, both squamous intraepithelial (e.g., carcinoma in situ) and invasive skin lesions, are those that involve the squamous epithelium of sun-exposed areas of the skin. The natural history of these lesions is much like that of their genital tract counterparts, which go through a long precancerous phase before progressing to invasive carcinoma. One important difference between the cervix and skin, however, might be the attributable risk of cancer associated with HPV infection. In the cervix, it appears that infection with an oncogenic HPV is necessary but not sufficient. In contrast, in the skin, HPV might not be necessary but may serve as a risk factor or cofactor along with solar radiation and/or other environmental exposures.

The data presented in the article by Shamanin et al. (1) raise a number of interesting questions about the biology of, and the relationship between, the HPV types detected and the associated skin neoplasms. In particular, one immunosuppressed patient had recurrent lesions that had HPV types detected that were different from those found in the primary lesion. This result was somewhat surprising, since the recurrent skin cancers had a histopathology similar to that of the primary cancers, yet these lesions contained different viruses. If the original tumors were not completely excised, one would expect the same viruses to be present in the recurring tumors. Are the dysplastic squamous intraepithelial lesions of the skin somehow more susceptible to new infection with different HPV types? Are these viruses truly pathogenic? Did they cause the lesions, or were they caused by a secondary infection? Are the recurring tumors truly recurrences rather than new, independent primary tumors with new virus types occurring in an injured and inflamed surgical excision site? These interesting issues need to be examined.

The next phase of research will be to develop a robust PCR system for the amplification of the broad spectrum of cutaneous HPV types. Such a methodology could then be implemented in molecular epidemiology studies and should allow determination of whether a limited set of cutaneous viruses is associated with skin cancers and what is the natural history of infection with these HPV types. The demonstration that HPV infection is causally related to skin cancer awaits rigorous epidemiologic investigation. If the answer is "yes," we will again turn to the molecular virologists to find out how. Moreover, if cutaneous cancers are in fact related to HPV infection, then they may be amenable to prevention with prophylactic vaccines or treatment with therapeutic vaccines.

References

It's Time to Take 5

Add sliced bananas or peaches to your cereal.

Keep a tangerine, apple or banana on your desk for a midday snack. Pick one up from a sidewalk fruit vendor or convenience store on your way to work.

IT'S EASY TO EAT FIVE OR MORE SERVINGS OF FRUITS AND VEGETABLES A DAY...

Keep a bowl of fruit on your kitchen counter or table, within easy reach.

Pour fruit juice in your ice cube tray and add toothpicks for homemade fruit pops.

Add more vegetables to your dinner tonight. Try chopped zucchini, cauliflower, carrots and green peppers.

Don't hide fruits and vegetables in your crisper. Keep them visible on the top shelf in your refrigerator.

Serve kids a glass of 100% orange, grapefruit or tomato juice for breakfast.

Pick up pre-cut vegetables or ready-to-eat salads at your supermarket's produce section or salad bar.

Drink a glass of 100% fruit juice after a ball game or workout.

Fruits & Vegetables eat 5 A DAY

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