

# Human Papillomaviruses May Contribute to Post-Organ Transplant Skin Cancer

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Image by Greg Brennan

Drs. Margaret M. Madeleine (left) and Denise A. Galloway (right) led the study investigating the risk of squamous cell skin cancer due to HPV infection after organ transplant.

After organ transplantation, patients are routinely placed on immunosuppressive therapy to prevent graft rejection. This immunosuppression substantially elevates these patients' risk for cancers with a viral etiology, including Kaposi's sarcoma (human herpesvirus 8) and non-Hodgkin's lymphoma (Epstein-Barr virus), presumably by reducing the immune control of these viruses. Squamous cell skin cancer (SCSC) is the most frequent cancer to develop in patients post-transplant; however, it is an open question whether this increased frequency of SCSC is virus associated. In a study recently published in *Cancer Medicine*, Drs. Margaret M. Madeleine (Public Health Sciences Division) and Denise A. Galloway (Human Biology Division) along with their collaborators demonstrate that some betapapillomaviruses may contribute to the increased occurrence of SCSC in patients post-transplant.

There are more than 100 known human papillomaviruses (HPV) and polyomaviruses (HPyV). Mucosal HPVs such as HPV16 and HPV18 are well established as oncogenic viruses causing cervical, anogenital, and oropharyngeal cancers, and cutaneous HPVs are thought to cause specific types of SCSC. Similarly, Merkel cell polyomavirus is the causative agent of the skin cancer Merkel cell carcinoma. In addition, rare mutations in human genes *TMC6* and *TMC8* may increase

patient susceptibility to HPV infection and also increase the risk of certain HPV pathologies including SCSC. The researchers conducted a nested case-control study to determine whether these factors also increase the risk of post-transplant SCSC.

The researchers tested pre-transplant serum for antibodies to assess prior exposure to multiple HPVs and HPyVs from 172 patients who developed SCSC after organ transplantation and 332 matched control patients. Most patients in this study, both cases and controls, were positive to multiple polyomaviruses, and the researchers did not find an increased risk of SCSC associated with any HPyV examined. Patients with antibodies to HPV15, HPV20, and HPV36 trended towards an increased risk of SCSC, but this association was not statistically significant. However, patients with antibodies to cutaneous papillomaviruses HPV37 (OR 2.0, CI 1.2-3.4, P = 0.005) or HPV1 (OR 1.9, CI 1.1 – 3.1, P = 0.042) had a higher risk of SCSC than seronegative patients.

To assess the contribution of genetic variation in the *TMC* genes to the development of SCSC, the researchers genotyped *TMC6* and *TMC8* in the patients using DNA collected at the time of the interview. They found three *TMC8* variants that were associated with increased seropositivity to betaHPVs in control patients. However, they did not identify any *TMC6* and *TMC8* alleles that significantly altered the risk of SCSC, although two *TMC6* variants trended towards a decreased risk of SCSC.

This current study suggests that at least some cutaneous HPVs, such as HPV1 and HPV37, may increase the risk of SCSC as well. Moving forward, the researchers are planning a prospective study, taking multiple samples both before and after immunosuppression to further investigate the link between HPV and SCSC.

[Madeleine MM, Carter JJ, Johnson LG, Wipf GC, Davis C, Berg D, Nelson K, Daling JR, Schwartz SM, Galloway DA.](#) 2014. Risk of squamous cell skin cancer after organ transplant associated with antibodies to cutaneous papillomaviruses, polyomaviruses, and *TMC6/8* (*EVER1/2*) variants. *Cancer Med.* Epub ahead of print. doi: 10.1002/cam4.280.