Letter to the Editor

Dear sir/madam

It is with great interest we read the Invited Medical Review entitled “National Prevalence of Oral HPV Infection and Related Risk Factors in the U.S. Adult Population” by AE Sanders, GD Slade and LL Patton and published in Oral Diseases: (2011) doi:10.1111/j.1601-0825.2011.01892x Pubmed.

We congratulate the authors on their work which extrapolates data from 4,846 adult subjects who had oral rinses examined for the presence of any HPV type to the first nationally representative estimates of oral HPV prevalence in the United States adult population. However, we feel it important to point out several issues which may otherwise result in over-interpretation of the significance of the data, especially from a health care providers’ point of view.

1. Firstly, in the title of the paper, use of the word ‘infection’ may give an impression that the population with detectable virus in their oral samples showed clinically observable manifestations attributable to HPV. Strictly, the word infection means the presence of a potential pathogen and of disease caused by that presumptive pathogen. A distinction between an infected individual and a carrier must be made. Furthermore, carriage and shedding of HPVs may be transient.

2. The so-called high-risk genotypes of HPV [principally HPV-16 and -18] are undoubtedly important in cancers of the head and neck, particularly squamous cell carcinomas of the tonsil and base of tongue (Gillison M, Koch W, Capone R, Spafford M, Westra W, Wu L et al 2000; Herrero R, Castellsague X, Pawlita M, et al 2003; Gillison M 2004). Indeed HPV-related oropharyngeal carcinomas are now recognised as a distinct subtype, which respond better to treatment than others. (Gillison ML, Koch WM, Capone RB, Spafford M, Wesra WH, Wu L, et al 2000, Li W, Thomson CH, Obrien CJ, McNeil EB, Scoyer RA, Cossart YE et al 2003; Fakhryh C, Westra WH, Li S, et al 2009, Rischin D, Young RJ, Fisher R, et al 2010). However, it is important to understand the molecular events which take place in HPV-associated carcinogenesis. Integration of an oncogenic strain of HPV into host genome is essential. Human papillomaviruses exert their oncogenic role after DNA integration, gene expression of E5, E6 and E7 loci and p53/pRb host protein suppression. These events lead to increased cell proliferation and contribute to malignant transformation. (Thomas M, Pim D, Banks L, 1999; Kadaja M, Isok-Pass H, Laos T, Ustav E, Ustav M, 2009).

In the present study, samples were evaluated for HPV using polymerase chain reaction (PCR) and DNA sequencing with a view to identifying HPV types. This shows only the presence of the virus with no indication of genomic change. Genomic integration occurs at low frequency, so the mere presence of HPV in saliva does not necessarily place an individual at a greater risk of developing cancer in the upper aero-digestive tract (Mark Lingen 2010).

3. Thought also needs to be given to mode of transmission. The literature on cervical cancer and HPV-related ano-genital cancer points to the fact that transmission of virus is primarily through “skin to skin” contact during sexual intercourse. [zur Hausen H 1994; zur Hausen H 2002, IARC 2007]. With regard to the association of HPV to oropharyngeal cancer, there is good indirect evidence that oral carriage is acquired through direct oral-genital contact (Anaya-Saavedra G, Ramirez Amador V, Irgoyen-Camacho ME, Garcia-Cuellar CM, Guido-Jiminez M, Mendez-Martinez R et al 2008). HPV does not replicate in saliva. It requires terminally differentiated squamous epithelial cells to

replicate: it is in these cells that the virus retains a high copy number, where viral genes are expressed, progeny viruses are produced and shed, in this case into oral fluids. There is as yet no evidence that saliva acts as an HPV transmission vehicle for oral or genital contamination, though given the presence of shed epithelium in oral fluids this is quite possible.

4. Finally, it is important to distinguish between a *marker* or an indicator of disease and a true risk factor. A risk factor should be directly part of the causal chain of disease, whereas a risk indicator or risk marker is associated with the disease and may or may not be causal. (Johnson NW 2003). In carcinogenesis, not all known risk factors have a direct aetiological role: Some may be contributory or predisposing factors [such as diets poor in antioxidants or trace elements]. Simply detecting HPV in tumour cells or detecting serum antibody markers of past or present HPV carriage does not necessarily demonstrate the direct involvement of HPV in the development of a given tumour (Snidgers PJ, van den Brule AJ and Meijer CJ 2003). In our opinion it is premature to draw conclusions such as “there would be a 4.7% reduction in incidence rate of head and neck cancer in the United States if oncogenic HPV infection could be prevented”!

5. In conclusion, whilst it makes sense to promote good hygiene in sexual behaviour, as in oral or food hygiene, for the maintenance of health, we submit that current knowledge does not permit the quantitative conclusions proffered in this interesting paper.

Yours faithfully,

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