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## Platinum Priority – Editorial and Reply from Authors

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# Oral Mucosa and Urethroplasty: It's Time to Change

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In this issue of *European Urology*, Kero and colleagues reported on the Finnish Family HPV Study, a longitudinal cohort study looking at the prevalence and incidence of oral human papillomavirus (HPV) infection in healthy men followed for 7 yr [1]. The most relevant findings they reported were a high prevalence of male oral HPV, ranging from 15% to 31%, and the confirmation that the most frequent genotype was HPV-16. In their conclusion, they advise the reader that oral mucosa is an important reservoir for the virus.

These data raise the following questions, which we will address below: (1) What does oral mucosa HPV infection have to do with urology? (2) Why should *European Urology* readers be interested in it? (3) What was the *European Urology* editor thinking when he decided to cover this topic?

HPV is the most common sexually transmitted infection worldwide [2] and, as such, should receive more attention from urologists. The overall HPV transmission rate was estimated to be 58.8 per 100 person-years from penis to cervix and 20.8 per 100 person-years from cervix to penis [3]. Less is known about oral HPV transmission. According to a recent survey, oral HPV infection is three times more common in US males than females [4]. As part of the National Health and Nutritional Survey, 5579 males and females aged 14–69 yr were screened for oral HPV. Analysis showed that 10.1% of men and 3.6% of women tested positive for the infection. Now Kero et al. have reported a higher prevalence, and their data support the theory that men are the primary risk group for oropharyngeal HPV-positive cancer [1].

Is this topic relevant for urology? Absolutely. The increase in HPV-positive cancers of the oropharynx in males has risen by 225% since 1980, and this increase might be attributable to the increasingly widespread practice of oral sex [4]. Urologic medical associations and urologic journals need to take

active roles in educating the younger population to prevent widespread HPV infection. Urologists should take an active role in presenting this medical information effectively, instead of leaving this subject to be discussed widely only in the media. In January 2011, BBC Three, a UK television channel with a target audience of 16- to 34-yr-olds, screened *Is Oral Sex Safe?*, a documentary on HPV and the oropharyngeal cancer that it causes. The program discussed the pros and cons of including boys in the HPV vaccination program. However, this is a far too complex subject to be adequately addressed in an hour-long documentary. Should urologists play a reference role? We believe they should. Should urologists recommend HPV vaccines for males? In October 2011, an advisory board to the US Centres for Disease Control and Prevention (CDC) recommended that the HPV vaccine be extended to males aged 9–21 yr (the CDC already recommends that females aged 9–26 yr routinely be vaccinated) [4]. This makes sense, but the efficacy of the HPV vaccine in tackling oral infection has yet to be clinically proven.

With the recognition that HPV is a causative agent in the development of cervical cancer, some studies have supported the hypothesis that circumcision protects against HPV infection and cervical cancer in female partners [5]. The prevalence of circumcision varies widely in both developing and developed countries. In view of the increased evidence from randomised trials that male circumcision reduces the risk of some sexually transmitted viral infections in male and female partners, urologists should consider male circumcision in high-risk populations. Recent findings add important evidence to the promotion of male circumcision in countries without well-established programmes for cervical screening. Additional interventions to reduce HPV infection, such as provision of vaccines for HPV prevention in men, are essential to reduce invasive cervical cancer worldwide. Male

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circumcision is associated with slight reductions in high-risk HPV, while licensed HPV vaccines effectively protect against only a limited number of HPV types. Therefore, the two interventions are likely to have important synergistic effects.

Oral mucosa still represents the most popular substitute material for urethral reconstruction, and from 1966 to 2006, 1267 studies were reported in the literature on the use of oral mucosa in reconstructive surgery [6], including 1353 cases involving oral mucosa-based urethroplasty for the repair of defects associated with urethral strictures and hypospadias/epispadias [6]. In these reports, 724 urethroplasties (53.5%) were performed for urethral strictures, while 629 (46.5%) were performed for hypospadias/epispadias repair [6]. Reconstruction for urethral stricture and hypospadias/epispadias was successful in 418 cases (66.5%) and 553 cases (76.4%), respectively [6].

Numerous articles have been published in the last 5 yr reporting a large number of patients treated using oral mucosa transplantation in the urethra and including a longer follow-up. Markiewicz et al. reported a detailed list of normal oral conditions that may necessitate delaying oral mucosa harvest until site conditions improve [7]. According to these authors, other pathologic oral conditions are strict contraindications for oral mucosa harvesting, although the presence of HPV in oral mucosa was not investigated [7]. In 2010, Barbagli et al. reported on a group of 350 patients with oral mucosa harvested from the cheek. Their results suggest that patients having an ongoing infectious disease of the mouth (Candida, varicella virus, herpes virus) were informed that the urethral reconstruction would be performed using genital or extragenital skin because these pathologic oral conditions are contraindications for oral mucosa harvesting [8].

Until now, the literature has not provided any indication of the prevalence of HPV infection in oral mucosa or any indication of the risk of transmission after urethral reconstruction. According to the study and data reported by Kero et al. [1], all patients scheduled for oral mucosa harvesting for urethral reconstruction should also be preoperatively screened for HPV via oral scrapings. Should patients showing a positive oral HPV test be excluded from harvesting of oral mucosa? The answer to that question is both yes and no. A rational approach to these patients would be to delay both harvesting and transplanting the oral mucosa and to repeat the oral scrapings for HPV testing a few months later. If patients test positive after the second oral HPV test, genital skin would be the preferred substitute material for urethroplasty.

Do patients who undergo oral mucosa urethroplasty really risk developing genitourethral HPV-related carcinoma or transmitting HPV infection to their partners? Unfortunately, the literature does not provide any information about the incidence of HPV-related disease in patients who undergo transplantation of oral mucosa into the urethra. Starting in 1992, oral mucosa was widely transplanted into the urethra in numerous patients all over the world, with >20 yr of follow-up [6]. So far, the literature has failed to report the incidence of HPV-related genital carcinoma in patients who undergo transplantation of oral mucosa into the urethra. No



**Fig. 1** – The autologous tissue-engineered oral mucosal graft (MukoCell; UroTiss, Dresden, Germany).

studies are available in the literature about the incidence of sexually transmitted HPV disease in the partners of patients who undergo oral mucosa transplantation to the urethra. From 1995 to 2012, we have transplanted oral mucosa in 853 patients requiring penile or bulbar urethroplasty, and no incidence of HPV-related carcinoma has been shown in these patients (all data can be downloaded from [www.urethralcenter.it](http://www.urethralcenter.it)). The study by Kero et al. [1] suggests introducing some changes in our daily clinical practice in patients requiring oral mucosa harvesting, namely,



**Fig. 2** – The tissue-engineered oral mucosal graft is ready to be transplanted inside the bulbar urethra as an inlay patch.

implementing a preoperative screening for oral HPV by taking oral scrapings from all patients.

Ultimately, using tissue-engineered material for urethroplasty might solve these issues. Tissue-engineered oral or urethral mucosa is now available in some countries, and these technologies are ready to be used worldwide. It is well known that tissue-engineered materials are safer than original tissue as far as the transmission of bacterial, viral, and other infectious agents is concerned. At present, we have performed 12 bulbar urethroplasties using a tissue-engineered oral graft (Figs. 1 and 2), and the success rate was 100% [9]. We are now starting to use this technique as standard procedure in any anterior urethroplasty, thus avoiding problems related to harvesting oral mucosa from the patient, including the risk of infection. For many years, oral mucosa represented an amazing source of substitute material for urethral reconstruction, and many patients have been successfully treated. It is now time to change as laboratory-engineered materials are available for our patients and will reduce complications, morbidity, and other risks of transmitted diseases [9,10].

**Conflicts of interest:** The authors have nothing to disclose.

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## Platinum Priority

**Reply from Authors re: Guido Barbagli, Salvatore Sansalone, Massimo Lazzeri. Oral Mucosa and Urethroplasty: It's Time to Change. *Eur Urol* 2012;62:1071–3**

**Oral Mucosa as a Reservoir of Human Papillomavirus: Implications for the Use of Oral Mucosal Transplants in Urethroplasty**

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In this issue of *European Urology*, we reported the prevalence, genotype distribution, and incidence of oral human papillo-

mavirus (HPV) infections among healthy men followed up for 7 yr in the prospective Finnish Family HPV Study cohort [1]. A high prevalence of oral HPV, varying from 15.1% to 31.1%, was detected during the follow-up, similar to what was previously reported in the urethral and/or semen samples of the same males at baseline [2]. These observations have several potentially important implications, as suggested but not extensively discussed in our paper [1].

First, these data substantiate our past hypothesis on oral mucosa as a potential source of HPV transmission. However, the anatomic sites of asymptomatic or latent HPV infection in the oral cavity are not known. We have speculated that gingival pocket epithelia could be one of these HPV reservoirs. Oral mucosa might be an even more important HPV reservoir among males than females because of the differences in their genital epithelia. The prevalence of HPV infection in the genital tract is age-related, being most prevalent in individuals aged 20–25 yr. A recent study from the United States supports the idea that oral HPV would be most prevalent among males >55 yr [3]. Second, elucidating the correlation between asymptomatic HPV carriage and HPV-associated disease (in both genders and in all age groups) is essential to accurately estimate the disease burden that is potentially preventable by the prophylactic HPV vaccines [2].

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