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A systematic review of the prevalence of mucosal and cutaneous human papillomavirus types

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ABSTRACT

Systematic reviews of the prevalence of different types of Human Papillomavirus (HPV) across a broad range of disease grades from normal to cancer are essential to gain basic knowledge of how widespread infections with the different HPV types are, and to provide information on the possible carcinogenicity of different HPV types. For HPV types that infect human mucosa, of which 12 are established causes of cervical cancer, we present the results of a systematic review and meta-analysis of 47 HPV types in cervical samples across the entire range of cervical diagnoses from normal to cervical cancer, restricted to studies using a number of well characterized PCR assays.

For the cutaneous HPV types, which have been linked to the development of squamous cell carcinoma of the skin, their presence has been measured in a variety of different sample types and by assays with variable performance. Therefore, we restricted a systematic review of their prevalence to studies that assayed for cutaneous HPV infection in a case-control format.

Introduction

Human papillomaviruses (HPVs) are a large and diverse group of viruses with 174 completely characterized types, with new HPV types being continuously found (Bernard et al., 2010; Bottalico et al., 2011; Chen et al., 2007; Chouhy et al., 2010; Ekstrom et al., 2011; Ekstrom et al., 2010; Foulongne et al., 2012; Kohler et al., 2011; Li et al., 2012; Nobre et al., 2009; Vasiljevic et al., 2008; Vasiljevic et al., 2007). There are five major HPV genera: Alphapapillomavirus, Betapapillomavirus, Gammapapillomavirus, Mu papillomavirus and Nu papillomavirus. HPVs infect epithelial cells in genital mucosa (alphapapillomaviruses only), oral mucosa or skin (representatives of all five genera). HPV types belonging to different genera have less than 60% similarity, based on the nucleotide sequence of the capsid protein L1. Different viral species within a genus share between 60 and 70% similarity. A novel HPV type has less than 90% similarity to any other HPV type (de Villiers et al., 2004). Novel HPV types are given a number only after the whole genome has been cloned and deposited with the International HPV Reference Center (Bernard et al., 2010; de Villiers et al., 2004), which was established in Heidelberg by Dr. Ethel-Michele deVilliers in 1985 and transferred to the Karolinska Institutet in 2012 (www.hpvcenter.se).

HPVs cause a wide range of diseases from benign lesions to invasive tumors (Duensing and Munger, 2004; Munoz et al., 2003). In 2009, an International Agency for Research on Cancer (IARC) working group classified 12 mucosal HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) as carcinogenic to humans (Group 1) (Schiffman et al., 2009; IARC, 2012) for their association with cervical cancer, hereafter also referred to as high-risk (HR) HPV types. These 12 types cluster together in the same evolutionary branch or "high-risk clade" that includes *Alphapapillomavirus* species groups 5, 6, 7, 9 and 11. Eleven additional types in the high-risk clade were classified as possibly carcinogenic (Group 2B) based upon their phylogenetic relatedness to Group 1 types,with the exception of HPV68, which was upgraded to probably carcinogenic (Group 2A). Other mucosal HPV types in the Alphapapillomavirus genus e.g. HPV6 and 11, can cause benign genital condylomas (Bernard et al., 2010).

The cutaneous HPV types are commonly found in several skin lesions such as benign skin warts (Pfister and Ter Schegget, 1997), actinic keratoses (AKs), non-melanoma skin cancers (NMSCs) (Curado et al., 2008) and keratoacanthomas (KAs) (Asgari et al., 2008; Forslund et al., 2003a). Cutaneous HPV types are also commonly detected on healthy skin (Forslund et al., 2004).

NMSCs such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are two of the most prevalent cancers among Caucasian populations worldwide (Oberyszyn, 2008). Ultraviolet

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radiation is a well-known risk factor (Alam and Ratner, 2001), but there may also be other risk factors (Boukamp, 2005; Reichrath, 2006). The increased incidence of SCC in immunocompromised individuals has suggested that an infection may be involved (Berg and Otley, 2002; Boukamp, 2005; Grulich et al., 2007; Lindelof et al., 2000), with HPV being the most commonly studied candidate infectious agent (Asgari et al., 2008; Forslund et al., 2007). Skin samples from SCC, AK, seborrheic keratosis (SK), and BCC commonly contain multiple HPV types, but typically at very low viral loads (Ekstrom et al., 2010; Forslund et al., 2003a, 2003b; Kullander et al., 2008; Vasiljevic et al., 2007, 2008). Cutaneous HPV types have also been implicated in the etiology of squamous-cell carcinoma of the conjunctiva (Ateenyi-Agaba et al., 2010).

Because of the extreme diversity of HPV types, it is an enormous undertaking to obtain an exact epidemiologic definition of which individual HPV types are associated with which diseases. In the field of mucosal HPV types, the use of cross-sectional meta-analyses across different disease grades have long been key to describing HPV type-specific prevalences and establishing the causality of individual HPV types with cervical cancer (Guan et al., 2013; Schiffman et al., 2009). Hence, in the present paper, we expanded a recently published meta-analysis that reported the prevalence of the 13 established or probably carcinogenic HPV types across the full spectrum of cervical diagnoses from normal cytology to cancer (Alam et al., 2003; Guan et al., 2013) to describe all other mucosal HPV types, many of which have been tested for in a smaller number of studies and samples than the most frequent high-risk types.

We reasoned that a systematic review of type-specific prevalences might be useful also for the cutaneous HPV types. However, the spectrum of pre-malignant lesions is less well understood in the skin than in the cervix. In addition, in the field of cutaneous HPV types, the variety in different types of samples and assays used meant that the simple pooling of prevalences from unmatched studies might be misleading. We therefore present a systematic review restricted to case-control studies that have investigated exposure to cutaneous HPV types in skin cancer cases and controls. Differences in types of sample and assays used would then be affecting both cases and controls in different studies, and could be adjusted for. Although this design is not bias-free, e.g. if assays have low specificity or non-informative types of samples have been tested, these biases will typically be conservative, biasing any association towards the null.

Results

Mucosal HPV types

Four hundred and twenty-three studies met eligibility criteria, including a total of 371,951 eligible women. HPV type-specific prevalence is presented for 47 mucosal HPV types across eight grades of cervical diagnosis in Table 1. Overall HPV prevalence increased with increasing severity of cervical disease from 12.6% in normal cytology to 89.5% in ICC (Table 1). HPV16 was by far the most frequently detected type in every grade. Among women with normal cytology, type-specific prevalence ranged from 0.4 to 2.6% for Group 1 (HR) types, from 0.1 to 1.1% for Group 2A/2B types and from <0.1 to 1.1% for Group 3 types.

All 13 HPV types classified as established or probably carcinogenic (Group 1/2A) by IARC were more commonly found among patients with ICC than among subjects with normal cytology (Table 1). Indeed, the prevalence of HPV16, HPV18 and 45 were higher in ICC than in any other grade of cervical diagnosis. Other carcinogenic types, however, were more frequently detected in intermediate cervical diagnoses than in ICC. Particular examples included HPV51 detected in 9.4 and 8.1% of LSIL and CIN1 respectively compared to only 1% of ICC, HPV52 detected in 10.1, 14.1 and 9.6% of CIN1, 2 and 3 respectively, compared to 3.2% of ICC, and HPV31 detected in 10.0 and 10.8% of CIN2 and CIN3 respectively compared to 3.5% of ICC.

Some HPV types classified as probably or possibly carcinogenic (Group 2A/2B), namely HPV26, 67, 68, 69, 73 and 82, were also more common in ICC than in normal cytology. Other Group 2A/2B types, for example HPV53 and 66, were more common in normal cytology than ICC and were also found in a higher proportion of low-grade diagnoses (e.g. 8.4 and 7.7% of LSIL respectively) than ICC (0.5 and 0.3% respectively).

Among other HPV types, that were relatively uncommon in normal cytology and invasive cancer, many were commonly detected in intermediate diagnoses, in particular the alpha-9 types 61, 62, 84 and 89.

The addition of individual type-specific prevalences within each disease grade produced totals well above above 100% for all diagnoses known to be caused by HPV, highlighting the frequent presence of multiple HPV types within the same women. Indeed, in a subset-analysis of studies providing the necessary data breakdown, the prevalence of multiple infections ranged from 12% in ICC up to 39% in CIN2.

Cutaneous HPV types

The initial search identified >1200 studies. After scanning of titles and abstracts, 119 studies were retained. Detailed investigation of abstracts identified 18 studies assessing exposure to cutaneous HPV types among patients with skin cancers (SCC, BCC) or precursor lesions (AK). Three studies (Feltkamp et al., 2003; Masini et al., 2003; Struijk et al., 2003) were excluded because the populations were overlapping. Finally 15 studies were included in the analysis.

Among the included studies, nine used hospital-based case-control design (Andersson et al., 2008; Asgari et al., 2008; Forslund et al., 2007; Iannacone et al., 2012, 2013; Stark et al., 1998; Steger et al., 1990; Struijk et al., 2006; Waterboer et al., 2008), one study used hospital-based case-control design among organ transplant patients (OTR) (Proby et al., 2011), four studies used a population based design to identify cases and controls (Andersson et al., 2012; Casabonne et al., 2007; Karagas et al., 2006; Termorshuizen et al., 2004) and two studies used a prospective follow-up study design (Plasmeijer et al., 2011; Andersson et al., 2012).

Results comparing prevalence of cutaneous HPV types in cases and controls are shown in Table 2. There have been few studies of cutaneous HPV types in the alpha genus.

For the beta genus, there have been a large number of studies of SCC using serology and/or detection of HPV DNA using various sample types. Upon combination of types at the species level, the prevalence of species Beta-1, Beta-2 and Beta-3 were each significantly elevated in SCC compared to controls, both using serology and DNA detection. At the individual type level, the prevalence of antibodies against HPV8 (Beta-1), HPV15, HPV17, HPV38 (Beta-2), HPV49 and HPV76 (Beta-3) were elevated in SCC in comparison to controls, but corresponding differences for DNA detection did not meet statistical significance. In contrast, the prevalence of DNA of HPV24 (Beta-1) was significantly higher in SCC than controls, but the corresponding difference in antibody prevalence did not meet statistical significance. Species Beta-4 was represented only by HPV92, for which DNA was significantly more prevalent in SCC than in controls (Table 1).

Data on HPV types of genus Gamma, Mu and Nu were fewer than for beta-types, deriving only from serology studies, and showed no significant differences in seroprevalence between cases and controls at an individual HPV type level, even if OR estimates

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