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Chromosomal gains and losses in human papillomavirus-associated neoplasia of the lower genital tract – A systematic review and meta-analysis

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Abstract ***Background:*** Overexpression of the human papillomavirus (HPV) oncogenes E6 and E7 is necessary for the development of distinct lower genital tract cancers. However, secondary cellular genomic alterations are mandatory to promote progression of HPV-induced premalignant stages. We aimed at identifying the chromosomal regions most frequently gained and lost and the disease stage at which the latter occurs. These regions might be relevant for carcinogenesis and could serve as diagnostic markers to identify premalignant lesions with high progression risk towards invasive cancer.

Methods: We performed a systematic literature review and meta-analysis of studies listed in PubMed that analysed chromosomal copy number alterations by comparative genomic hybridisation (CGH) in HPV-positive and -negative cancers or premalignant lesions of the anogenital tract (cervix, anus, vagina, penis and vulva).

Findings: Data were extracted and analysed from 32 studies. The most common alterations in cervical squamous cell carcinoma (SCC) (12 studies, 293 samples) were gains at 3q with a rate of 0.55 (95% confidence interval (CI) 0.43–0.70), losses at 3p (0.36, 95%CI 0.27–0.48) and losses at 11q (0.33, 95%CI 0.26–0.43). Gains at 3q were particularly frequent in HPV16-positive cervical SCC (0.84, 95%CI 0.78–0.90). Also more than one quarter of high grade cervical intraepithelial neoplasia (CIN) harboured gains of 3q (0.27, 95%CI 0.20–0.36), but the rate in low grade CIN was low (0.02, 95%CI 0.00–0.09). For HPV-associated vulvar SCC (four stud-

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ies, 30 samples) the same common alterations as in cervical SCC were reported. Studies on non-cervical and non-vulvar SCC and premalignant lesions of the lower genital tract are scarce.

Interpretation: 3q gains were most frequently found in HPV16-positive cervical SCC. The results suggest the selection of HPV-transformed cell clones harbouring 3q gains in high grade premalignant lesions, while alterations in low grade lesions are rare.

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1. Introduction

Infections by high risk human papillomaviruses (HR-HPV) are highly prevalent in the general population, but cause relevant cellular changes only at distinct anatomic regions and in only a small fraction of infected individuals [1,2]. Biologically the prevalent 'acute/productive or permissive' epithelial infections are characterised by the virus replicating itself and producing virus progeny particles, while persistent HR-HPV infections of the human anogenital tract may in some instances progress to 'transforming infections' that are characterised by overexpression of the HPV oncogenes E6 and E7 [3,4]. In the lower anogenital tract these premalignant and potentially progressing HR-HPV infections are morphologically reflected as intraepithelial neoplasia (cervical/vaginal/vulvar/anal/penile intraepithelial neoplasia, CIN/VaIN/VIN/AIN/PIN, respectively) [5].

The key event for the transition from the prevalent virus particle producing 'acute/permissive' to the rarer 'transforming infection' is the deregulated expression of the viral oncogenes E6 and E7 [4,6]. Besides directly interfering with critical cell cycle pathways (p53, pRB) and thereby promoting cell proliferation, the expression of E6 and E7 leads to alterations of the cellular genome integrity, including structural and numerical chromosomal instability resulting in chromosomal mis-segregation and aneuploidy [7]. Clinically, epithelial lesions associated with transforming HPV infections show a heterogeneous course with only a proportion of high grade lesions progressing to invasive cancer [8,9], thus biologically the progression towards cancer is likely the consequence of accumulation of specific and multiple cellular changes that promote the outgrowth of distinct cell clones. The risk for progression of a premalignant lesion to cervical cancer is further linked to the HPV genotype: infection with HPV 16 and 18 are substantially more likely to progress in less time in comparison to lesions induced by other high-risk HPV types [10].

While in the cervical epithelium virtually all premalignant lesions and cancers are caused by HPV and chromosomal instabilities can herewith coherently be linked to the effect of deregulated E6 and E7 expression [11], a proportion of other premalignant lesions and cancers of the lower genital tract (anal, vulvar, vaginal, penile) cannot be attributed to HPV oncogenes but follow alternative pathogenic pathways as mutational inactivation or epigenetic silencing of distinct tumour suppressor genes (e.g. *p53, CDKN2A*) which can eventually result in chromosomal instability and promotion of malignant outgrowth.

The identification of chromosomal regions most frequently affected by chromosomal copy number alterations may help to identify genomic regions potentially relevant for carcinogenesis and progression, as they might have been positively selected during tumour evolution. Further, the identification of alterations already present in premalignant stages and particularly in progressing lesions may help to design diagnostic approaches. Whole chromosome arm and chromosome region copy number gains and losses have been analysed in detail in cervical cancers and CIN and in some other anogenital tract cancers most comprehensively using comparative genomic hybridisation (CGH) assays, where the analysed genome is hybridised to either reference metaphase chromosomes or bacterial artificial chromosome (BAC) clones or synthetic oligonucleotides in newer arrays. This analysis provides a systematic appraisal of the literature on chromosomal copy number alterations in human lower genital tract cancers and premalignant lesions analysed by CGH with the aim of identifying common alterations and to reveal gaps in knowledge for upcoming future analyses.

2. Methods

A systematic literature search was performed to identify studies listed in NCBI PubMed by August 20, 2013 using the following keywords: ({gene} OR {genes} OR {genome} OR {genomes} OR {genomic} OR {chromosome} OR {chromosomes} OR {chromosomal}) AND ({abnormality} OR {abnormalities} OR {alteration} OR {alterations} OR {aberration} OR {aberrations} OR {ploidy} OR {aneuploidy} OR {polyploidy} OR {instability} OR {instabilities} OR {translocation} OR [12] OR {deletion} OR {deletions} OR {amplification} OR {amplifications} OR {insertion} OR {insertions} OR {loss} OR {losses} OR {gain} OR {gains}) AND ({tumour} OR {tumours} OR {tumour} OR {tumours} OR {cancer} OR {cancers} OR {carcinoma} OR {carcinomas}) AND ({cervix} OR {cervical} OR {vulva} OR {vulvar} OR {vagina} OR {vaginal} OR {anus} OR {anal} OR {penile} OR {penis}).

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