



## Progress in eliminating HPV-associated disease



### 1. Introduction

This special collection (Editors Peter L. Stern & Karen Canfell) consists of a series of reviews summarizing some of the key insights presented and discussed at the 32nd International Papillomavirus Conference (IPVC) and Asia-Oceania Research Organization in Genital Infection and Neoplasia (AOGIN) 2018, which was held in October 2018, in Sydney Australia. The conference was held at a pivotal moment for the International Papillomavirus Society, AOGIN and for HPV research: it came hard on the heels of the announcement by the Director-General of the World Health Organization (WHO) that cervical cancer elimination was within reach and that WHO would focus on the development of a draft strategic plan for elimination. Accordingly, the excitement was palpable as those involved in cutting-edge research in the basic sciences, clinical research and public health in this field came together to discuss the latest findings and insights in the genetics, cellular and molecular biology of HPV infection and carcinogenesis as well as the impact of current primary and secondary prevention strategies and the means for their further optimization.

The first seven articles focus on more basic considerations of the natural history of HPV infection and disease. Importantly, all have important implications for the development and implementation of optimal screening or preventative or therapeutic regimes for HPV associated cancers.

To begin, Brown & Leo [1] discuss the appropriate methodologies to identify relevant genetic factors in HPV infection and cervical neoplasia. Rare high and more common low penetrance host factors have been identified as influencing HPV persistence. The strongest associations are with Major Histocompatibility Complex (MHC) (Human leucocyte antigen, HLA) polymorphisms (implicating the immune response) and could potentially identify individuals at particular risk. Disease associated single nucleotide polymorphisms (SNPs) can also be used to identify populations with an increased risk for cervical cancer but more studies are required to identify the non-MHC factors.

The next article by Doorbar [2] considers the cells in the epithelial tissue structures of the cervix (and other vulnerable tissues) that provide the targets for productive HPV infection and but also the potential for latency. This is important in considering the issues of HPV persistence, the critical factor in risk for developing cervical neoplasia.

The next two articles examine the details of uptake and internalization of HPV during the infection process. The extracellular events are discussed in the context of wound healing whereby HPV hijacks normal cellular processes to facilitate virus entry, as discussed by Ozbun [3]. The HPV capsids interact with heparin sulphate proteoglycans (HSPG) and other molecules for cell binding and subsequently trigger post-entry trafficking to the nucleus. Mikuličić & Florin [4] describe the virus associated entry complex and clathrin independent

endocytosis process. Tetraspanins and annexin provide spatial organization of the HPV associated molecules through recruitment of trafficking factors and L2 membrane penetration for virus entry. These events are critical to the understanding of how prophylactic vaccines may work or be further optimized.

For a productive infection, HPV genome replication is linked to differentiation of the epithelial tissue and the latter involves remodeling of genome. Clearly such epigenetic differential methylation events significantly influence the HPV cell cycle. Doebertz and Prigge [5] present the case for initiation of transformation as linked to methylation of the HPV E2 binding sites in the upstream regulatory region (URR). The potential for such events may also relate to the target cell status in the tissue hierarchy.

Smola [6] describes the consequences of a persistent HPV infection leading to chronic inflammatory responses which reinforce the infection and undermine otherwise potentially curative immune responses. In time, inadequate DNA repair provides for genetic mutations that can allow for further escape from natural tissue or immune control mechanisms driving neoplasia. This article emphasizes the importance of a functional immune system to enable the clearance of natural HPV infections. Given the emerging impact of some cancer immunotherapies these observations highlight the need to consider multifactorial approaches in treatment development.

The biology of the beta PVs associated with cutaneous infections are somewhat different from the mucosal high risk PVs. As reviewed by Tomassino [7], the development of cutaneous squamous cell carcinoma appears to require UV exposure with the beta HPV infection necessary but thereafter dispensable. Thus therapeutic approaches targeting viral oncogenes where expression is obligatory for cancer driven by mucosal types is not a viable approach in skin cancers.

The latter half of the special edition focuses on some of the successes, as well as the upcoming clinical and public health challenges and opportunities, in HPV prevention.

The major burden of disease for HPV-related cancer is in low- and middle-income countries (LMIC), and for many of these, particularly in the sub-Saharan African region, human immunodeficiency virus (HIV) infection is endemic. Lacey [8] discusses the increase in risk of progression of HPV-related cancer in HIV-positive individuals. It is well established that immune responses to vaccination are not optimal in those with HIV infection, although anti-viral therapy (ART) plays a modulating role. However, there is currently limited and inconsistent direct evidence on the effectiveness of HPV vaccination in HIV-positive individuals. If standard HPV vaccination regimes prove to be less effective in HIV-positive individuals, possible public health responses might include the delivery of alternate vaccine regimes and/or dosing schedules in HPV-endemic populations or in individuals known to be HIV-positive. However, Lacey notes that the clinical evidence is

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required to support such approaches - establishing such evidence should thus be a high priority.

Most high-income countries have now implemented large-scale prophylactic vaccination initiatives. Brotherton [9] comprehensively summarises the extraordinary success experienced to date with HPV vaccination initiatives, across multiple countries, for health outcomes including HPV infection prevalence, anogenital warts and cervical precancerous lesions (cervical intraepithelial neoplasia, CIN2/3). She also deals with current challenges of surveillance for cancer outcomes – there are some complexities in detecting changes in rates of HPV-related cancer in the post-vaccination era, and these include the requirement to have a large enough base population to detect differences in cancer rates in younger people (where vaccination effects will be initially seen), and the complexities in surveillance of vaccination impact introduced by the effects of earlier detection of invasive cervical cancer in countries who have transitioned to HPV-based screening. Ongoing typing studies for invasive cervical cancer will play an important role in understanding vaccination impact going forward and should be prioritized, along with establishing effective cancer registration systems. Brotherton also discusses the current challenges in HPV vaccine supply and the need to prioritise vaccination for young adolescent girls in LMIC and in marginalised populations in high income countries, as the most effective means by which the overall burden and inequities of HPV-related cancer can be reduced.

Despite the high efficacy of prophylactic HPV vaccination in unexposed individuals, achieving major global impact towards reducing cervical cancer over the next fifty years will continue to require a focus on the effective and efficient delivery of cervical screening to older cohorts of women who have already been exposed to HPV.

As discussed by Kitchener [10], in high income countries a transition to primary HPV screening from cytology-based screening will improve the overall effectiveness of screening programs and will thus save more lives as a result of the increased sensitivity and predictive value of HPV testing. At the same time, HPV-based screening allows the safe extension of screening intervals for HPV-negative women because the negative predictive value of the test is so high and means that the likelihood of a women developing invasive cervical cancer over the next 5–10 years is extremely small. However, HPV-based screening also requires careful implementation to optimise outcomes. In particular, HPV triaging and/or early recall strategies for HPV-positive women need to be judiciously used in order to minimize the potential for over-referral to colposcopy. The UK Pilot Sites for primary HPV screening are a large-scale experience of the early recall strategy. As Kitchener notes, HPV vaccination will change the picture for screening in the future and modelling done to date supports the future de-intensification of screening in cohorts offered HPV vaccination as young adolescents.

De Sanjose and Holme [11] consider the needs for successful scale-up of screening in low and middle-income countries, which have, to date, experienced inconsistent and often ineffective efforts to expand cervical screening access. The WHO draft strategic plan for elimination targets screening coverage of 70% of women aged 35–45 years with 90% of detected precancerous lesions being effectively treated. Scale-up of cervical screening in LMIC will likely require a mix of approaches including the use of strategies to increase access to HPV-based screening. These include HPV self-collection, and accessible and locally appropriate triaging protocols and treatment modalities for HPV-positive women. Again, strengthening health systems around screening initiatives will be required for their effective delivery - for example, there will need to be infrastructure in place to record screening events and to recall women for triaging, treatment or re-screening (as required). There are also a range of linked challenges in establishing appropriate provider training, community education, operational management and quality control processes. Ultimately, the methods and frequency of the delivery of HPV testing and the specific clinical pathways for the management of HPV positive women will need to be tailored to the local setting in a country, with cost-effective approaches needing to be identified.

Stern and Roden [12] discuss current opportunities to improve immune-based prevention of HPV-associated cancers while Frazer and Chandra discuss the current status and challenges for effective immunotherapy for HPV-associated cancer. Stern and Roden identify several opportunities including the possibility of effective 1-dose vaccination (also discussed by several other authors), delivery of HPV vaccination as part of a childhood immunisation schedule, development of lower cost locally manufactured vaccines (as is now being considered particularly in India and China) which in future, perhaps, could involve bacterial systems or utilisation of additional L2 epitopes. Infant immunisation against HPV is an exciting possibility but would require extensive clinical validation including bridging, dose-efficacy and safety studies. Although extending vaccination to older ages (sometimes known as *HPV-Faster*) or vaccinating boys as well as girls, will somewhat increase the speed and extent of the impact on HPV-related cancer outcomes, the cost-effectiveness of such strategies will need to be established for countries considering such approaches. Additionally, in the context of current vaccine supply challenges (discussed by Brotherton), vaccination of young adolescent girls should be the priority for LMIC. Via herd immunity, HPV-related cancers in men will also be reduced by vaccinating young girls, and this strategy will maximise the impact of vaccination on the overall burden of HPV-related cancers.

Frazer and Chandra [13] posit that tumour immunotherapy modalities used to date have not addressed all of the recognized barriers to the delivery of effective immunotherapy. They categorize the barriers as lack of presentation of tumour specific antigens on the tumour or to the host immune system (potentially addressable with cytokine therapy), failure of T cell priming (addressed by antigen specific immunotherapy), failure of primed T cells to access the tumour (for which new strategies are needed), local active immune suppression (can be overcome via checkpoint inhibition and macrophage elimination) and continuous generation of tumour subclones with new evasion strategies (which will require combination therapy with non-antigen specific immunotherapy and immunotherapy targeting multiple antigens). Overall, they suggest that effective treatment of HPV-related tumour will ultimately require an integrated, combination approach including traditional radiotherapy and chemotherapy, HPV antigen-specific immunotherapy, either (therapeutic) immunisation or CAR-T cell therapy, and perhaps also non-specific immune therapy or interventions to re-program the immunoregulatory environment.

In the final chapter, Canfell [14] summarises the current status of the global push towards the elimination of cervical cancer, which is spearheaded by WHO. WHO, in consultation with its member states, advocacy and aid organisations, and a range of other stakeholders, is currently working on the draft plan for elimination. This involves defining goals and targets for a three-pronged push for the effective scale-up by 2030 of vaccination, cervical cancer screening, and treatment of cervical precancer and cancer. Although the main focus of WHO's current effort is cervical cancer, by implication, a push to scale-up HPV vaccination to 90% coverage in females globally over the next decade will have major positive impact over the longer term on other HPV-related cancers in females, and via herd immunity, in males. In addition, a push to scale-up cervical cancer treatment services such that 90% of those that develop cervical cancer are offered effective treatment by 2030, would be likely to have major positive flow-on effects for other cancers in LMIC, including for other HPV-related cancers.

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In the lead up to the next IPV meeting, to be held in Barcelona in 2020, we are now poised on the threshold of major global action towards the elimination of HPV-associated disease. In this era of such major public health initiatives, the papillomavirus community is adopting novel strategies and resources for medical communication and dissemination of information, considering the needs of different audiences. Summaries of the consolidated evidence using e-formats and e-learning methodologies should be adopted on a widespread basis to inform the tens of thousands of health professionals that operate in different languages and cultural environments, and who represent for our field the front line for effective delivery of cervical cancer prevention interventions. The PVR journal is proud to host such scientific summaries and will promote them in further editions in association with IPV conferences.

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