



## Meeting Report

### Summary of the Eurogin 2011 conference: Highlighting the recent advances in HPV-related cancers

#### Introduction

The Eurogin 2011 conference was held in Lisbon, Portugal, from May 8 to 11, 2011. The meeting attracted 1930 participants from institutions worldwide including clinicians, laboratory scientists, epidemiologists and public health officials. This review highlights some of the 153 presentations. All the references cited are from the abstract book of the Eurogin 2011. See <http://www.eurogin.com/2011>.

#### HPV vaccines

The initial clinical trials of the quadrivalent vaccine, Gardasil, and the bivalent vaccine, Cervarix, continue to provide a rich source for analysis of vaccine safety, immunogenicity and efficacy. In the per protocol analysis of a phase III trial of Gardasil in men, the vaccine significantly decreased vaccine type-associated external genital lesions by 90.4% [1]. Among men who have sex with men (MSM), the vaccine had 94.9% efficacy against persistent anal canal infection and 74.9% efficacy against AIN 2/3.

Among HPV naïve women from the PATRICIA trial of Cervarix, an efficacy of 91.9% was observed against the development of ASCUS+ associated with vaccine types HPV-16/18 and a 24% efficacy against ASCUS+ associated with the 10 most common non-vaccine HPV types. There was a 29% reduction in colposcopy referrals and a 70.2% reduction in cervical excision therapies, suggesting that the vaccine may result in healthcare cost savings [2]. Among naïve women enrolled in the FUTURE II trial of Gardasil [3,4], the incidence rates in a long term follow-up study of CIN due to non-vaccine HPV types did not differ significantly in the follow-up period compared to the rates seen during the phase III studies, suggesting an absence of any increase in disease associated with non-vaccine HPV types (type replacement). Despite these encouraging results there is insufficient data to confirm that protection is maintained. Investigators from Australia reported that vaccination may reduce the population-based incidence of genital warts and high grade cervical abnormalities [5]. However, data linkage between the National HPV vaccination program and Pap test registers needs to be conducted to confirm that the observed declines are indeed due to HPV vaccination. Data presented on vaccine efficacy following one, two or three doses of the vaccine revealed that primary cervical cancer could be cost-effective for low resource settings, if randomized studies confirm the net benefit of administering fewer than three doses [6]. In his summary of recent advances and gaps in HPV research, Castle [7] noted that for primary prevention by vaccination we still do not have answers to several key questions including who should be vaccinated, how long does protection endure, what is the impact of vaccination on transmission, and how can vaccines be deployed in the developing world in a cost-effective manner.

#### HPV transmission between heterosexual couples

HPV is efficiently transmitted between sexual partners, and rates of genital transmission from women to men are higher than that from men to women. Cross-sectional studies have shown relatively high rates of HPV type specific concordance, and HPV viral load, HIV status, and condom use may influence type specific HPV concordance [8]. However, the development of comprehensive HPV prevention and control strategies, which incorporate HPV vaccine usage and contraceptive practices, is impeded by lack of information on the risk and routes of sexual transmission between heterosexual and homosexual partners and potential genotype-specific differences in transmission efficiency [9].

#### Cervical cancer screening

There is overall agreement that screening for cervical cancer will continue to be necessary after introduction of HPV vaccines [10].

Some adolescents continue to be screened despite the recommendation to start cervical cancer screening at age 21–25. To avoid subjecting these young women to unnecessary procedures, a recommendation was made to manage patients with abnormal smears by observation with repeat cytology [11]. Due to the high prevalence of HPV infections and the very low risk of disease, population-based screening is not effective when started too early and primary prevention in adolescents should focus on HPV vaccination and not cancer screening. Data from 5 large clinical trials showed that overall hrHPV testing in baseline screening detects 22% more CIN3+ lesions and 30% more CIN2+ lesions compared to cytology at the cost of 4–6% lower specificity [12]. The second peak prevalence of HPV around the age of menopause varies geographically [13]. In some low resource countries, HPV prevalence also remains elevated among older women and might affect the efficiency of HPV screening programs in these countries [14]. For women over 30 years of age, cervical cytology screening is recommended every 3 years if they have had 3 consecutive normal Pap test results. Prolonging screening intervals reduces the risk of detecting transient HPV-induced events not destined to become CIN3, AIS, or cervical cancer [15].

There is strong evidence that HPV-based screening and treatment strategies reduce CIN 2 at 36 months in both HIV– and HIV+ [16].

#### Local immune response, HPV recurrence and viral latency

A presentation on the immune response to HPV emphasized that the response seen at later stages of cervical carcinogenesis is likely to be a result of systemic cell-mediated immune response and that the anal and cervical mucosal responses are similar but occur independently of each other [17]. Longitudinal studies have shown that cervical HPV DNA detection can be intermittent and could reflect

re-infection from a HPV infected partner, autoinoculation from the anus or vagina, replication of virus below the level of detection, reactivation of a latent viral infection, or simply inadequate sampling [18].

### HPV-related diseases in males

Penile cancer is a rare disease in developing countries. The incidence rate of penile cancer reported in Denmark was 1.7 per 100,000 persons [19]. Not all penile cancer is associated with HPV. Prevention of penile cancer is not a sufficient justification for male vaccination. Vaccines should be considered in a context of a broader spectrum of male HPV-related disease [20]. Compared to women, HPV prevalence in men appears to peak in slightly older ages and remains constant or decreases slightly with increasing age, suggesting persistent HPV infection or a higher rate of re-infection than that seen in women [21].

### Anal HPV associated and HIV-1 co-infection

There is overall agreement that HIV-infected patients practicing anal intercourse or with a history of HPV lesions should be screened. The triad of cytology, high resolution anoscopy, and biopsy are probably the best tools for screening [22,23]. It is widely believed (although still unproven since clinical studies have not yet been done) that treatment of high-grade AIN will reduce the risk of anal cancer, similar to treatment of CIN 2/3 to prevent cervical cancer [24].

It is also possible that the pro-inflammatory environment induced by HIV infection contributes to an accelerated, immune-mediated clearance of HPV infection [25]. In conclusion, it is likely that HPV vaccination will be effective in the prevention of anal cancer, and anal screening is important in high risk groups [23,24].

### Oral HPV epidemiology, head and neck cancer

HPV-16 infection is a risk factor for a subset of head and neck cancers, yet the epidemiology of oral HPV infection is not well understood. Little prospective data has been collected on oral HPV infection to date. As such, there are no stable estimates of oral HPV persistence, clearance, or incidence. Incidence at 6 months for HIV positive individuals was 20%, whereas incidence among healthy people was 10% after two years [26].

The newly appreciated role of HPV in head and neck cancers provides new avenues for cancer prevention and screening, a new target for therapy, and may have important implications for the current standard of care [27]. HPV vaccines may have a preventive effect against HNC [28] in addition to other HPV-associated upper respiratory tract diseases including respiratory papillomas and carcinomas [29]. A meta-analysis revealed a significantly higher proportion of HPV infected subjects in patients with esophageal squamous cell carcinoma (OSCC) or precancer compared with health controls [30].

### Biomarkers

There is a need for biomarkers to provide a more objective definition of CIN2+ because cervical histopathology and cytology are highly subjective and treatment is expensive. Several studies have demonstrated the high sensitivity of p16/Ki-67 dual-stained cytology for the detection of underlying CIN2+ [31,32]; p16 is also a potential prognostic and predictive marker in cancers of the vulva and head and neck cancers [33].

### Conclusions

While the Eurogin 2011 conference highlighted many important advances in the HPV field, there are still many gaps in research that need to be addressed.

Among these gaps are the necessity to identify suitable triage and follow-up strategies for HPV DNA positive patients, assessment of cost-effectiveness, safety, and liability for providers of HPV vaccines, and identification of the optimal screening intervals for both vaccinated and unvaccinated woman [34], moreover whether vaccination against HPV will reduce the risk of development of high grade AIN due to vaccine types needs to be addressed [35].



### Conflict of interest statement

The author has no conflict of interest to declare.

### Acknowledgments and disclaimer

AFN acknowledges the editorial assistance of Raphael Viscidi, and the support of CNPq, Brazil and Eurogin.

### References

- [1] Guiliano A. New evidence for vaccination of males. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [2] Romanowski B. Early benefits and prevention of abnormal cervical smears with the bivalent HPV vaccine. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [3] Paaonon J, Rana M, et al. Long-term efficacy of human papillomavirus vaccination against CIN 3 and invasive carcinoma: registry based follow up of a phase III Trial (FUTURE II). Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [4] Dillner J. Long-term follow-up (LTFU) study of HPV-type-specific disease in previously Gardasil™ vaccinated women. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [5] Brotherton JML. Real life impact of HPV vaccine at the population level: the Australian experience. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [6] Kreimer AR, Rodriguez AC, Hildesheim A, et al. Evaluation of the efficacy of fewer than three doses of a bivalent HPV 16/18 vaccine. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [7] Castle PE. Recent advances and gaps in research: conclusions. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [8] Giuliano A. Role of epidemiology in our understanding of HPV transmission. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [9] Goodman MT. Reservoir genital sites in HPV transmission. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [10] Jeronimo J. Current management of cervical pre-cancer in low-resource settings. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [11] Moscicki AB. Age specific HPV infection and disease: adolescents and young women. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [12] Chris Meijer JLM, Rijkaart D, Dijkstra M, Heideman D, Berkhof H, Kemenade F, et al. HPV screening: current programmes and implementation procedures the Dutch program. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [13] Gravitt P. Menopause. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [14] Wentzensen N. Natural history revisited: age specific relationship and implications for clinical practice. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [15] Cox TJ. Optimal screening intervals. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [16] Denny L. HPV screen and treat in HIV infected women. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [17] Moscicki AB. Local immune response to HPV and neoplasia. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [18] Moscicki AB. Viral latency vs recurrence new infection. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [19] Olsen J. Incidence and costs of anal, penile, vaginal and vulva cancer in Denmark. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [20] D'Hauwers KWM, Depuydt CE, Bogers JP, Tjalma WAA. The burden of HPV associated penile cancer. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [21] Smith JS, Gilbert P. Age-specific prevalence of infection with Human Papillomavirus in males: a global review. Paper presented at: Eurogin; 2011.
- [22] Abramowitz L, Benabderrahmane D, Soudan D. Who should be screened? Is screening an effective tool? Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [23] Goldstone SE. Diagnosis of anal intraepithelial neoplasia. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [24] Palefsky J. Anal neoplasia: epidemiology, diagnostics and prevention. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [25] Gravitt P. Role of HPV in HIV transmission. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [26] Kreimer AR. Oral HPV infection and head and neck cancer risk. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [27] Gillison ML. Evidence of a causal association between HPV and head and neck cancer. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [28] Kjaer SK. The potential impact of HPV vaccines in head and neck cancer. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.

- [29] Broker TR. Recurrent respiratory papillomatosis. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [30] Syrjanen S, et al. Human Papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [31] Reuschenbach M, Seiz M, et al. Combined expression of p16ink4a and ki-67 in cervical epithelial cells indicates high grade intraepithelial neoplasia and cancer. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [32] Bergeron C, Schmidt D, Denton KJ, Ridder R. Triage of ASCUS and LSIL cytology results with p16/ki-67 dual-stained cytology. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [33] Stoler M. P16 immunohistochemistry: a potential objective biomarker standard in cervical and non-cervical histopathology. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [34] Franco E. Cervical cancer screening as a post-vaccination surveillance activity. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.
- [35] Palefsky J. Anal neoplasia: epidemiology, diagnostics and prevention. Paper presented at: Lisbon, Portugal: Eurogin; May 8–11, 2011.

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18 April 2011