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EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease

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Abstract

The EUROGIN 2011 roadmap reviews the current burden of HPV (human papillomavirus)-related morbidity, as well as the evidence and potential practice recommendations regarding primary and secondary prevention and treatment of cancers and other disease associated with HPV infection.

HPV infection causes approximately 600,000 cases of cancer of the cervix, vulva, vagina, anus and oropharynx annually, as well as benign diseases such as genital warts and recurrent respiratory papillomatosis. Whereas the incidence of cervical cancer has been decreasing over recent decades, the incidence of anal and oropharyngeal carcinoma, for which there are no effective screening programs, has been rising over the last couple of decades.

Randomised trials have demonstrated improved efficacy of HPV-based compared to cytology-based cervical cancer screening. Defining the best algorithms to triage HPV-positive women, age ranges and screening intervals are priorities for pooled analyses and further research, whereas feasibility questions can be addressed through screening programmes.

HPV vaccination will reduce the burden of cervical precancer and probably also of invasive cervical and other HPV-related disease in women. Recent trials demonstrated that prophylactic vaccination also protects against anogenital HPV infection, ano-genital intraepithelial lesions and warts associated with vaccine types, in males; and anal HPV infection and anal intraepithelial neoplasia in MSM. HPV-related oropharyngeal cancer could be treated less aggressively because of better survival compared to cancers of the oropharynx unrelated to HPV.

Key findings in the field of cervical cancer prevention should now be translated in cost-effective strategies, following an organised approach integrating primary and secondary prevention, according to scientific evidence but adapted to the local situation with particular attention to regions with the highest burden of disease.

Keywords

cervical cancer; vulvar cancer; anal cancer; penile cancer; head & neck cancer; genital warts; incidence; mortality; human papillomavirus; HPV; screening; vaccination

INTRODUCTION

A multidisciplinary group of experts from five continents have summarised the highlights of the last EUROGIN conference entitled “HPV Associated Diseases and Cancer: From Reality Now to the Future” (Lisbon, Portugal; 8-11 May, 2011). As in previous three EUROGIN reports, the fourth EUROGIN Roadmap updates knowledge on the current burden and recent trends of cervical cancer and discusses the development of new policies incorporating HPV-based cervical cancer screening in developed and developing countries. In addition, this fourth Eurogin Roadmap describes recent experiences and early effects of HPV vaccine introduction and addresses also the primary prevention of precursors of vulvar, anal and penile cancer, experimental treatment of vulvar intraepithelial neoplasia, potential screening for anal cancer in high-risk groups and the prevention of anogenital disease through male circumcision. Finally, particular attention is focused on the increased incidence of HPV-related oropharyngeal cancer and new prognostic insights which encourage treatment modifications in HPV-positive patients with oropharyngeal squamous cell carcinoma (OSCC).

DISEASES RELATED TO HPV INFECTION

hrHPV infection is causally related to cancer of the cervix, vagina, vulva, anal canal, penis and oropharynx[1].

Cervical cancer

HPV is detectable in virtually 100% of cervical cancer cases[2], although individual studies may show lower estimates which are generally explained by technical issues. HPV16 is the most common type and combined with HPV18 account for over 70% of all cases of cervical cancer[3,4].

Other ano-genital (pre-)cancers

HPV may cause over 70% of all cancers of vagina and anus, whereas HPV attribution for penile and vulva cancers is lower ranging from 40% to 47% (Table 1). Most vulvar cancers (92%) are squamous cell carcinomas[5]. HPV prevalence is high in vulvar intraepithelial neoplasia (VIN) (>80%) and in invasive vulvar cancers of the basaloid/warty type (86%) but only 6% in keratinizing squamous vulvar carcinoma[6,7,8]. HPV16 accounts for 85% of HPV-positive vulvar cancers.

Approximately 95% of invasive penile cancers are squamous cell carcinomas (SCC)[9,10]. HPV is commonly detected in basaloid and warty tumours, but is less common in keratinizing and verrucous tumours. Approximately 60-100% of penile intraepithelial neoplasia (PIN) lesions are HPV DNA positive. In invasive penile tumours, HPV16 was the most common type detected (40%), followed by HPV6 (22%), HPV52 (15%), and HPV11 (4%)[11].

In a recent study, HPV DNA was found in 97% of 366 anal cancers. HPV 16 was the most prevalent genotype (75%). HPV16 or18 were found in 78% of all cases[12].

Oropharyngeal cancer

HPV attribution for oropharynx cancers varies between studies and anatomical sub-sites (5-70%)[13]. A recent meta-analysis showed that HPV prevalence in head-and-neck tumours increased significantly from 41% prior to 2000 to 72% after 2004 and that HPV16 accounted for 96% of HPV-positive OSCC[14]. Further, HPV prevalence was higher among OSCC in North-America (60%) versus Europe (40%) and all other regions (33%).

Interestingly, regional differences were significant only prior to 2000. Trends were independent of methods used for HPV detection. It appears that within two decades, HPV has replaced tobacco and alcohol as the major cause of OSCC in North-America and Western-Europe[14].

Cancer of the oral cavity

The role for HPV in the pathogenesis of oral cavity carcinomas remains controversial. A meta-analysis of the association between oral HPV infection and oral cavity SCC and potentially malignant disorders was performed[15]. It was estimated that any oral HPV or HPV16 infection confers a four-fold increase in the odds of developing oral cavity cancer (OR=3.98, 95%CI:2.62-6.02 and OR=3.86, 95%CI:2.16-6.87, respectively). A similar four-fold increase in the odds of potentially malignant oral lesions was also observed. The causal relation between oral cancer or precancerous conditions cannot be established with certainty since misclassification of OSCC as oral cavity cancers and alternative explanations cannot be excluded. Moreover, other recent large case-control studies reported no association between HPV and oral cavity carcinoma[16]. Further research is needed to clarify the etiological role of HPV in oral cancers.

Lesions associated with low-risk HPV

Genital warts are largely attributable to HPV types 6 and 11 although co-infections with hr-HPV are also frequently detected[17]. These two HPV types also cause the majority of RRP[18].

BURDEN OF HPV-RELATED DISEASE

Cervical cancer

Approximately 530,000 new cases of cervical cancer were estimated for 2008[18]. This number could increase to ~665,000 by 2020, if current trends and demographic effects are taken into account. Cervical cancer is the third most common cancer in women worldwide and the second most common in developing regions (www.who.int/hpvcentre).[18,19]

Approximately 47% of new annual cervical cancer cases are diagnosed in women aged <50 years, whereas this proportion is only 26% for all cancers. Eighty-six percent of the global burden occurs in less developed regions, where it accounts for 13% of all cancers in women[19]. Cervical cancer is the most common cancer in women in Sub-Saharan Africa, South-Central Asia and Melanesia. Incidence rates are low (world age-standardised incidence rate [ASIR] <6 per 100,000) in Western-Asia, North-America and Australia/New-Zealand[19].

Worldwide, the ratio of mortality to incidence is 52%. An estimated 275,000 women died from cervical cancer in 2008, about 88% of which occurred in less developed regions[19]. Overall, 0.9% of women die from the disease before the age of 75 years.

Cervical cancer contributed 3.4 million years of life lost (YLL) worldwide in 2004, and was the greatest single cause of YLL from cancer in women from low-income countries accounting for 20% of premature cancer deaths (22% in women aged 15-59 years) (see Figure 1)[16]. Cervical cancer is a paradigm of global health disparity; it takes a toll on young women from the poorest countries and the most disadvantaged populations.

Cancer of the vulva and the vagina

An estimated 30,000 and 15,000 new cases of cancer of the vulva and the vagina, respectively, occur annually (ASIR=0.2-1.6/100,000 and 0.3-0.5/100,000, worldwide)[20]. Vulvar cancer accounts for approximately 4% of gynaecological malignancies[21]. The

incidence of vulvar cancer and VIN has been reported to increase in recent years, particularly among younger women[22].

Anal cancer

Globally, there are about 30,400 new cases every year[23]. Since the 1970s, the incidence of anal cancer has been increasing in developed countries by about 2% per year in the general population[24]. The median age of diagnosis of anal cancer is 57 years among men and 68 years among women. Anal cancer is more common in certain high-risk groups; these include: MSM (men having sex with men) [25], anyone with a history of anal warts or high-grade CIN/VIN/cervical or vulvovaginal cancer; immunosuppressed populations, including those with human immunodeficiency virus (HIV) infection and organ graft recipients)[26].

In the general population, anal cancer affects more women than men[23]. Between 1998 and 2003, in the United States, the average annual incidence of anal cancer was 1.0/100,000 among men and 1.5/100,000[27] among women. Between 2003 and 2007, the incidence of anal cancer had risen to 1.4/100,000 among men and 1.8/100,000 among women. The incidence of anal cancer among MSM was estimated to be as high as 37/100,000 prior to the onset of the HIV epidemic[28], and is even higher among HIV-seropositive MSM[29]. The advent of antiretroviral therapy has not led to a reduction in the incidence of anal cancer[30]. The incidence may continue to increase as this population lives longer with HIV disease.

Penile cancer

Globally, the annual burden for penile cancer has been estimated to be 26,300 cases[23] with incidence rates strongly correlating with those of cervical cancer[31]. Invasive penile cancer is rare and most commonly affects men aged 50-70 years. Incidence of penile cancer in the US is highest among Hispanics and men who live in the Southern US or areas with high levels of poverty[32]. Incidence is also higher in less developed countries, where penile cancer accounts for up to 10% of male cancers in some parts of Africa, South America and Asia[10]. PIN lesions are rare.

Oropharyngeal cancer

About 137,000 new cases of cancer of the pharynx (excluding nasopharynx) and 96,000 associated deaths occurred worldwide in 2008[23]. The majority of head and neck cancers are associated with high tobacco and alcohol consumption. HPV has been mainly associated with the oropharynx (e.g. tonsil and tongue base)[33]. In these locations, HPV detection ranges from 5-64%, making overall HPV burden difficult to estimate[16,34]. High and increasing prevalence rates have been reported recently in the US, Canada, the Netherlands, Finland, Sweden, United Kingdom and Australia. Increased practice of oral sex has been postulated as an explanation in these societies where smoking, a major risk factor, is decreasing although the natural history is still unclear.

Incidence rates for OSCC and tonsillar cancer, in particular, have significantly increased over the last three decades in several countries. Through direct analyses of tumours, HPV is considered as the underlying cause of this increase in the US[35], Sweden[36] and Australia[14]. In the US, incidence rates for HPV-positive OSCC increased by 225% from 1988 to 2004, whereas rates for HPV-negative cancer declined by 50%[35]. Similar trends were observed in Sweden, where the proportion of HPV-positive OSCC increased from ~23 to 93% from 1970 to 2007[36]. In all countries, rates increased more sharply in younger birth cohorts, consistent with the hypothesis that sexual behavioural changes have led to increased HPV exposure while, concomitantly, tobacco exposure has declined.

Genital warts

Two to eleven of sexually active men and women in the general population of the US or European countries report ever being diagnosed with genital warts[37-39]. Incidence rates vary from 1 to 2 per 1000 person-years with highest rates in 16-24 year-old females (up to 1% episodes per annum) and slightly lower rates in 25-29 year old males[40-42].

PREVENTION OF CERVICAL CANCER

Screening in high resource settings

Recently, randomised controlled trials (RCTs) have provided evidence that HPV-based screening is more effective than cytology-based cervical screening[43]. In Europe, four randomised trials consistently showed, in the second screening round, a significant reduction in the incidence of CIN3+ (average relative risk [RR] of 0.45; 95%CI 0.34-0.60)[44], and even of even of invasive cancer (average RR=0.22; 95%CI 0.08-0.58 [3 trials]) by screening with a validated HPV assay compared with cytology (Figure 2)[45-49]. The specificity of HPV-based screening is lower than screening with cytology, but this loss of specificity could be minimised by avoiding HPV screening in young women, using more specific HPV tests, and by appropriate triage algorithms. Most currently available evidence from RCTs indicates that reflex cytology could be recommended for triage of HPV-positive women. Other candidate markers for triage, which could be considered, but for which evidence is today still insufficient, are: restricted HPV genotyping (types 16 and 18), p16 immunocytochemistry or p16Ki67 double staining. Also HPV screening using a more specific test such as the APTIMA RNA assay[50] or Hybrid Capture-2 at a higher viral load cut-off[51] increases specificity and PPV with no or a small loss in cross-sectional sensitivity[51]. The results from the RCTs suggest that HPV screening in women older than 30-35 years, followed by cytology triage of HPV-positive women does not cause substantial increases in diagnostic work-up and over-treatment. This knowledge can now be transferred into pilot implementation in organised and quality-controlled programmes to demonstrate feasibility. Further research is needed to optimise the screening protocols with HPV, such as age to start and screening intervals. The planned pooled analysis of individual data of the RCTs will be crucial for these points. The Netherlands is the first country with an official recommendation to introduce HPV-based primary screening.

Management of screen-positive women

Management of HPV-positive women requires further research. Recent interesting results from the combined use of genotyping and cytology are available[52]. However, comparison with other possible markers, such as p16 and mRNA, both in terms of cross-sectional and longitudinal accuracy, is needed to find optimal strategies for diagnostic work-up[53].

Testing for hr-HPV DNA has been shown to be an efficient triage tool for ASC-US cytology in the framework of cytology-based screening[54] and has been widely implemented in clinical practice. However, the high prevalence of hr-HPV DNA among women with LSIL results limits the utility of hr-HPV testing for this cytology category[54]. Among women with ASC-US, those positive for HPV16 or HPV18 have the highest risk of high grade CIN compared to those positive for other hr-types[55], potentially warranting different management strategies. Several biomarkers, including hr-HPV RNA and cellular proliferation markers have been evaluated for cytology triage. In triage of ASC-US, p16INK4a and the APTIMA-mRNA assay showed higher specificity and similar sensitivity compared to HC2. In LSIL triage, both tests showed increased specificity but, sensitivity for cervical precancer was lower for p16INK4a but similar for APTIMA [56,57]. Correct ascertainment of high grade CIN in women referred for abnormal screening test results can be compromised at the level of colposcopy and at the level of cervical histology. Increasing

the number of biopsies during colposcopic evaluation improves the detection of CIN3[58,59]. There is an ongoing debate as to whether taking multiple random, or multiple directed biopsies, is the more efficient approach. The incremental benefit of taking multiple directed biopsies is currently being evaluated in the NCI-led Biopsy Study. Structured colposcopy teaching has been also suggested to improve colposcopic accuracy. Recently, it was demonstrated that evaluation of cervical histology in conjunction with p16 staining improves reproducibility and can achieve similar accuracy as expert pathologist adjudication of conventional histology slides[60,61].

Screening in low resource settings

Cervical cancer prevention efforts in the past 15 years have focussed on alternative technologies to cytology screening and approaches allowing management of screen-positive women at the same time as the screening visit ("screen and treat").

An RCT, conducted in South-Africa, used HPV testing with HC2 and VIA testing in un-screened women aged 35-65 years[62]. In Arms 1 and 2, all HPV- and VIA-positive women, respectively, were treated with cryotherapy without colposcopy/histology confirmation. In Arm 3 (control), management was delayed. After a follow-up of 36 months, there was a sustained significant decrease in the detection of CIN2+ lesions in arm 1 (1.5%) and arm 2 (3.8%), compared to the control arm (5.6%), corresponding with a risk ratio of 0.27 (95%CI: 0.17-0.43) and 0.68 (95%CI:0.50:0.92), respectively.

Another landmark RCT enrolled 131,746 Indian women aged 30-59 years who were assigned to screening with 1) HPV testing with HC2, 2) cytological testing, 3) VIA or 4) routine care without screening as the control group[63]. Women who had positive tests underwent colposcopy with directed biopsies and those with cervical cancer precursors were treated. The 8-year cumulative incidence of cervical cancer stage-2 or higher and death rates from cervical cancer were significantly reduced in women screened with HC2 (hazard ratios of 0.47, 95%CI:0.32-0.69 and 0.52, 95%CI;0.33-0.83, respectively), whereas no significant reductions were observed in the VIA or cytology arms. Further, the age-standardised incidence rate of invasive cancer among women who had negative test results with cytological or VIA testing was more than four times greater the rate among HPV-negative women.

These data provide evidence for the superior performance of HPV DNA testing as a primary screening compared to VIA and cytology and demonstrated feasibility and effectiveness of screen and treatment approaches.

Recently, a large population-based screening program was set up in China, and currently covers 10 million women aged 35-59 years who are offered screening with cytology or VIA[64]. The low-cost careHPV assay, which can be easily used in field conditions, was shown to have a sensitivity and specificity for detection of CIN2+ (90 and 84%, respectively) comparable to HC2 which requires laboratory infrastructure[65]. These results are encouraging and may enable the use of HPV testing in developing countries at an affordable cost.

HPV vaccination

Vaccination coverage—According to the WHO (2010), 33 countries are using the HPV vaccine as part of their national immunization programme, mainly in developed countries. Coverage rates come from a variety of sources and will be standardised through the WHO. They are highest in countries with organised programmes, usually though school-based delivery (see Table 2).

Pilot introduction in developing countries has proven successful through donor programs. For example, in April 2011, Rwanda started nationwide HPV, school-based vaccination (6th grade of primary level) and in out-of-school girls aged 12 years through health centres, reaching virtually complete coverage for the first dose. In the Americas, Panama, and Mexico have included HPV vaccination in their immunisation programmes:and Argentina, Guyana, Peru, and Suriname have been planning to implement national programs in 2011 [66].

Impact of vaccination—With high HPV vaccination coverage for 12-17-year-olds, Australia has observed early effects. In sentinel sexually transmitted disease clinics, a 77% reduction in genital warts was observed amongst vaccine age eligible females as well as a 44% decrease among unvaccinated but age-matched heterosexual males between 2007 and 2010[67]. A significant reduction in genital warts of 25% amongst older (non vaccine eligible) heterosexual men is also becoming apparent, suggesting increasing herd immunity[68]. Trend analysis of data from the Victorian Cervical Cytology Registry has indicated a decline in the incidence of high-grade CIN2+ in women under the age of 18 years between 2007 and 2009, but no similar declines in low-grade CIN or in older women[69]. Whilst linkage the individual level is required to confirm that this ecological correlation is due to vaccination, the early observed decline is promising and in agreement with pre-vaccination predictions[70].

When vaccinated cohorts will reach the target age currently defined for screening, screening policies may require adaptation with less frequent screening and more specific HPV-based screening methods[71].

Evidence-based guidelines for cervical cancer prevention—Systematic reviews on new screening and vaccination strategies are often conducted simultaneously in several countries and institutions. This results in multiplication of resources, dilution of competencies, and sometimes yields contradictory findings, generating confusion among stakeholders, health professionals and the general public. International coordination is needed involving specialists skilled in health-technology assessment, HPV epidemiology and clinical experts, allowing for balanced interests[72].

PRIMARY PREVENTION AND TREATMENT OF VULVAR PRECANCEROUS LESIONS

In 2004, the International Society for the Study of Vulvar Disease (ISSVD) revised vulvar precancer terminology according to the recognition of two forms of vulvar squamous cell cancer, one related to HPV, termed *VIN usual type,* as it is the most frequent form of VIN, and one not related to HPV, termed *differentiated VIN*[73]. HPV related precancer lesions were thus collated into a single category, which includes what was previously categorised as VIN2 or VIN3, and VIN1 was excluded because it represents HPV infection and the term lacks reproducibility. Therefore trials including only VIN2/3 patients will be termed simply as “VIN”.

High protection against HPV16/18-related VIN or worse disease has been shown in a pooled analysis of randomised prophylactic vaccination trials with quadrivalent HPV vaccine (100% in baseline HPV16/18-negative women, and 62% in women including those who were HPV16/18 positive at baseline)[74].

Currently, no evidence is available supporting screening for VIN or vulvar cancer. In addition, after surgical treatment of VIN, poorer quality of life and sexual function[75] and recurrence are frequently reported [76]. Randomised trials have demonstrated that topical treatment of VIN with imiquimod reduces lesion size[77,78], however side effects were common.

Favourable results have been reported from randomised trials evaluating the therapeutic effect of vaccination of HPV16-positive VIN patients, using E6 and E7 peptides or fusion HPV16 E6E7L2 protein primed by topical imiquimod treatment[79,80].

PRIMARY AND SECONDARY PREVENTION OF ANAL CANCER

Prevention efforts fall into two categories: screening for and treatment of high-grade anal intraepithelial neoplasia (HGAIN**,** AIN grade 2 or 3), the anal cancer precursor, and prevention of anal HPV infection through HPV vaccination. Screening for anal cancer and HGAIN is proposed for high-risk groups but not for the general population. The main argument in favour of screening is the analogy with, and success of screening and treatment for CIN to prevent cervical cancer. The primary argument against anal screening is the absence of studies showing that HGAIN treatment reduces the incidence of anal cancer. It is critical to set up such trials as well as studies on biomarkers to predict progression from HGAIN to cancer [81].

Currently, the primary screening tool for anal HPV-associated diseases is anal cytology, with referral of screen-positive individuals for high resolution anoscopy and anal biopsy, with treatment decisions based on the grade of AIN. HGAIN can be treated using a variety of approaches depending on size and location. Some clinicians screen high-risk patients with standard anoscopy[82].

HPV vaccination holds promise for the reduction of the incidence of anal cancer in the long term. A recent RCT in HIV-negative MSM has shown that the quadrivalent vaccine has 74.9% efficacy against HGAIN (95%CI:8.8-95.4) in the per-protocol population and 54.2% (95%CI:18.0-75.3) in the intention-to-treat population[83]. Prevention of AIN and anal cancer was approved by the U.S. Food and Drug Administration (FDA) as an indication for the quadrivalent HPV vaccine in men and women aged 9-26 years[84]. The bivalent vaccine was recently shown to reduce the risk of acquiring anal HPV infection in women[85], but has not yet been studied for efficacy against AIN. It will likely be several decades before a reduction in anal cancer is detected among the vaccinated population.

PREVENTION AND TREATMENT OF HPV-RELATED MALE GENITAL LESIONS

Anogenital warts are the most common clinical manifestation of HPV infection[86]. Though they are benign and not associated with mortality, they are a source of psychosocial distress and can cause physical discomfort including pain, bleeding and itching. Genital warts are highly infectious; approximately 65% of people whose sexual partner has genital warts will develop warts themselves. Warts appear between 3 weeks and 8 months after an HPV infection[87,88]. Although perhaps 20-30% of genital warts spontaneously regress, recurrence of warts is common, resulting in high medical costs for treatments. A high lifetime number of female sexual partners significantly increase the risk of genital warts, while frequent condom use was protective in some, but not all studies.

Prevention of genital HPV infection and genital warts through vaccination

In a phase III trial in men aged 16-26 years, the efficacy of the quadrivalent vaccine against HPV-6/11/16/18 related external genital lesions (EGLs) in the intent-to-treat population was high (65.5%, 95%CI:45.8-78.6), as was efficacy against development of EGL regardless of HPV type (60.2%, 95%CI:40.8-73.8)[89]. In the per protocol population, vaccination reduced the incidence of HPV-6/11/16/18-related EGLs by 90.4% (95%CI:69.2-98.1). Efficacy against genital warts in this population was 89.4% (95%CI:65.5-97.9). In addition, the vaccine protected against HPV-6/11/16/18-related persistent infection.

Prevention of genital HPV infection and disease through circumcision

Circumcision at young age has long been known to be associated with a decreased risk of penile cancer. Recent RCTs showed that adult male circumcision resulted in ~50% decreased incidence of HIV infection, as well as a significant lower incidence of. penile hr-HPV infection in both HIV-negative and -positive men, and in female partners of HIV-negative men but not in the female partners of HIV-positive men[90]. Therefore circumcision of neonatal boys and adult males contributes directly to HPV control, as well as to the control of other sexually transmitted diseases acting as co-factors for HPV transmission.

PRIMARY PREVENTION, DIAGNOSIS AND TREATMENT OF HPV-RELATED OROPHARYNGEAL CANCER

HPV and prognosis of oropharyngeal cancer

Tumour HPV status is now established as a significant predictor of survival for patients with loco-regionally advanced OSCC[91] corresponding with a 60% lower risk of death, equivalent to a 30% difference in absolute five-year survival[34]. The survival difference is attributable to multiple factors: younger age, higher performance status, less co-morbidities among HPV-positive patients, increased response rates to both cisplatin-based chemotherapy and radiotherapy and lower risk of second primary tumours[34]. Importantly, a history of ≥10 pack-years of cigarette smoking reduces survival for HPV-positive patients. Treatment strategies for the low-risk group (HPV-positive/<10 pack-years) are now investigating whether treatment intensity and thus long-term morbidity can be reduced without compromising survival. By contrast, strategies to improve survival for the other risk-groups include addition of molecularly targeted agents to the platform of concurrent cisplatin-based chemoradiotherapy. Clinical trials are now stratified by tumour HPV status. Furthermore, routine testing of OSCC tumour HPV status is now recommended in US guidelines.

Diagnostic challenges in the diagnosis of OSCC

Introduction of HPV testing in the clinic has been hindered by the absence of validated assays. HPV in situ hybridization (ISH) or a surrogate of HPV E7 oncoprotein function, p16 immunohistochemistry (IHC), were most frequently used in trials that established HPV as a prognostic factor. Available algorithms in the literature with sensitivity and specificity for HPV16 E6/7 oncogene expression (the gold standard) approaching 100% have combined p16 IHC with PCR detection of HPV DNA in fresh frozen tumour and are therefore unlikely to be feasible in a routine pathology laboratory[92]. p16 IHC has shown high sensitivity (≥90%) and moderate-to-high (>80%) specificity for HPV16 E6 mRNA expression as well as high inter-reader agreement[82,93]. Commercially available ISH assays show variable sensitivity and specificity estimates[94,93]. In the future, the decreased prevalence of HPV16/18-related precancer resulting from prophylactic vaccination will warrant more specific and less frequent screening.

Future directions

Areas for future research include: (1) the role of HPV in non-oropharyngeal cancers of the head and neck; (2) the molecular underpinnings for the improved response rates to chemotherapy and radiotherapy for HPV-positive patients; (3) the prevalence and distribution of oral HPV infection in the population; (4) the natural history of oral HPV infection; (5) the efficacy of HPV vaccines in preventing oral HPV16 infections; (6) the potential utility of oral HPV testing for screening; (7) the precise characterisation of HPV-positive premalignant lesions, and (8) identification of novel surrogate markers of HPV infections and/or HPV-induced (pre-)malignant lesions.

CONCLUSIONS

The EUROGIN roadmaps represent a continuing effort to update and interpret information on primary and secondary prevention of cervical cancer. This year the roadmap widened its focus and also addressed the burden and prevention, diagnosis and treatment of other HPV-related disease.

HPV infection causes approximately 600,000 cases of cancer of the cervix, vulva, vagina, penis, anus and oropharynx annually, as well as benign diseases such as genital warts and RRP. Whereas the incidence of cervical cancer has been decreasing over recent decades, the incidence of other HPV-related cancer for which there are no effective screening programs has been rising over the last decades.

Cervical cancer screening effectiveness may be improved by replacing frequent cytology with HPV screening of women aged 30-35 years or older every 5 to 8 years, using validated assays. Defining the best triage algorithms, age ranges and screening intervals are priorities for research. The specificity of HPV-based screening could be improved by using more specific tests or by applying more specific triage strategies (for instance higher viral load cutoffs, mRNA testing, genotyping, p16 and other biomarkers).

HPV vaccination will reduce the burden of cervical precancer and probably also of invasive cervical and other HPV-related disease in women. In the future, the decreased prevalence of HPV16/18-related precancer resulting from prophylactic vaccination will warrant less frequent and more specific screening.

These promising findings should now be translated in cost-effective strategies, by preference following an organised approach integrating primary and secondary prevention, according to scientific evidence and adapted to the local situation with particular attention for regions with the highest burden of disease.

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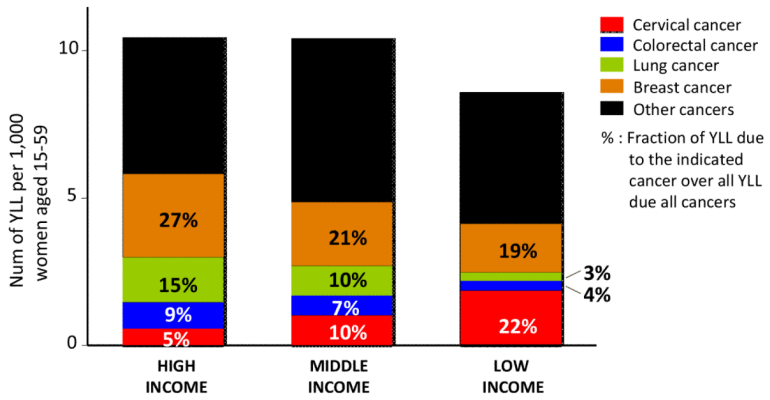

Figure 1.
Years of life lost (YLL) lost to cancer in women aged 15-59 y by income of the country.

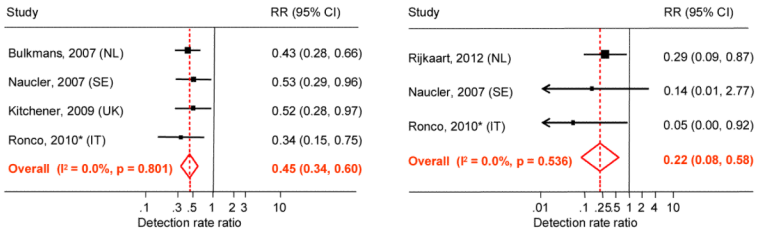

Figure 2.

Meta-analysis of the main outcomes from randomised trials comparing HPV- and cytology-based cervical cancer screening. Relative detection rate of CIN3+ (left panel) and cervical cancer (right panel), observed in the second screening round among women who were HPV-negative versus cytology-negative at enrolment. * restricted to women 35 years or older.

Table 1

Cancers associated with high-risk HPV infection and with HPV16 and 18 infection.

Site	Attributable to hrHPV	Of which HPV16/18	Number of cancers: Total	Number of cancers: Attributable to hrHPV	Number of cancers: Attributable to HPV16/18
Cervix	100% [2]	71% [4]	529,500 [19]	529,500	375,945
Penis	47% [9]	74% [9]	26,300 [23]	12,361	9,098
Vulva	40% [95]	93% [95]	30,000 [23]	12,000	11,100
Vagina	70% [95]	93% [95]	15,000 [23]	10,500	9,750
Anus (female)	84% [95]	94% [95]	15,900 [23]	13,356	12,561
Anus (male)	84% [95]	94% [95]	14,5900 [23]	12,180	11,455
Oro-pharynx (female)	19% [96†]	89% [13]	12,900 [97]	2,394	2,138
Oro-pharynx (male)	19% [96†]	89% [13]	48,900 [97]	9,291	8,299
All sites (females)	**9.4%**	**6.8%**	**6,044,710**	**567,750**	**411,494**
All sites (males)	**0.5%**	**0.4%**	**6,617,844**	**33,832**	**28,852**
All sites (both sexes)	**4.8%**	**3.5%**	**12,662,554**	**601,582**	**440,346**

hrHPV: high-risk human papillomavirus

† weighted average of region-specific estimates (derived from de Martel *et al*, 2012)[96]

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Table 2

HPV vaccination policies and coverage (for the third dose) of prophylactic HPV vaccination in a selection of developed countries (web table)

Country	Region	Organisation	System	Target group	Period	Vaccine	Definition coverage	Coverage (3rd dose)	Report date	Source
Australia	Whole country	Organised, school-based	Routine	12-13 y	Since 2009	4-valent	12-13 y* 14-15 y	73% 72%	Mar/11	http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv
		Organised, school-based +GPs+ community providers	Catch-up	12-26 y	2007-2009	4-valent	16-17 y 18-19 y 20-26 y	66% 38% 30%	Mar/11	
Belgium	Whole country	Opportunistic (partially reimbursed)	On pre-scription by physician	12-18 y	Since Nov 2007: 12-15 y; since Dec 2008: 12-18 y	2 & 4-valent	Dec, 2009 C1991 C1992 C1993 C1994 C1995	10% 69% 64% 51% 37%	Oct/11	WIV/IMA 2011; Arbyn, Gynecol Obstet Invest 2010; Simoens, Fabri et al, Eurosurveillance 2009 Lefevere, Vaccine 2012
	Flemish Community	Organised	Routine	1st yr secondary school; (GPs, paediatricians)	Since Sep 2010	4-valent	C1998 (school yr 2010-11)*	83%	Oct/11	www.zorg-en-gezondheid.be/HPV/
	French Community	Organised	Routine	2nd yr secondary school	Planned to start in Sep 2012	2-valent	-	-	-	www.sante.cfwb.be
Canada	British Columbia	Organised	Routine	Grade 6 and 9	Since September 2008	4-valent	Grade 6 (2008) Grade 9 (2008)	62% 62%	-	
	Quebec	Organised	Routine	Grade 4 and 9. Doses at months 0 and 2 and year 5	Since September 2008	4-valent	Grade 4, 1st 2 doses (2008)	80%	-	-
							Grade 9, 3rd dose (2008)	81%		
	Ontario	Organised	Routine	Grade 8	Since Sept 2007	4-valent	-	-	-	
Denmark	Whole country	Organised	Routine, via GPs	12 y	Since Jan 2009	4-valent	C1993 C1994 C1995	77% 82% 83%	May/11	www.ssi.dk.EPI-NEWS, National Surveillance of Communicable Diseases, Statens Serum Institut, Dept. of Epidemiology, Copenhagen, No. 18, 2011
			Catch-up, via GPs	Cohorts 1993-95 Oct 08- Dec 10 (13-16 y)	Since Jan 2009	4-valent	C1996 C1997	79% 70%	May/11	

Country	Region	Organisation	System	Target group	Period	Vaccine	Definition coverage	Coverage (3rd dose)	Report date	Source
France	Whole country	Opportunistic (partially reimbursed)	On pre-scription by physician	Priority: 14 y Adolescents 15-23 y if not or <1 y after start sexual activity	Since Jul 2007	4-valent*	C1991* C1992 C1993 C1994	25% 28% 24% 15%	Aug/11	http://www.invs.sante.fr/publications/2010/
the Nether-lands	Whole country	Organised: mass campaigns by GGDs*	Routine	12 y	Since 2010	2-valent	C1997	52%	Feb/11	www.rivm.nl
			Catch-up	Cohorts 1993-96 (age 13-17)	In 2010 only	2-valent	C1993-96	52%	Feb/11	
New Zealand	Whole country	Organised	Routine	13 y	Schoolyr 2009-10: Schooly 2010-11	4-valent	C1997 C1998	49% 34%	Oct/11	
New Zealand	Whole country	Organised by GPs	Catch-up	Girls 14-20 y	2008-11	4-valent	C1990-91 C1992-96	41% 49%	Oct/11	
Spain	Whole country	Organised (school based or via GPs)	Routine	1-year cohort in the 12-14 (last yr primary school)	Since 2009	2-valent & 4-valent	School year 2009-10, 12-14 y	:64%	Sep/2011	www.msc.es/profesionales/saludPublica/prevPromocion/vacunaciones/coberturas.htm
UK	Scotland	Organised, school-based	Routine	2nd yr secondary school (aged ~12-13 y)	Since Sep 2008	2-valent	School yr 2009-10	87%	Aug/11	www.isdscotland.org/
		Organised, school-based	Catch-up	4th & 5th yr secondary school (aged ~14-16y)	Sep 2008-Sep 2011	2-valent	School yr 2009-10	80%	Aug/11	
			Routine & catch-up combined	All targets group above *	Since Sep 2008	2-valent	C1990 C1991 C1992 C1993 C1994 C1995 C1996	32% 51% 69% 68% 80% 89% 86%	Feb/11	
UK	England	Organised, school-based	Routine	12-13 y	Since school year 2008/09	2-valent	~C1996 ~C1997	84% 76%	Dec/10	http://www.dh.gov.uk/health/category/publications/

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Country	Region	Organisation	System	Target group	Period	Vaccine	Definition coverage	Coverage (3rd dose)	Report date	Source
		Organised, school-based+GPs+community centres	Catch-up	13-18 y	School years 2009/10 & 2010/11	2-valent	~C1991 ~C1992 ~C1993 ~C1994 ~C1995	47% 39% 42% 69% 69%	Dec/10	
USA	Whole country	Opportunistic through providers offices (partially reimbursed)	Routine	Priority:11-12 y	Since Jan 2007	4-valent	(2010; age at interview) 13-17 y 13 y 14 y 15 y 16 y 17 y	32% 23% 31% 32% 37% 38%	Aug/11	National Immunization Survey (chart-verified survey)
		Opportunistic through providers offices (partially reimbursed)	Catch-up	13-26 y	Sep 2008-Sep 2011	4-valent	(2009) 19-26 y	17%	Aug/11	National Health Interview Survey, http://www.cdc.gov/vaccines/stats-surv/nhis/2009-nhis.htm#04

* Australia: Coverage is reported by age as at mid 2007 (start of the program) using estimated resident populations as the denominator and doses notified to the National HPV Vaccination Program Register as the numerator. Notification of doses outside of school programs was not compulsory, leading to underestimation of true coverage, and consumers may opt off having their details recorded.

* Belgium, whole country, coverage estimated from health insurance claims (obligatory insurance, corrected for vaccinations funded by additional insurance).Source: Belgian experience in HPV vaccine implementation: Arbyn M, Fabri. Istanbul, WHO European Regional Meeting on Cervical Cancer Prevention, 11-12 October 2011.

* Belgium, Flemish Community: Corrected for incomplete registration of vaccinations by GP/paediatrician

* France: estimation for girls having the age of 14-17 y in the period Jul2007-Jul2009

* France: extended to the 2-valent vaccine (Haut Conseil de la Sante Publique, 17 December 2010)

* Part of total vaccine cost reimbursed: 91% in Belgium; 65% in France

* the Netherlands: GGD: Gemeentelijke Gezondheidsdienst (Municipality Health Service)

*England: The catch-up period was in several regions brought back to one school-year 2009/10

* New Zealand: girls still have the possibility to obtain free HPV vaccination by GPs until the age of 20y.

* Scotland: Also including vaccination of new school leavers

*United States: Coverage is reported by age at vaccination. US tracks vaccination coverage among adolescents aged 13 through 17 years through the National Immunization Survey-Teen (NIS-Teen), a random-digit dialed sample of telephone numbers of household. After securing permission to contact vaccination providers, survey staff members mail questionnaires to obtain vaccination histories from the medical records. In 2010, the Council of American Survey Research Organizations (CASRO) response rate for NIS-Teen was 58.0%. A total of 19,488 adolescents with provider-verified vaccination records were included in this analysis, representing 59.2% of all adolescents with completed household interviews. US track vaccination coverage among young adults aged 19-26 y through the National Health Interview Survey (NHIS), a household survey of US households. The NHIS are not verified against medical charts.