

The Burden of HPV-Associated Ano-Genital Cancers

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Key words: Human papillomavirus; cervical cancers; anal cancer; penile cancer; vaginal cancer; vulval cancer; HPV vaccination; cervical screening.

Abstract

The epidemiology of ano-genitals cancers is under going substantial change. Cervical cancer remains a major public health concern, particular in resource-limited settings. Cancers of the anus, penis, vaginal and vulva are relatively uncommon cancers, but may be increasing in incidence. The change in occurrence of ano-genital cancers may be due to increasing HPV transmission secondary to changes in sexual behaviour. The screening programme and the HPV vaccine offer optimism that ano-genital cancers can in the future be prevented. This article reviews the epidemiology of ano-genital cancers with a focus on Scottish data.

Introduction

The epidemiology of human papillomavirus (HPV)-associated ano-genital cancers of the cervix, anus, penis, vagina and vulva is changing. Cervical cancer is a major health burden, particularly in less developed world regions, but screening and vaccination programmes give hope that this cancer will become progressively less common. Other HPV-associated ano-genital cancers including cancers of the anus and vulva are increasing in incidence. This increase may be associated with a rise in oncogenic high-risk HPV (HR-HPV) infections. The HPV vaccine, although designed to protect against cervical lesions, may be effective against other ano-genital cancers associated with HR-HPV types 16 and 18. This review article describes the current epidemiology of HPV-associated ano-genital cancers, recent time trends with a focus on Scottish data, and the potential impact of prevention on future occurrence.

Cervical cancer

Cervical cancer is a major public health concern worldwide: it is the fourth most common cancer in women, with an estimated half a million incident cases in 2012 [1]. Cervical cancers arise from the junction of the ecto- and endo-cervix, in a region called the transformation zone. The major histologic type of cervical cancer is squamous cell carcinoma, which accounts for up to two-thirds of cases. Adeno- or adeno-squamous carcinoma are the next most common types.. Infrequent or rare histologies include neuroendocrine or small cell carcinomas, rhabdomyosarcoma, primary cervical lymphoma and cervical sarcoma. Cervical cancer progresses from a pre-invasive lesion called cervical intra-epithelial neoplasia (CIN). Low-grade CIN lesions most likely regress, but high-grade lesions require complete treatment [2]. For high-grade CIN, the estimated rate of progression to invasive cancer if untreated is about 30-50% within 30 years but adequate treatment reduces this lifetime cancer risk to less than 1% [2].

There is marked geographical variation in the incidence of cervical cancer. To aid comparison of the burden of cervical cancer between countries, GLOBOCAN 2012 has estimated age-standardised incidence rate (ASR) by country and region [1]. The worldwide ASR is reported as 14 per 100,000 women of all ages per year. A number of countries in Sub-Saharan Africa and South America have an ASR for cervical cancer greater than 50 per 100,000 women. In contrast, rates of cervical cancer are less than 7 per 100,000 in the majority of Western Europe, Middle East, Western

Asia, Australia and New Zealand. The geographical variation in incidence of cervical cancer broadly mirrors the availability of universal cervical pre-cancer screening. Less developed regions of the world tend to lack the resources needed to implement cervical screening programmes and hence approximately 85% of new cases occur in this setting [3].

Risk factors for cervical cancer and pre-invasive disease are well characterised and include early onset of sexual activity [4], multiple sexual partners [4], smoking [5], a history of sexually transmitted diseases [6] and chronic immunosuppression including HIV infection [7]. Cervical cancer is less common in the sexual partners of circumcised men [8].

Comprehensive population screening programmes for cervical dysplasia and cancer have had a substantial impact on the incidence of cervical cancer [9]. Cervical cancer incidence data from the Scottish Cancer Registry illustrates the influence of such an intervention (Figure 1) [10]. In Scotland, cervical screening of a limited population began in the 1960s. A national programme was subsequently introduced in 1988 and triennial cervical screening is now offered to all eligible women aged 20-60 years [11]. The downward trend in incidence of cervical cancer in Scotland (Figure 1) parallels the introduction and increasing coverage of the national programme. European age-standardised rates per 100,000 women (EASR) in Scotland have fallen from 17.7 to 11.8 between the 5-year periods of 1972-1976 and 2007-2011 (Table 1) [10]. At the most recent census date in 2013, about 70% of women eligible for cervical screening in Scotland had been tested in the previous 3.5 years [11]. Similar observations of reduction in overall incidence of cervical cancer with time have been reported from countries that run a national cervical screening programme including Nordic countries, Canada and the USA [3].

Despite overall declines in cervical cancer rates, the cervical screening programme in Scotland has had little impact on cervical cancer incidence among young women and rates may actually be increasing in this demographic (Figure 1). The incidence rate in women aged 25-29 years in Scotland has increased from 6.6 to 16.4 per 100,000 women during the past three decades [10]. This increase reflects reduced attendance for cervical screening among younger women with continuing risk of HPV transmission [3,11]. Uptake for cervical screening for women in Scotland varies by age: in 2012/13 only about half of women aged 20-29 years attended compared to a near 80% uptake amongst women aged 40-49 years [11]. In the United Kingdom, increases in cervical cancer incidence have been reported in successive generations of women born since the 1930s [12]. Generation-specific increases in cervical cancer incidence driven by an increasing trend in risk among young women are also evident in data from Finland, Denmark and Sweden [3,13,14].

Global mortality rates depend upon interventions that are most likely to be available in developed countries: the presence of cervical screening programmes; and availability of both effective treatment and the prophylactic human papillomavirus vaccination [15]. Reported mortality ASR range from about 50 per 100,000 women in East and Southern Africa to less than 2 per 100,000 women in Western Europe, Australia and New Zealand [1]. Disease stage is the most important prognostic indicator for survival from cervical cancer [16]. In low-income settings the vast majority of those diagnosed with cervical cancer will die from the disease because the

presentation is often after extensive spread and cancer treatment modalities are limited [15]. Two-year cancer survival rates of less than 20% are reported in women undergoing radiotherapy in Kenya [17] and similarly dismal survival has been reported from other countries in sub-Saharan Africa [15]. In countries with health services that can provide screening and multimodality cancer care, 5-year case-survival rates between 60-70% are achieved [16].

Anal Cancer

Squamous carcinoma of the anus and anal canal is a relatively rare malignancy comprising approximately 2% of cancers of the digestive system [10,18]. Anal cancer arises from the anal mucosa where glandular elements of the gastrointestinal tract transition into squamous mucosa. Persistent infection with HR-HPV is considered responsible for a large proportion of anal cancers [19]. The reported worldwide ASR is about 1.0 per 100,000 [9]. In Scotland there are about 100 cases diagnosed annually [10].

The majority of risk factors associated with the development of anal cancer are associated with sexual activity [19,20]. Women with anal cancer are more likely to have reported ten or more lifetime sexual partners [21], a sexually transmitted disease (HSV2, chlamydia trachomatis, gonorrhoea) [21,22], genital warts [22], or receptive anal intercourse with two or more partners [22]. A strong relationship has been shown between developing anal cancer and other genital cancers (cervical dysplasia, cervical cancer and cancers of the vagina and vulva) [23,24]. In a prospective national population-based study of Swedish women the incidence rate ratios of anal cancer were five-fold higher and increased over time in women with a history of high-grade CIN [23]. In a study in the United States using data from the Surveillance Epidemiology and End Results (SEER) programme, women with cervical cancer had a relative risk of about five for subsequent anal cancer. Women with a background of vulvar intraepithelial neoplasia (VIN) and vulvar cancer also had a significantly increased risk of anal cancer [25]. Among men, the development of anal cancer was associated with receptive anal intercourse and a history of genital warts or gonorrhoea [22]. Cigarette smoke has been reported to be associated with an increase in anal cancer in both men and women [26].

Similar to cervical cancer, anal cancer may progress from a pre-invasive condition called anal squamous intraepithelial neoplasia (AIN) [27]. There is a paucity of data on the natural history of AIN and studies are currently underway to address this. AIN is prevalent in groups at risk for anal cancer with the most important risk factors being high-risk sexual behavior, HIV-infection, iatrogenic immunosuppression and a history of other HPV-associated genital cancers [27].

Although a relatively rare cancer overall, within certain risk groups, such as men who have sex with other men and HIV-infected people, the incidence is increased [27,28]. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) analysed data from 13 cohorts (including 34,189 HIV-infected and 114,260 HIV uninfected individuals) and reported the following anal cancer incidence rates per 100,000 person-years: 131 for HIV-infected men who have sex with men (MSM), 46 for other HIV-infected men, and 2 for HIV-uninfected men [29]. The increased risk of HPV-associated disease in HIV-infected populations is due to a high

prevalence of HPV infections and alterations in cell-mediated immunity among individuals co-infected with HIV [27,28]. The rate of anal cancer among HIV-infected people increases with duration of HIV illness [30,31]. Presumably as more time is available for HPV infection to persist and cause oncogenic changes. The use of antiretroviral therapy has not led to a decline in the incidence of anal cancer in England [31]. Indeed, in the era of ART two studies from the USA report a slowly rising incidence of anal cancer [30,32]. This disappointing trend may be related to increased survival (with ART lengthening time at risk for the development of malignancy) and the result of recent increased use of anal screening increasing the number of new cases diagnosed. The risk of anal cancers is also increased among individuals with chronic iatrogenic immunosuppression including renal transplant recipients [33]. A national longitudinal study following solid organ transplant patients in Sweden reported a 10-fold increased risk of anal cancer [34]. Anal cancer incidence in excess of 12 per 100,000 has also been reported from chronic immunosuppressed transplant recipients in Denmark [33].

Although anal cancer is a relatively uncommon, the incidence has been reported to be increasing in countries including the USA [35], Scotland [36], Denmark [37] and Australia [38]. In Australia the annual incidence of anal cancer increased for all ages between 1982 and 2005 by more than 50%, from 0.65 to 1.00 per 100,000 [38]. Figure 1 shows the incidence rates of anal cancer stratified by age group over time in Scotland: between 1972-1976 and 2007-2011, incidence rates for cancer of the anus have increased 4.6-fold in women (from 0.5 to 2.3 EASR) and 2.3-fold in men (from 0.7 to 1.6 EASR) (Table 1) [10]. The most pronounced increase is in women between the ages of 40 and 65 years [10]. The Danish Cancer Registry has reported a similar observation with an increasing upward trend in anal cancer that is particularly evident in women [39]. Between 1978–1982 and 2003–2008, the age-standardised incidence rate of anal cancer increased from 0.68 to 1.48 per 100,000 person-years in women and from 0.45 to 0.80 per 100,000 person-years in men [39]. The average annual percentage change in incidence cases was over 5% for women under the age of 60 years and between 1-2% for older women and men of all ages [39]. A study using English cancer registry data compared estimated age-specific incidence rates of anal cancer in different birth cohorts and reported that the increase in anal cancer occurred in cohorts born around 1940 [40]. Changes in sexual practice during the “sexual revolution” of the 1960s may be responsible. Increasing rates of high-grade AIN and anal cancer have been reported in San Francisco and these increasing rates have been attributed to the increase risk in MSM and HIV-infected populations [41,42]. However, it is unlikely that any single high-risk group contributes to the increasing trend observed in general population cancer registries, such as in Scotland.

Curative treatment for anal cancer is based on a combination of chemotherapy and radiotherapy. Five-year relative case-survival rates from health resource-rich regions have improved over the past few decades and, for individuals under the age of 75 years, are in excess of 60% [43].

Penile Cancer

Squamous cell carcinoma of the penis is a rare malignancy in Europe and North America where it accounts for less than 1% of all cancers in men [10,44]. In resource-rich settings, the ASR in men is about 0.5–0.1 per 100,000 [9]. However, incidence

rates are greater in countries of the developing world, where it may account for 10% of reported cancers. Malawi, Uganda, Brazil, Paraguay, Columbia, Vietnam and India report an ASR greater than 2.0 per 100,000 [9,45].

The incidence rates of penile cancer reflect the presence of underlying risk factors for the disease. Risk factors largely relate to genital hygiene, chronic inflammation and persistent HPV infection [45,46,47]. Circumcision is protective and is associated with a three-fold reduction in risk of penile cancer [46]. Circumcision protects the male from some sexually transmitted infections including HPV, and is associated with reduction in the rates of penile inflammatory disease as well as easier hygiene [47]. Penile cancer is typically a disease of older men and is associated with low socioeconomic status [44]. In population based case-control studies men who developed penile cancer were more likely to report a prior history of genital warts, chronic penile rash, penile injury and phimosis [46]. Penile cancer is not an AIDS-defining malignancy, but the incidence is eightfold higher in HIV-infected men compared to that in non-HIV-infected men [48]. Smoking is an independent risk factor for penile cancer [46,47].

Early detection and treatment of pre-malignant penile lesions is important as it may prevent malignant progression and avoid penile amputation. However, penile intraepithelial neoplasia (PIN) is a relatively poorly defined condition. High-grade PIN is considered a precursor lesion to invasive penile cancer but the risk factors for development and progression to frank malignancy for the condition are not clearly known. Studies have consistently identified an association between PIN and HPV infection [47]. Risk factors for penile HPV infection include a higher number of sexual partners [49,50], lack of circumcision [49], having a sexual partner with CIN [51], a history of other sexually transmitted diseases [50], and a history of smoking [52].

Information on the time trends of penile cancer is sparse due to its rarity. Reports from Zimbabwe [53,45] and Uganda [55,56] suggest that the incidence may be falling; a finding potentially due to the roll out of ART and improved hygiene practices. However, in Scotland (Figure 1) and England the temporal rates of penile cancer appear to have remained constant (Table 1) [10].

The most important prognostic factor for survival in men with penile cancer is nodal status. The five-year cancer-specific survival among individuals with no lymph node metastasis is between 80-100%, dropping to less than 15% with extensive nodal disease [57]. Curative treatment requires a surgical approach, with chemotherapy and radiotherapy reserved for irresectable disease.

Vaginal cancer

Cancer of the vagina is a relatively uncommon cancer, with an ASR of 0.2–0.7 per 100,000 in most countries [58]. The median age at diagnosis of squamous cell carcinoma is 69 years, although the disease is seen occasionally in the third and fourth decades [59]. The majority of neoplasms are squamous cell carcinoma, but melanoma and adenocarcinoma also occur. Secondary vaginal cancer is more common than primary and may occur by direct extension from the cervix, vulva or endometrium [59].

Case-control studies suggest that women with vaginal cancer are more likely to report five or more lifetime sexual partners, to have an early age at first intercourse, and to be current smokers at diagnosis [59]. Approximately one-third of women presenting with a vaginal cancer have been treated for a prior ano-genital tumour, most often of the cervix [59]. Women previously treated for high-grade CIN are at a four-fold increased risk of developing invasive vaginal cancer [60]. Immunosuppression is also a risk factor with increased risk of vaginal cancer among women with HIV and following solid organ transplant [48,61].

Vaginal cancer may be preceded by vaginal intraepithelial neoplasia (VaIN). The natural course of VaIN has not been fully characterised. Although there have been no prospective studies, several retrospective investigations of various treatment modalities of VaIN have reported that up to 5% of cases progress to invasive vaginal carcinoma [62,63]. VaIN is consistently associated with prior or concurrent neoplasia elsewhere in the lower genital tract. In most studies, between 50 to 90% of patients with VaIN have a history of or current intraepithelial neoplasia or carcinoma of the cervix or vulva [64,65].

In Scotland, incidence rates for vaginal cancer have remained fairly constant since the early 1970s (Table 1, Figure 1) [10]. Similar results have been reported from England. However, cohort rates in England have increased in recent generations from 0.42 in women born in the 1940s to 0.82 per 100,000 in women born in the 1960s [40].

Diagnosis of cancer of the vagina is considered difficult due to lesions being missed on visual inspection or obscured by the blade of the speculum. This is important, as tumour size and invasion are key prognostic indicators [66,67]. There is little consensus as to the management of vaginal carcinoma and treatment may include surgery, pelvic radiotherapy and brachytherapy. Cancer-specific survival exceeds 70% at 5-years for early stage disease [67].

Vulvar cancer

Vulvar cancer comprises about 4-5% of cancers of the female genital tract [10,18]. The ASR of vulvar cancer for countries worldwide lies mostly between 1.0 and 1.8 per 100,000 [58]. The United States estimate about 5000 new cases per year [18], while a country with a relative small population such as Scotland reports about 100 incident cases per annum [10]. The mean age at diagnosis is about 65 years, but may be falling [68]. A 10% increase in incidence of vulvar cancer over the past decade has been reported among women less than 50 years [68]. Squamous cell carcinoma predominates, with a small number with other histopathologies including melanoma and sarcoma [9].

Risk factors for vulvar cancer include vulvar dystrophy (e.g. lichen sclerosus), cigarette smoking, HPV infection, and a history of one or more of the following: cervical cancer [69], VIN [70], CIN [23], and immunodeficiency syndromes [71]. A national study of women in Sweden reported over double the risk of vulvar carcinoma among women with a history of high-grade CIN compared to those with no history [23].

VIN is a recognised precursor lesion of vulvar cancer [70]. However, the available literature suggests that the progression rate to invasive vulvar carcinoma is low [72]. The incidence of VIN is increasing worldwide, primarily due to the increasing occurrence of this disease in young women [68,73]. In the USA, the SEER database reported an increase in VIN of 411% between 1973 and 2000 [73]. The risk factors for VIN are similar to those for vulvar cancer and include HPV infection [74], smoking [70] and HIV infection [75].

In Scotland, the incidence of vulvar cancer has increased over the past three decades, particularly among younger women (Figure 1) [10]. In Scotland: between 1972-1976 and 2007-2011, the European age-standardised incidence rates for cancer of the vulva have increased from an EASR of 3.3 EASR to 4.2 (Table 1) [10]. This finding is mirrored in the United States, where analysis of data from the National Cancer Registry revealed that the incidence of vulvar cancer has increased by 20% between 1973 and 2000 [73]. A similar finding has also been reported in Central Europe [68]. Generational factors may be important: age-standardised rates for vulvar cancer in England increased from 1.65 to 2.51 per 100,000 between birth cohorts of the 1940s and 1960s [40].

Definitive surgery is the treatment of choice for early stage vulvar cancer and, as in penile cancer, nodal status is the most important prognostic factor for survival. Reported five-year case-survival ranges from 70-90% for patients with negative lymph nodes, to 25-40% for those with positive nodes [76,77].

The role of HPV in ano-genital cancers

A uniting common risk factor for genital cancers is persistent infection with HPV [78]. Viral genotypes of HPV can be broadly split into “high-risk” (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and “low-risk” (6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81) types based upon their association with the development of cervical cancer [78]. HPV is also associated with condyloma acuminata, ano-genital (vaginal, vulvar, penile, and anal) squamous intraepithelial lesions and malignancy, and head and neck cancer [78]. HPV types 16 and 18 are the most commonly isolated carcinogenic HPV types in cancer [78].

The association between HPV and ano-genital cancers has been extensively analysed and reported by the International Agency for Research on Cancer (IARC) [78]. The worldwide distributions of HR-HPV genotypes has been well characterised in cervical cancer. HPV-16/18 is estimated to account for 70% of all cervical cancers worldwide, although the estimated HPV-16/18 fraction is slightly higher in more developed (72-77%) than in less developed (65-72%) regions [79]. About 20% of cervical cancers are not associated with HPV-16/18, and the six next most common HPV types are the same in all world regions and are namely HPV types 31, 33, 35, 45, 52 and 58 [79]. The HPV profile in HIV-infected women is similar to that in HIV-negative women [80].

For ano-genital cancers other than cervical cancer, studies are limited but HR-HPV types are consistently linked with cancer development. HPV 16 remains overwhelmingly the most predominant type associated with genital cancers, with HPV 18 the next most common [58]. The HPV Information Centre World Report

2014 estimates the proportion of ano-genital cancers attributable to oncogenic HPV16/18 for malignancy of the anus, penis, vagina and vulva to be 73%, 38%, 58% and 36% respectively [58]. For anal cancer, HPV 6, 11, 31 and 33 are found in a small proportion of tumours, although this may represent sampling of skin rather than the true anal canal [78]. HPV 6 and 11 appear to play a small but significant role in cancer of the penis [78]. In vaginal and vulvar cancers, HPV types 31, 33, 35 and 45 are found in a small but significant number of cases [78].

HPV is predominately a sexually acquired infection. Sexual transmission is reflected by the rapid increase in HPV prevalence reported after sexual debut and the significant increase in risk of HPV with increasing numbers of sexual partners [78]. Acquisition of genital HPV infection through non-penetrative sexual intercourse or other practices has been reported. These routes likely account for a very small proportion of acquisition. In a cohort of schoolgirls resident in Tanzania, who reported not having passed sexual debut, HR-HPV genotypes were detected in 5.3% of self-administered vaginal swabs [81]. An underreporting of sexual activity may account for this finding, as may the practice of intra-vaginal cleansing, an activity common in East Africa. HR-HPV has also been detected on the fingers of female University students studying in the United States [82], and may facilitate transmission of the virus to and from the genital region through self-inoculation.

The key steps necessary for HPV driven carcinogenesis include HPV infection, persistence of infection, progression to pre-malignant lesions and frank invasion. Provided that an invasive malignancy has not developed, the precursor lesions are reversible [78]. Infection of HPV in the ano-genital area manifests as a “field” effect. The genital tissues have a common embryological origin and are susceptible to infection and dysplastic change from similar carcinogenic factors. Infection with HPV can induce pre-malignant and malignant change across the entire ano-genital region.[23,25]. The higher incidence of cancers of the cervix compared to other ano-genital sites suggests that susceptibility and/or persistence of HPV infection in the transformation zone of the cervix is greater at this site.

The future of preventing ano-genital HPV-associated cancers

The future patterns of occurrence of HPV-associated ano-genital cancers are dependent on the balance between risk (largely driven by HR-HPV transmission) and prevention (by a combination of screening and vaccination).

Changing Risk of HPV transmission

Sexual intercourse is the primary route of transmission of genital HPV infection. In women aged less than 35 years, rises in HPV 16 genital infection has been reported both in Finland and in Sweden during the 1970s and early-1980s [83,84]. Increased HPV transmission likely reflects social changes in sexual behavior. The United Kingdom’s Third National Survey of Sexual Attitudes and Lifestyles (Natsal), reports sexual debut occurring at an increasingly earlier age and an increase in the number of lifetime sexual partners [85]. Both these behaviors are associated with increased HPV transmission and are risk factors for the development of HPV-associated genital cancers [78]. A study conducted among adolescents in Danish High Schools also reported a similar trend with teenagers reporting earlier sexual

debut and less use of safe-sex practices in more recent time periods [86].

Safe-sex practices including the use of condoms may reduce HPV transmission. Condom use has been associated with a reduction in the risk of acquiring HPV infection, clearance of infection, and higher rates of regression of CIN in women and penile lesions in men [87]. Circumcision also reduces the risk of HPV transmission [88,89]. Two randomized controlled trials in both HIV-seronegative and HIV-seropositive men have demonstrated that male circumcision reduces acquisition and increases clearance of high-risk HPV among men who have undergone circumcision compared with men who had no intervention [88,89]. Worldwide the prevalence of male circumcision is largely related to religious beliefs and programmes of action against HIV care. The populations with prevalence of circumcision among men exceeds 80% are located in North Africa, the African Horn and the Middle East [58].

Prevention of HPV-associated ano-genital disease

Prevention of HPV-associated genital cancers is theoretically achievable through screening and vaccination. Well-organised population-level screening strategies for cervical cancer are effective at reducing the incidence and mortality from cervical cancer [58]. Unfortunately the majority of countries worldwide continue to have only opportunist screening or no access at all [58]. The Papanicolaou (Pap) smear screening test samples cells from the junction of the ecto- and endocervix at the transformation zone using a brush or spatula. These cells are then placed directly on a slide and fixed (conventional) or suspended (liquid-based) into a liquid transport medium. It was first introduced in the USA in 1941 and has led to a reduction in cervical cancer incidence and mortality [3,14]. The cytological result from the Pap smear requires confirmation with a tissue biopsy to distinguish between cervical intraepithelial neoplasia and cervical carcinoma. HPV testing for high-risk genotypes is a recent addition to cervical screening and has a role either alone or in combination with a cervical smear [90, 91]. Combined results from four European studies comparing HPV testing (largely in conjunction with cytology) to screening by cytology alone, suggested that HPV testing reduced cervical cancer incidence [91]. However, this protection against the development of cervical cancer comes at the expense of increased number of colposcopies and cervical biopsies. Cervical screening in resource-limited settings relies on visual inspection. This has limited specificity but requires only basic equipment and health infrastructure, and gives immediate results. Two large randomised trails conducted in India have reported that visual inspection with acetic acid (VIA) screening followed by treatment reduces the rate of cervical cancer compared with no screening [92,93].

In the era of HPV vaccination, the efficacy of screening for cervical cancer and the target population for any such programme is currently under review. As the prevalence of cervical dysplasia decreases, the positive predictive value of the Pap test will also decrease and as a result, more women will be referred for unnecessary diagnostic procedures and follow-up that can lead to not insignificant morbidity [94]. Screening may need to continue for at least a further 50 years until unvaccinated sexually active women have passed the screening age and perhaps indefinitely; approximately 30% of cervical cancers are associated with HR-HPV types not contained in the current vaccine and cancers caused by these sub-types may persist despite good uptake of vaccination. In Scotland it has been recently announced that

the screening age will be raised from 20 to 25 years in 2015 when the first cohort of girls given the HPV vaccine reach screening age.

Screening for non-cervical ano-genital cancers remains in its infancy. The rarity of these cancers brings into question the feasibility of population-level screening. However, targeted screening in high-risk groups remains a possibility. The majority of work on screening in non-cervical ano-genital cancers is for anal lesions. AIN is analogous to those of cervical intraepithelial neoplasia. High-grade AIN has been demonstrated to progress to invasive anal cancer in limited series, providing the rationale for active treatment [95].

The prophylactic HPV vaccine was designed to reduce the incidence and mortality from cervical cancer and in order to be effective the recipient must not have been previously infected with the virus [96]. Two vaccines have been developed, a quadrivalent vaccine that targets HPV 6, 11, 16, and 18 (Gardasil) and a bivalent vaccine that targets HPV 16 and 18 (Cervarix). HPV genotypes 16 and 18 are associated with the majority of cervical cancers and CIN worldwide, and HPV genotypes 6 and 11 are associated with the vast majority of genital warts. The prophylactic HPV vaccine also protects against vulvar, and vaginal cancers and their precursor lesions (VaIN and VIN) caused by HPV 16 and 18 [97]. Cervarix demonstrated partial protection against acquisition of the non-vaccine HPV types (HPV 31/33/45/52/58) that cause approximately 20 percent of cervical cancers [98,99]. In men, Gardasil has demonstrated efficacy against the development of genital warts and AIN related to HPV 6, 11, 16, and 18 [100]. The HPV information center estimates that there are about half a million new cases of ano-genital cancers worldwide per year attributable to HPV 16/18 and hence preventable by the prophylactic HPV vaccine [58].

At least 110 countries have licensed Cervarix and over 120 countries have licensed Gardasil. However, inclusion of the HPV vaccine into national immunisation programmes remains more limited; in 2013 over 50 countries were implementing national HPV vaccination programmes, but few were resource-poor nations where the majority of cervical cancers occurs [101]. Key barriers to national rollout include financial constraints and lack of health systems to deliver the vaccine [101].

Worldwide HPV vaccination has tended to target girls, with only USA, Canada, Austria, and Australia recommending gender-neutral vaccination. The policy in Scotland was based on a lack of cost effectiveness for male vaccination but critics claim that the burden of HPV-associated disease including genital warts and anal pre-cancers and cancers was not fully accounted for in cost effectiveness models [102]. Critics of this policy in Scotland [103] argue that in today's mobile global population, men may not benefit from herd immunity from vaccinated Scottish girls. Nor will men who have sex with men and this is significant as this population have a relatively high burden of genital warts, AIN and anal cancers [100]. .

Conclusion

If recent trends are any guide, the next few decades will likely see dramatic changes in the burden of HPV-related ano-genital cancer. Resource poorer countries have a major challenge to rollout both HPV vaccine and cervical screening. The benefits of

HPV vaccination for boys will remain an emotive issue in many countries. The prophylactic HPV vaccine will likely protect against anal, penile, vaginal and vulvar cancers, but targeted screening of genital cancers in high-risk populations will be needed. For women in developed countries, governments must continue their commitment to both screening and vaccination programmes for the aim of eliminating cervical cancer to become a reality.

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Table 1. Trends in incidence of cancer of the cervix, anus, penis, vagina and vulva in Scotland.

Site		Combined 5 year periods							
		1972-1976	1977-1981	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006	2007-2011
Cervix	Number of cases: All Ages	2,048	2,038	2,166	2,243	1,884	1,652	1,433	1,584
	EASR per 100,000 (Incidence)	17.7	17.3	18.2	18.6	15.0	12.7	10.9	11.8
Anus	Number of cases: All Ages	97	140	216	250	312	311	376	476
	EASR per 100,000 (Incidence)	0.6	0.8	1.1	1.3	1.6	1.4	1.6	1.9
Penis	Number of cases: All Ages	144	143	129	170	185	181	202	285
	EASR per 100,000 (Incidence)	2.0	1.8	1.7	2.2	2.2	2.0	2.1	2.7
Vagina	Number of cases: All Ages	113	151	110	129	124	106	105	117
	EASR per 100,000 (Incidence)	1.0	1.4	1.0	1.1	1.0	0.9	0.8	0.9
Vulva	Number of cases: All Ages	359	389	374	380	449	459	481	562
	EASR per 100,000 (Incidence)	3.3	3.6	3.3	3.2	3.7	3.7	3.8	4.2

Source: Scottish Cancer Registry, ISD

Data extracted: March 2014

Cancer of the Cervix is defined as ICD-10 C53.

Cancer of the Anus and Anal Canal is defined as ICD-10 C21.

Cancer of the Penis is defined as ICD-10 C60.

Cancer of the Vagina is defined as ICD-10 C52.

Cancer of the Vulva is defined as ICD-10 C51.

EASR: age-standardised (using the 2013 European Standard Population) incidence rate per 100,000 person-years at risk.

Five year periods are as follows, 1972-1976, 1977-1981, 1982-1986, 1987-1991, 1992-1996, 1997-2001, 2002-2006 & 2007-2011.

Figure 1: Time trends of incidence rates of ano-genital cancers based on data from the Scottish Cancer Registry [10].

Panel A; Cancer of the Cervix defined as ICD-10 C53.

Panels B, C and D; Cancer of the Anus and Anal Canal defined as ICD-10 C21, for females and males combine, females only and men only respectively.

Panel E; Cancer of the Penis defined as ICD-10 C60.

Panel F; Cancer of the Vagina defined as ICD-10 C52.

Panel G; Cancer of the Vulva defined as ICD-10 C51.

