Increased risk of HPV-associated genital cancers in men and women as a consequence of pre-invasive disease

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Abstract

To assess the excess risk of HPV-associated cancer (HPVaC) in two at-risk groups – women with a previous diagnosis of high grade cervical intraepithelial neoplasia (CIN3) and both men and women treated for non-cervical pre-invasive ano-genital disease.

All CIN3 cases diagnosed in 1989-2015 in Scotland were extracted from the Scottish cancer registry (SMR06). All cases of pre-invasive penile, anal, vulval, and vaginal disease diagnosed in 1990-2015 were identified within the NHS pathology databases in the two largest NHS health boards in Scotland. Both were linked to SMR06 to extract subsequent incidence of HPVaC following the diagnosis of CIN3 or pre-invasive disease. Standardised incidence ratios were calculated for the risk of acquiring HPVaC for the two at-risk groups compared with the general Scottish population.

Among 69714 females in Scotland diagnosed with CIN3 (890360.9 person-years), 179 developed non-cervical HPVaC. CIN3 cases were at 3.2-fold (95% CI: 2.7 to 3.7) increased risk of developing non-cervical HPVaC, compared to the general female population. Among 1235 patients diagnosed with non-cervical pre-invasive disease (9667.4 person-years), 47 developed HPVaC. Individuals with non-cervical pre-invasive disease had a substantially increased risk of developing HPVaC - 15.5-fold (95% CI: 11.1 to 21.1) increased risk for females and 28-fold (11.3 to 57.7) increased risk for males.

We report a significant additional risk of HPV-associated cancer in those have been diagnosed with pre-invasive HPV-associated lesions including but not confined to the cervix. Uncovering the natural history of pre-invasive disease has potential for determining screening, prevention and treatment.

Summary box

What is already known?

A history of CIN3 confers a significant risk of HPV-associated cancer.

What is this study adds?

A history of non-cervical ano-genital pre-invasive disease is associated with significant additional risk of HPV associated cancer.

Determining risk of pre-invasive disease has potential for determining screening, prevention and treatment strategies. HPV vaccination for this high-risk group may provide benefit.

Introduction

The incidence of human papillomavirus (HPV)-associated, non-cervical cancers is increasing globally and Scotland is no exception. The increase in incidence of oropharyngeal cancer (OPC) has been the best documented and evidence that the HPV positive status in OPC confers an improved clinical outcome has focused much research into finding an explanation for this observation. However, other non-cervical genital HPV associated cancers are also increasing and this is less documented in the literature as is, arguably, the role of HPV status in the clinical outcome of those affected. In Scotland, the age-standardised incidence of cancers of the anus, penis, vagina and vulva rose by 1.6, 1.1, 0.1 and 0.9 per 100,000 respectively during 1970 – 2014 [1]. This trend is mirrored elsewhere in countries that have robust cancer registry data [2].

Reasons for the increase in cancers of the anus, penis and vulva are not fully understood although an increase in HPV infection supported by temporal changes in sexual practices and behaviors has been suggested. Individuals interviewed as part of the National Survey of Sexual Attitudes and Lifestyles (NATSAL) report younger age of first intercourse, increased number of lifetime heterosexual partners and an increase in the number of individuals reporting same-sex experience compared to earlier surveys [3]. In the USA, inferred trends in sexual behaviour over the past decades have paralleled the increasing incidence of HPV-related cancers [4]. This said, the differential influence of risk factors, including and beyond sexual behaviours makes the generation of a broad conclusion to explain this increase challenging.

It is important to monitor incidence of these neoplasms to determine the associated morbidity and mortality that could be preventable by HPV vaccination in future generations. However, the current HPV vaccines will not wholly protect individuals already infected with HPV, nor prevent disease associated with all 13 oncogenic types. As a consequence, the challenge remains of how to optimally manage and treat what can be particularly morbid cancers from a clinical and psychological perspective. To this end, a clear understanding of their epidemiology will help inform the requirement and nature of interventions for their detection, management and treatment.

The national organized cervical screening programme was introduced in Scotland in 1988 with the aim of reducing the incidence of invasive cancer of the cervix and has been a success. The European age standardized rate of invasive cervical cancer has reduced from 18/100,000 in 1988 to 10/100,000 in 2009, rising subsequently to 13/100,000 in 2015. The percentage of eligible women who were recorded as screened adequately was 73.4% [4]. However, in Scotland there is currently no coordinated/ organized surveillance for non-cervical genital cancers in any population group or guidance for surveillance of these sites in high risk groups except for enhanced cervical screening in HIV-positive women. This raises the concern that early diagnosis of curable non-cervical genital cancers may be missed despite individuals being seen regularly by medical services. Furthermore, gaining an understanding of particular groups who may be at increased risk of non-cervical genital cancers could aid a focused and standardised approach to the monitoring.

We have used national population data available in Scotland to systematically assess the excess risk of HPV-associated disease compared to the general population in two populations perceived to be at additional risk of associated disease: (a) women with a history of CIN 3 and (b) individuals with a history of non-cervical pre-invasive disease.

Methods

Data collation for women diagnosed with CIN3 and assessment of subsequent cancer risk

A retrospective cohort study of national data was performed in order to estimate the risk of HPV associated cancers (HPVaC) in those diagnosed with CIN 3**.** All individuals resident in Scotland are uniquely identified in National Health Service (NHS) datasets via their community health index (CHI) number. All cases of CIN3 (ICD10: 233.1) were extracted from the Scottish Cancer Registry (SMR06) [6]. As full introduction of national cervical cancer screening was introduced in 1988 [5], extraction of CIN3 from SMR06 was limited to Jan 1989 - Dec 2015 (with the latter year representing the most recent year for which data was available at time of extraction). Variables collected were gender, date of birth, health board and date of diagnosis of CIN3. All individuals with CIN3 were then linked to SMR06 to extract incidence of HPVaC (tonsil, base of tongue, soft palate, oropharynx not otherwise specified, cervix, vulva, vagina, penis, anus) (ICD10: C09, C01, C05, C10, C53, C51, C52, C60, C21, respectively) in addition to rectal cancer (ICD10: C20) which was used as a baseline comparator with no known association with HPV. Cancers with evidence of both vaginal and cervical malignancy were classified as cervical cancer. The analysis focussed on individuals over 18 years old given that over 95% of cancers listed above are diagnosed after this age [1]. Date of death/emigration was also captured in order to obtain the date of censoring due to loss of follow-up.

Data collation for individuals diagnosed with pre-invasive penile, anal, vulval and vaginal disease and assessment of subsequent cancer risk

All cases of pre-invasive penile, anal, vulval and vaginal disease and invasive malignancy diagnosed between 1990 and 2015 were identified within the NHS pathology databases associated with the two largest health boards in Scotland – NHS Greater Glasgow and Clyde (GGC) and NHS Lothian that together cover 2 million people and thus around 40% of the Scottish population. Data, collected as part of routine clinical care, on gender, date of birth, health board, date of diagnosis and degree of dysplasia were extracted. Subsequent HPVaC, rectal cancer and date of death/emigration were linked from national data as explained previously.

Statistical analysis

For each of the two at-risk populations, person time at risk and the number of observed cancers were stratified by age group in 5 year bands (18-19, 20-24, 25-30,…, 84-89, 90+), gender and year of diagnosis. The expected numbers of cancers occurring among the at-risk population, assuming the same incidence as that observed for the general population in Scotland (for patients with CIN3 history) or in GGC and Lothian (for pre-invasive cohort) stratified by the same age groups, gender and year of cancer diagnosis, was calculated by multiplying the person time at risk in each group by the corresponding average cancer incidence. The Standardised Incidence Ratio (SIR) was defined as the ratio of the observed to expected number of cancers and the confidence interval (CI) was calculated assuming that the observed number followed a Poisson distribution.

We excluded patients with a diagnosis of any HPVaC before a diagnosis of CIN3 or pre-invasive non-cervical disease. The person time at risk started counting at one year after CIN3 or pre-invasive non-cervical disease diagnosis and ended at earlier incidence of first HPVaC, death, emigration or the end of study (2015-12-31). Those with an HPVaC occurring within one year of CIN3 or pre-invasive non-cervical disease diagnosis were excluded in the baseline analysis to avoid mis-classification of concurrent disease as sequential disease events. A sensitivity analysis, considering an exclusion time of 0, 3, 6, 9 months, was conducted to examine the influence of this exclusion upon the results.

All analysis was conducted using R version 3.2.1.

Results

Risk of HPVaC following CIN3 diagnosis

Overall, 72153 women in Scotland had a diagnosis of CIN3 recoded in SMR06 between 1989-2015. Figure 1 presents the denominators of the at-risk populations, related exclusions and start and end point(s) of the analysis. After excluding the patients with HPVaC before or during the year directly after the diagnosis of CIN3, the denominator reduced to 69714, contributing 890360.9 person years (Table 1). The CIN3 population had a median of age of diagnosis of 30 (IQR 26-36) and of these 490 women had a diagnosis of any HPVaC more than one year after diagnosis of CIN3 corresponding to an SIR of 2.3 (95% CI 2.1-2.5) compared to the general female population in Scotland (Table 1).

The risk of developing a non-cervical HPVaC varied by the anatomical subtype - SIR ranged from 2.3 (95% CI 1.6-3.2) for oropharyngeal cancer to 9.6 (95% CI 7-13) for vaginal cancer (Table 1). The risk among women with CIN3 for anal and vulvar cancer was increased by more than 2-fold compared to the general female population. The SIR for non-HPV related rectal cancer did not differ substantially from unity (SIR = 1.1 95% CI 0.9-1.5) (Table 1).

The SIR for developing any non-cervical HPVaC in the context of a cervical screening programme was higher than that for cervical cancers (SIR for non-cervical HPVaC = 3.2, 95% CI 2.7-3.7; SIR for cervical cancer = 2.0, 95% CI 1.8-2.2) (Table 2). The SIR for non-cervical HPVaC increased with age at diagnosis CIN3 (SIR = 3.1 95% CI 2.2-4.1 for age <=30; SIR = 7.4 95% CI 0.9-26.8 for age >70). There was no time trend identified for the risk of non-cervical HPVaC by year of diagnosis of CIN3. Interestingly, there was no reduction in risk of developing a non-cervical HPVaC with increasing time from CIN3 diagnosis; the risk between 1-2 years from CIN3 diagnosis was similar to that more than 20 years after CIN3 diagnosis.

The risk of cervical cancer was significantly increased in all birth cohorts, except for the women born after 1965, for whom the risk did not differ from the general population. The greatest risk of cervical cancer was observed in the oldest cohort (women born before 1935: SIR = 10.1 95% CI 5.8-16.4; born 1936-1945: SIR = 7.4 95% CI 5-10.4). The risk of cervical cancer was increased in all ages when diagnosed after 30 years, with an increasing SIR for those diagnosed CIN3 at older age (SIR = 2.5 95% CI 2.1-3 for age 31-40; SIR = 14.3 95% CI 1.7-51.6 for age >70). There was no time trend observed in SIR by year of diagnosis of CIN3 and there was no decreasing trend in SIR for time since the CIN3 diagnosis – even after 20 years since diagnosis of CIN3 there remained an increased risk of cervical cancer (SIR = 2.6, 95% CI 1.6-4.1).

Risk of HPVaC following after non-cervical pre-invasive disease

Overall, 2309 patients had a diagnosis of pre-invasive (all degrees of dysplasia) and invasive penile, anal, vulvar and vaginal disease in GGC and Lothian. After excluding the patients with HPVaC before or during the year directly after the diagnosis of pre-invasive disease, the denominator for analysis reduced to 1235 (Figure 1). For each anatomical site of dysplasia, the majority were classified as severe dysplasia or dysplasia NOS (n=782, 63.3%) with a small proportion classified as having mild or moderate dysplasia (Table A2). For the cohort of each dysplasia site, the median age ranged from 41 (Interquartile range (IQR) 35-47) year for female perineum and 57 (IQR 39-64.5) years for penis (Table A2).

Overall 1035 women had pre-invasive disease in the ano-genital region (vagina, vulva, perineum and anus), contributing 8464.5 person years of follow-up (Table 3). Among them, 40 developed HPVaC one year or more after the diagnosis of pre-invasive ano-genital disease. Compared to the general female population resident in GGC and Lothian, the incidence of HPVaC for women with a history of pre-invasive disease was 15.5 times higher (95% CI 11.1-21.1). The SIR was highest for the patients with anal dysplasia (SIR = 38.9 95% CI 15.6-80.1) but lower for those with vaginal dysplasia (SIR = 9.4 95% CI 4.3-17.8).

198 male patients had pre-invasive anogenital disease (penis, perineum and anus), contributing 1202.9 person years (Table 3). Among them, 7 developed HPVaC one year or more after the diagnosis of pre-invasive disease. Compared to the male population resident in GGC and Lothian, the SIR for men with a history of pre-invasive

ano-genital disease to develop HPVaC was 28 (95% CI 11.3-57.7). The risk of cancer was highest for the patients with anal dysplasia (SIR = 36.4 95% CI 9.9-93.1) and lowest for those with penile dysplasia (SIR = 21.4 95% CI 4.4-62.6).

Sensitivity analysis

Sensitivity analysis was conducted for the CIN3 cohort to investigate the effect of changing the cancer exclusion period from the baseline choice of 1 year to 0, 3, 6 or 9 months. If no exclusion was applied, 631 cervical cancer cases were observed among CIN3 patients (SIR = 3.8), likely representing concurrent diagnosis. When a 3 months exclusion period was used, 374 cervical cancer cases were observed (SIR = 2.3) – similar to baseline analysis of 1 year (SIR = 2). The SIR did not materially change for developing non-cervical genital cancers when different exclusion periods were applied (Table A1).

For the non-cervical pre-invasive cohort, 741 patients with prior HPVaC were excluded for the following reasons: 1) the site of the pre-invasive disease matched the site of the prior HPVaC (Table A3); 2) The time difference between the diagnosis of pre-invasive and prior HPVaC was short (median 60 days IQR 20-238). Sensitivity analysis was performed again changing the exclusion period from 1 year to 0, 3, 6 and 9 months. SIRs for exclusion period of 3, 6 and 9 months were close to the baseline results (Table A4). However if no exclusion period was applied, a higher number of subsequent HPVaC cases was observed and the SIR inflated substantially compared to the baseline analysis.

Discussion

In the present evaluation which spanned 36 years and incorporated national data, we describe two groups at substantially increased risk of HPV associated cancer: those who have been diagnosed with high grade cervical lesions and those who have been treated for non-cervical pre-invasive disease to any degree. Notably, women who have had a CIN3 diagnosis (identified via screening) were at 3.2 fold increased risk of developing a non-cervical HPVaC (including a 9.6-fold risk of developing vaginal cancer) compared to the general female population in Scotland. In addition, individuals with non-cervical pre-invasive disease had a substantially increased risk of developing HPVaC, reflected as a 15.5 fold and 28 fold increased risk for females and males respectively compared to the general population. The additional risk was highest in patients with pre-invasive disease of the anus for both genders.

In women diagnosed with CIN3, the greatest risk of both non-cervical and cervical HPVaC was associated with older age at diagnosis but the magnitude of that risk was unaffected by time since diagnoses.

The observation that a history of CIN3 confers a significant risk of HPV associated cancer is consistent with other studies [7-14] such as the one performed by Kalliala and colleagues [10] who reported SIRs for vulvar, vaginal and anal canal cancer as 4.1 (95% CI: 1.5-8.9), 12 (2.9-28) and 5.7 (1.2-17) respectively. Strander et al [11] also reported SIRs for cervical and vaginal cancer as 2.3 (2.2-2.5) and 6.8 (5.6-8.2). Ebisch et al [14] reported incidence rate ratios for anal, vulvar, vaginal and oropharyngeal cancer as 3.9 (2.3-6.4), 5 (3.3-7.6), 86.1 (12-618.1) and 5.5 (1.2-24.8). In our study, SIRs for cervical, vulvar, vaginal and anal cancer were 2 (1.8-2.2), 2.8 (2.2-3.6), 9.6 (7-13), and 2.6 (1.9-3.6), which are in line with the Nordic studies [10,11], notwithstanding the fact that the authors did not exclude the patients with a previous diagnosis of HPVaC as we have in the present analysis. Strander et al and Ebisch et al document a duration of risk of at least 20 years, similar to the present findings [11,12,14].

The risk of HPV associated cancer in those with non-cervical pre-invasive disease is not well documented in the literature in contrast to the risk after CIN3. There is a particular paucity of studies which have taken into account large national data sets; rather the existing literature has focussed more on small cohort studies of HPV associated disease progression at a particular site with no comparator/control group [15,16]. Joura et al [17] reported that compared with those who underwent cervical surgery, those who were diagnosed with vulvar disease were at nearly 3 fold increased risk of developing any subsequent HPV related disease. To our knowledge the present analysis represents the first population based study of risk with comparison/contextualisation to the general population.

Ideally, screening or surveillance guidelines and management strategies should take into account the additional risks conferred on those with pre-invasive disease. This is easier to apply for cervical disease given the existence of an organised screening programme. Most countries that offer cervical screening now offer molecular HPV testing as part of post treatment follow up of CIN [18]. Further developments in the cervical screening in the UK (and beyond) which include the implementation of primary screening using molecular HPV testing are likely to identify those at risk of subsequent cervical disease earlier as demonstrated in trials of HPV vs Cytology screening, [19,20]. The sensitivity and earlier "warning" signal of an HPV test may thus deliver benefits to those with (any) HPV associated pre-invasive disease although this was not specifically investigated in the aforementioned trials. Furthermore, treatment for women with CIN3 by the gynaecologists should also include inspection of vaginal, vulva and perineum.

The most effective strategy to manage non-cervical HPV associated disease is more challenging. There is no population based screening programme or surveillance for AIN in Scotland, and so the risks reported in this study are likely to underestimate its occurrence. Screening for anal disease has been considered using a variety of approaches (cytology, high resolution anoscopy, HPV testing, biomarkers and various combinations thereof). However, currently, there is no evidenced, effective model for an anal screening and treatment pathway that would reduce risk of anal cancer. Given that treatment of anal lesions is associated with significant morbidity, further research is required. Longitudinal studies such as the Australian Study of the Prevention of anal cancer "SPANC" which monitors viral, cytopathological and anoscopy outcomes over time in an MSM population will be helpful in this regard [21,22].

Notwithstanding the limitations of the data on anal screening, arguably considerably more attention and research has been channelled into this area compared to screening for other non-cervical HPV associated cancers. This is likely attributable to the comparative rarity of penile, vulvar, & vaginal cancer, and the fact that OPC does not have a monitorable precursor phase, with patients presenting with symptomatic disease. Kreimer et al [23,24] showed that HPV-16 E6 serology can identify those at greater risk of subsequent anal and oropharyngeal cancer but not other HPV associated cancers; HPV16 E6 seropositivity was present in 29.2% of individuals who later developed anal cancer compared with 0.6% of controls [24] and in the prediagnostic samples of 34.8% of patients with oropharyngeal cancer and 0.6% of controls [23].

Another important point for consideration is why those with preinvasive lesions are at additional risk of subsequent cancer. Part of this explanation could of course be to do with the continuation of risk-associated behaviours after the initial diagnosis (including the key factors of smoking and social deprivation) which we did not assess in this study. Similarly, while Strander et al [12] adjusted for follow-up duration, treatment period, and age at treatment the authors did not adjust for behavioural/environmental influences. This said, the CIN3 population described in the present analysis represented women who were engaged in cervical screening. The study population was thus biased towards those from less deprived backgrounds with a lower risk of HPV infection and disease [25]. However, future studies which endeavour to capture behavioural data or surrogates will be important to (a) determine the key behavioural factors that confer risk of subsequent disease which could inform focussed management (b) quantify the extent of risk which remains after adjustment for such factors. With respect to the latter, it is entirely plausible that the efficacy and capacity of innate immune responses play a continued role in the susceptibility to HPV associated disease [26]. Only 5% of those infected with HR-HPV develop high grade cervical lesions the majority of which will resolve naturally, but immunocompromised patients have a higher risk of developing high grade disease [27-30]. However, the lack of understanding of the mechanisms determining persistence makes development of a therapeutic vaccine challenging. A further factor is the widespread colonisation of ano-genital, perineal and oral squamous mucosa by HPV. Treatment at one site in the absence of other measures to promote HPV clearance will not affect HPV burden at other infected sites, and so will not mitigate the risk of subsequent disease

Although current HPV vaccines are delivered as prophylactic regimens i.e. before HPV infection, there may be merit in vaccinating high-risk groups with preinvasive lesions. It is possible to stimulate HPV-specific antibodies in older women who have previously been diagnosed with abnormal pap smears through quadrivalent vaccination [31]. Furthermore, adjuvant administration of quadrivalent HPV vaccine has been shown to be associated with a significant reduction in recurrent high-grade anal intraepithelial neoplasia (HGAIN) in MSM [32]. Joura et al demonstrated a significant reduction in HPV related vulvo-vaginal disease in women who had been both vaccinated and also treated following vaccination for cervical disease [17]. Opportunistic HPV vaccination for our high-risk populations may prove to be beneficial in preventing subsequent development of HPV-related cancers, while gender-neutral HPV immunisation is associated with profound decreases in most of the clinically relevant oncogenic HPV types and will significantly reduce risk of HPVaC in men and women with preinvasive non-cervical ano-genital disease [33].

In summary in this analysis we demonstrate the significant additional risk of HPV associated cancer in individuals who have been diagnosed with preinvasive lesions including but not confined to the cervix. Further investigation into mechanistic and behavioural drivers that explain this phenomenon will inform screening and therapeutic strategies. Given the increasing incidence of HPV associated cancers in genital and non-genital sites within unvaccinated populations, this should be a priority for research.

Contribution

JP: performed statistical analysis and prepared manuscript

KK: supervised the study, contributed to design of the study, as well as drafts and revisions of the manuscript

KC: contributed to design of the study, contributed to drafts and revisions of the manuscript.

KP, DG, DM, SB, SG, AW, MC, TP: contributed to drafts and revisions of the manuscript.

KW: Obtained funded, supervised the study, contributed to design of the study, as well as drafts and revisions of the manuscript

Ethics approval

All data linkage was performed by the electronic Data Research and Innovation Service at National Services Scotland (NSS) Information Services Division (ISD). No patient identifiers were available to the study team with CHI replaced by a unique study ID prior to analysis. Linked data were accessed remotely via a secure connection to the National Safe Haven [34]. Information Governance approval for the study was granted by NHS NSS Privacy Advisory Committee, PAC number PAC54/14.

Competing interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: we had financial support from through Sanofi-Pasteur and the Beatson Cancer Charity for the submitted work but no conflict of interest. KCs institution has received research funding and or consumables to support research from the following entities in the last 3 years - Hologic, Cepheid, Qiagen, Euroimmun, LifeRiver, Genomica, Gene-First and SelfScreen. Other than this, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Role of the funding source

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Transparency declaration

The leading author of this article (Jiafeng Pan) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient and Public Involvement statement

A patient representative (FT) have reviewed and commented the manuscript.

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Reference

1. ISD Scotland. Cancer Statistics. Available at: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Female-Genital-Organ/ and http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Male-Genital-Organs/
2. Wakeham K, Kavanagh K. The Burden of HPV-Associated Anogenital Cancers. Curr Oncol Rep. 2014; 16:402.
3. Erens B, McManus S, Prescott A et al. National survey of sexual attitudes and lifestyles II. Available at: http://natsal.ac.uk/media/2083/reference_tables_and_summary_report.pdf
4. Ryser MD, Rositch A, Gravitt PE. Modeling of US Human Papillomavirus (HPV) Seroprevalence by Age and Sexual Behavior Indicates an Increasing Trend of HPV Infection Following the Sexual Revolution. J infect Dis. 2017; 216(5):604-11.
5. ISD Scotland. Cervical Cancer Screening. Available at: http://www.isdscotland.org/Health-topics/Cancer/Cervical-screening/
6. NHS Scotland. SMR06 – Scottish Cancer Registry. Available at: http://www.adls.ac.uk/nhs-scotland/scottish-cancer-registry-smr06/?detail
7. Gaudet M, Hamm J, Aquino-Parsons C. Incidence of ano-genital and head and neck malignancies in women with a previous diagnosis of cervical intraepithelial neoplasia. Gynecol Oncol. 2014; 134: 523-6.
8. Edgren G, Sparen P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. Lancet Oncol. 2007; 8:311-6.
9. Evans HS, NewnhamA, Hodgson SV et al. Second primary cancers after cervical intraepithelial neoplasia III and invasive cervical cancer in Southeast England. Gynecol Oncol. 2003; 90:131-6.
10. Kalliala I, Anttila A, Pukkala E et al. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. BMJ. 2005; 331:1183-5.
11. Strander B, Andersson-Ellström A, Milsom I et al. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. BMJ. 2007; 335 (7629):1077.
12. Strander B, Hällgren J, Sparén P. Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and morality. BMJ 2014; 348: f7361.
13. Jakobsson M, Pukkala E, Paavonen J Tapper AM et al. Cancer incidence among Finnish women with surgical treatment for cervical intraepithelial neoplasia, 1987-2006. Int J Cancer. 2011; 128(5): 1187-91.
14. Ebisch RMF, Rutten DWE, IntHout J et al. Long-Lasting Increased Risk of Human Papillomavirus–Related Carcinomas and Premalignancies After Cervical Intraepithelial Neoplasia Grade 3: A Population-Based Cohort Study. J Clin Oncol 2017; 22:2542-2550.
15. Stanley MA, Winder DM, Sterling JC et al. HPV infection, anal intra-epithelial neoplasia (AIN) and anal cancer: current issues. BMC Cancer 2012; 12: 398.
16. Jones, RW, Rowan, RM. Vulvar Intraepithelial Neoplasia III: A clinical study of the outcome in 113 cases with relation to the later development of invasive vulvar carcinoma. Obstet Gynecol. 1994; 84(5): 741-5.
17. Joura EA, Garland SM, Paavonen J et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ 2012; 344:e1401.
18. Cuschieri K, Bhatia R, Cruickshank M et al. HPV testing in the context of post-treatment follow up (test of cure). J Clin Virol. 2016; 76 Suppl 1:S56-61.
19. Kitchener HC, Gilham C, Sargent A et al. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. Eur J Cancer. 2011; 47(6):864-71.
20. Ronco G, Dillner J, Elfström KM et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014; 383(9916):524-32.

21. Jin F, Roberts JM, Grulich AE et al. The performance of human papillomavirus biomarkers in predicting anal high-grade squamous intraepithelial lesions in gay and bisexual men. AIDS. 2017; 31(9):1303-11.
22. Machalek DA, Jin F, Poynten IM et al. Prevalence and risk factors associated with high-grade anal squamous intraepithelial lesions (HSIL)-AIN2 and HSIL-AIN3 in homosexual men. Papillomavirus Res. 2016; 2:97-105.
23. Kreimer AR, Johansson M, Waterboer T et al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol. 2013; 31(21):2708-15.
24. Kreimer AR, Brennan P, Lang Kuhs KA et al. Human papillomavirus antibodies and future risk of anogenital cancer: a nested case-control study in the European prospective investigation into cancer and nutrition study. J Clin Oncol. 2015; 33(8):877-84.
25. Tanton C, Soldan K, Beddows S et al. High-Risk Human Papillomavirus (HPV) Infection and Cervical Cancer Prevention in Britain: Evidence of Differential Uptake of Interventions from a Probability Survey. Cancer Epidemiol Biomarkers Prev. 2015; 24(5):842-53.
26. Song D, Li H, Li H et al. Effect of human papillomavirus infection on the immune system and its role in the course of cervical cancer. Oncol Lett. 2015; 10(2):600-6.
27. Rodríguez AC, Schiffman M, Herrero R et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst. 2008; 100(7):513-7.
28. Munro A, Powell RG, A Cohen P et al. Spontaneous regression of CIN2 in women aged 18-24 years: a retrospective study of a state-wide population in Western Australia. Acta Obstet Gynecol Scand. 2016; 95(3):291-8.
29. Macdonald M, Smith JHF, Tidy JA et al. Conservative management of CIN2: National Audit of British Society for Colposcopy and Cervical Pathology members' opinion. J Obstet Gynaecol. 2017: 1-7.
30. Reusser NM, Downing C, Cuidry J et al. HPV Carcinomas in Immunocompromised Patients, J Clin Med. 2015; 4(2):260-81.
31. Dhar JP, Essenmacher L, Dhar R et al. The effect of history of abnormal pap smear or preceding HPV infection on the humoral immune response to Quadrivalent Human Papilloma virus (qHPV) vaccine in women with systemic lupus erythematosus. Hum Vaccin Immunother. 2018; 30:1-5.
32. Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis. 2012; 54: 891-898.
33. Lehtinen M, Luostarinen T, Vänskä S et al. Gender-neutral vaccination provides improved control of human papillomavirus types 18/31/33/35 through herd immunity: Results of a community randomized trial (III). Int J Cancer. 2018 May 30. doi: 10.1002/ijc.31618. [Epub ahead of print]
34. NSS ISD. Use of the NSS National Safe Haven. Available at: http://www.isdscotland.org/Products-and-Services/EDRIS/Use-of-the-National-Safe-Haven/