



Syndemic synergy of HPV and other sexually transmitted pathogens in the development of high-grade anal squamous intraepithelial lesions

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ABSTRACT

Background: Anal intraepithelial neoplasia is associated with high-risk human papillomavirus (hrHPV) as a precursor to anal cancer. However, factors other than hrHPV are likely to be involved and further study of cofactors is required because of the possibility of syndemic interactions.

Methods: Three hundred and fourteen patients underwent 457 operations. Histopathology and hrHPV testing using the Digene Hybrid Capture 2 (HC 2) method were performed. Demographic factors and sexually transmissible infections (STIs) were recorded.

Results: Results showed that hrHPV alone was associated with HSIL (OR = 4.65, $p < 0.001$). None of the other STIs were alone associated with HSIL but amplification of risk was found when hrHPV infection occurred with HIV (OR = 11.1); syphilis (OR = 5.58); HSV 2 (OR = 7.85); gonorrhoea (OR = 6.45) and some other infections.

Conclusions: These results suggest that hrHPV is a sufficient cause of anal HSIL. Seropositivity for HIV, HSV 2, *T. pallidum*, HBV and HCV and a history of gonorrhoea or chlamydia exert a powerful amplifying factor increasing the risk of HSIL above the risk with hrHPV alone. Other co-factors which are associated with an increased risk of HSIL are increased age, male gender, MSM behaviour and self-reported history of more than 50 sexual partners. This pattern of disease in patients with warts is characteristic of a syndemic with potential serious increased risk of anal carcinoma.

1. Introduction

Anal intraepithelial neoplasia is thought to be associated with high-risk human papillomavirus (hrHPV) as a precursor to anal cancer. Anal warts are associated with high rates of intraepithelial neoplasia especially in human immunodeficiency virus (HIV)-infected patients [1,2]. Anal cancer is increasing in many parts of the world in both men and women, particularly in men with HIV infection. Screening of the anal canal to detect probable precursors is being promoted for men with HIV infection where the standardised incidence rate of anal cancer has

increased 4 fold between 1992 and 2003 to 78.2/100,000 person years [3]. In addition the introduction of antiretroviral therapy (ART) has not been demonstrated to reduce the prevalence of anal squamous intraepithelial lesions [4] except in one study [5]. Anal warts are also recognised to be linked to the development of anal cancer [6]. Acquisition of genital warts has also been linked to progression to a higher level of squamous intraepithelial lesions (HSIL) in both HIV-positive and negative men [7]. Gonorrhoea was found to be associated with the development of anal cancer but to date no association with anal pre-cancer has been described [8]. Chlamydia has been previously

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associated with cervical intraepithelial neoplasia [9,10]. Because of the high rates of intraepithelial neoplasia (IN) associated with anal warts [1] and the fact that hrHPV has not been found in all anal cancers [11], we explored other possible associations with HSIL.

The emerging concept of a disease syndemic [12] where the disease/outcome risk is seen as a combination of biological, behavioural and social factors appears to apply to anal cancer as the existing literature indicates.

There are many risk factors associated with the development of anal cancer. In addition to HPV infection [13–16], other risk factors include receptive anal intercourse (before the age of 30) [6,16,17], lifetime number of sexual partners [6,17], female gender [18], current cigarette smoking [15,19,20], genital warts [6,20], immune-suppression post-organ transplantation and HIV infection [16,21–23]. Persistence of cervical HrHPV in women with genital warts has been observed in a recent Danish population study [24]. Anal fistulae and epithelial trauma are also associated, possibly because of access for HPV to the basement membrane [25–27].

A history of genital warts on the anus has a strong association with the development of anal cancer (OR 15.1, 95%CI: 6.8–33.5) [6]. Anal warts preceded anal cancer by about ten years with a shorter time interval for homosexual men compared to heterosexual men and women [6]. Anal squamous cell carcinoma has been demonstrated to arise out of anal warts [28–33]. In addition the presence of HSIL in association with anal warts has been under-recognised, with HSIL being present in 52% of HIV positive men, compared to 20% in HIV negative men, and 2.8% in HIV negative women with warts. Further evidence of an interaction between high and low-risk viruses comes from the EXPLORE study where the odds of developing high-grade squamous intraepithelial lesions in HIV-negative men was 23 times higher (95% CI 9.6–53) with combined high and low-risk HPV, compared to lower risks for high-risk HPV alone OR 6.4 (95% CI 2.7–15) and low-risk HPV alone OR 5.8 (95% CI 2.3–14) [34]. Similarly, Hessol et al. also found a 7.7 times increased risk (95% CI 5–38) of developing HSIL in women infected with both low and high-risk HPV. The increase in anal cancer in the last 30 years has been attributed to changed sexual patterns [35,36] including increased anal sex [36,37] and increased partner number for both MSM, women, and HIV infection [38].

MSM have a high prevalence of HPV infection in the anal canal (47.2–88.9%; pooled 63.9%) and HIV-positive men have even higher rates (74.6–97.7%, pooled 92.6 [39,40]). Anal HPV infection is almost universal in HIV-positive MSM [4,40–42]. Rates of anal HPV have been consistently demonstrated to be higher in HIV positive men compared to HIV-negative men [5,39,41,43–47], and in studies that compare HIV-positive to negative men, HPV has been associated with HIV infection. Whether ART alters the risk of anal cancer remains to be determined with some studies describing progression [48], others regression [49,50]. A more recent study found there may be some benefit with prolonged ART (OR = 0.32 95% CI: 0.16–0.63, $p = 0.001$) [51].

Patients with genital warts have a significantly increased risk of anogenital cancer and other cancers such as head and neck cancers [52]. This paper explores the role of infectious and demographic co-factors for HSIL as a syndemic in a case series of men and women with anogenital warts requiring surgical treatment and as such it is unique in that it is able to address behaviour and HrHPV confounding that exists in other studies.

2. Materials and methods

2.1. Study sample and design

In this case series, 460 operations were performed in 317 patients undergoing scissor excision of perianal and/or anal condylomata acuminata or mapping biopsies under general anaesthesia between December 1995 and November 2016. Patients with missing surgical material were excluded from the analysis (4). We examined the Royal

Perth Hospital Anogenital Wart Database (established in December 1995) for variables that might be associated with HSIL. Demographic data were collected on each patient including age, sex, sexual preference, lifetime sexual partners (0–10, 11–50, > 50), cigarette smoking (current, ever, never), and a history of gonorrhoea and chlamydia, wherever possible confirmed by evidence from the patient clinical record at the time they were enrolled for surgery. Serological data were obtained for the following infections: HIV 1 and 2 antibodies, syphilis [*Treponema pallidum* haemagglutination assay (TPHA), Rapid Reagin Index (RPR)], past or present HBV infection (HBsAg, HBcAb), HSV 2 antibodies (EIA), and HCV antibodies.

2.2. HPV testing

HPV testing of the anal canal by Digene Hybrid Capture-2 (HC2) for high-risk strains was used as a standard part of the surgical procedure from June 2005 onwards. Just prior to surgery, a proctoscope was inserted and using direct visualisation a HC2 sampler for hrHPV was then rotated from just above the dentate line to the anal and perianal skin as the proctoscope was removed. The Digene brush was placed into the Digene Transport buffered container for HPV testing. Excised surgical material labelled by site (perianal, anal) was placed in formalin and then processed in paraffin. No material was discarded at the bedside.

2.3. Reporting of surgical material

Biopsy material was stained with haematoxylin and eosin then routinely reported with other surgical specimens. Lesions were classified using the same concepts and criteria described in the LAST criteria [53]. Accordingly, HSIL in this study comprises AIN 2 and AIN 3 together with anal cancer (Table 2).

2.4. Statistical analysis

Samples with hrHPV results were examined for associations between hrHPV, other STIs and HSIL. Statistical analysis used percentages and appropriate means with confidence intervals for descriptive purposes. For variables that had a log-normal distribution the geometric mean was used because it is an unbiased estimate of the average under these circumstances. The chi-squared statistic and clustered linear logistic regression analysis were used to determine p-values with interaction terms to examine the independence of possible predictive variables. Because the data was clustered with samples nested within patients robust multi-level analyses were conducted. Multivariable logistic regression analysis was used to examine associations with HSIL and ordinal logistic regression analysis was used for histopathology grade, both with control for possible confounding factors. During the analysis it became clear that the STIs were not independent of each other and this multi-co-linearity was addressed by using boosted regression analysis [54] and structural equation models. The influence of missing data was assessed using the ‘missing-completely-at-random’ test of Little [55]. A p-value that was less than 0.05 was considered to be statistically significant. Statistical analysis was conducted using the Stata software package (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). The research was approved by the Royal Perth Hospital Ethics Committee.

3. Results

The RPH Genital Wart Database contained records for 463 patients who were examined during 536 operations. High-risk HPV data was available for 314 patients from 460 operations and this sample was used for most of this analysis (Table 1). Sixty eight percent of these patients had a single operation, 20% had two operations and 12% had more than two operations over the period from December 1995 to November 2016.

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