Author's response to reviews

Title: HPV infection, anal intra-epithelial neoplasia (AIN) and anal cancer: current issues.

Authors:

   Margaret A Stanley (mas1001@cam.ac.uk)
   David M Winder (dmw24@cam.ac.uk)
   Jane C Sterling (jcs12@cam.ac.uk)
   Peter KC Goon (pg336@cam.ac.uk)

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Author's response to reviews: see over
Reviewer 1:

Major compulsory revisions

Discussion- first paragraph. The authors should include immunosuppression, both HIV-related and non-HIV sources of immunosuppression such as solid organ transplant as a risk factor.

*The following sentence has been added: “Immunosuppressed individuals, such as solid organ transplant recipients and HIV-infected patients, are also more susceptible to HPV-related cancers [1, 2].”*

Discussion—second paragraph. The authors present data on the proportion of Scottish women who have practiced anal intercourse. This figure is lower than that reported from some studies in the U.S., and suggests that there are true population differences or, more likely, some degree of under-reporting among the Scottish women. The authors might want to comment on that.

*The following section has been added: “The proportion of Scottish women reporting the practise of anal intercourse is significantly lower to similar studies in the U.S., where prevalence of 22 – 29% has been documented [3, 4]. These discrepancies may represent true population behavioural differences or, perhaps more likely, under-reporting. Even anonymised studies may show significant bias when reporting behavioural aspects, especially when studies are smaller”.*

Discussion- general comment. The article highlights the most important research done to date but should also reference a meta-analysis paper that was recently published online (Machalek DA et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012 Mar 22. Epub ahead of print. This recently published article concludes that the progression rate from HGAIN is not high enough to warrant
routine screening and treatment of HGAIN, even in the highest risk groups except in a research setting. Data summarized in this article by Stanley et al. emphasize that the information on HGAIN progression to cancer is limited but suggest that it is similar to that of progression of high-grade vulvar and cervical intraepithelial neoplasia to vulvar and cervical cancer, respectively. The authors might also want to comment on the conclusions of the Machalek paper in this light.

The following has been added: “However, a recent meta-analysis has indicated that progression rates from high-grade AIN (HGAIN) to anal cancer are approximately one in 600 per year in HIV-positive MSM and one in 4000 per year in HIV-negative MSM patients [5], substantially lower than the one in 80 per year observed in comparable cervical disease [6]. One possible explanation for this discrepancy is that these estimates were based on multiple cross-sectional studies and pooled prevalence rates of HGAIN and anal cancer incidence rates, rather than prospective follow-up studies. However, it cannot be excluded that HGAIN might regress more often than CIN 3, perhaps being partially attributable to the fact that HGAIN encompasses both AIN 2 and AIN 3, with AIN 2 probably containing a mixture of HG and LG HPV types”.

Discretionary revisions

Discussion—second paragraph. The authors describe the higher incidence of anal cancer among women compared with men, and tie that to the relative differences in the proportions of women and men who reported a history of anal intercourse and imply that it is this relative difference that accounts for the differences in anal cancer rates between men and women. The authors could carry the argument a bit further. Further linking risk of anal cancer to anal intercourse, the authors might want to explicitly mention here that it is also likely that among men, MSM account for a disproportionate amount of anal intercourse and anal cancer.

The following sentence has been added: “Nevertheless, it is likely that among men, MSM account for a disproportionate amount of anal intercourse and anal cancer”.

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The authors might wish to expand on where they think the field should be going next, e.g., do they believe that there is a need for more studies on progression of HGAIN to cancer, or for data on the efficacy and effectiveness of treatment of HGAIN to reduce the incidence of anal cancer.

*The summary now includes “There is now a need for multi-centre prospective studies on the progression of AIN 3 to cancer and on the effectiveness of treatment to reduce the incidence of anal cancer”*

**Minor essential revisions**

Abstract- line 26 should read “There is also less evidence….”
Abstract- line 33 should read “There is strong evidence….”

*Both have been changed as requested.*
Reviewer 2:

Minor essential revisions

1. Abstract, pg 2, line 34: Suggest changing some data on the progression of AIN into invasion TO some data on the progression of AIN to invasive cancer

   Done.

2. Discussion, pg 4, line 71: consider changing 0.37 per 100,000 in men, 0.55 in women to 0.37 per 100,000 in men and 0.55 in women

   Done.

3. Discussion, pg 5, line 84: consider changing includes to including

   Done.

Discretionary revisions

1. Background, pg 3, line 48: consider changing other HPV-cancers to other HPV-related cancers

   Done.

2. Discussion, pg 4, line 74: I think this is a good logical argument but would also consider adding a sentence regarding the anatomic proximity of the vaginal introitus to the anus, which may facilitate a greater amount of auto-inoculation that may also help to explain the gender difference.
The following has been added: “Furthermore, the anatomic proximity of vaginal introitus to the anus also facilitates non-sexual and auto-inoculation in women via vaginal secretions, digital or fomite transference [7, 8].”

3. Discussion, pg 4, line 82: paucity of data from the heterosexual male and non-HIV positive or non-high risk female population (largest sections of the general population) has been a problem. Consider modifying for clarity to: (largest sections of the general population who make up a substantial number of anal cancer patients) has been a problem in the clinical management of these patients, particularly in determining the rationale and feasibility of instituting a screening program.

Done.


The following has been added “Interestingly, one study showed that 6 month persistence of HPV 16 was absent in heterosexual men, whereas it occurred in 5.1% of MSM patients [9].”

5. Discussion, pg 6, line 122: On section describing high-grade intra-epithelial neoplasia … consider adding specific statement: HGAIN can be identified using high-resolution anoscopy (HRA) or colposcopy of the anus and perianus after application of 3-5% acetic acid. In comparison to the number of cervical colposcopists, however, currently there are far fewer trained experts in HRA and this partly explains why there is even less data published on the prevalence of HGAIN in the general population. Since there are no recommendations for screening, many patients are either diagnosed serendipitously during surgery for benign anal conditions or occasionally during colonoscopy or if they present with anal symptoms.

(1: Darragh TM, Winkler B. Anal cancer and cervical cancer screening: key
6. Summary, pg 7, Consider adding for clarity: There are supportive data for the contention that HGAIN is a precursor, however, there is limited data on the prevalence of HGAIN in the general population.

Done.

References: