Screening for anal cancer: endpoints needed

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Anal cancer is very rare in the general population, but much more common in well defined, high-risk populations, including women with a previous cervical precancer, men who have sex with men (MSM), and individuals with HIV.

Infection with carcinogenic human papillomavirus (HPV) has been increasingly recognised to cause anal cancer. In *The Lancet Oncology*, Dorothy Machalek and colleagues report their findings from a systematic review and meta-analysis of anal HPV infection and associated lesions in MSM, underscoring the disease burden in HIV-positive MSM.[1] They recorded a prevalence of high-risk anal HPV in HIV-positive MSM of 73·5% (95% CI 63·9–83·0). In the same population, the prevalence of high-grade anal intraepithelial neoplasia (AIN) was 29·1% (22·8–35·4) and the estimated annual cancer incidence was 45·9 per 100 000 HIV-positive MSM (95% CI 31·2–60·3).[1]

Secondary prevention of cervical cancer by screening for and treatment of precancers has been very successful.[2] Several key factors have made this success possible: sufficiently high prevalence of precancers, the ability to directly sample the tissue at risk, diagnostic markers that provide sufficiently reliable risk estimates, and an intervention that removes the tissue at risk, effectively interrupting natural history without causing major harm. Although screening to prevent cervical cancer was introduced without full understanding of its natural history, research during the past 30 years has led to the development of a progression model that explains the relevant steps from HPV infection to cervical cancer (figure).

With the high level of understanding about HPV-related carcinogenesis and experience from cervical cancer screening, efforts to address screening for anal cancer should have a head start. HIV-positive MSM are a well-defined population—they are often followed up closely at specialised clinics to monitor antiretroviral therapy and for surveillance of AIDS-related disease. Machalek and colleagues report a high disease burden in HIV-positive MSM,[1] which is similar to the burden of cervical lesions in women. Targeted sampling of the tissue at risk

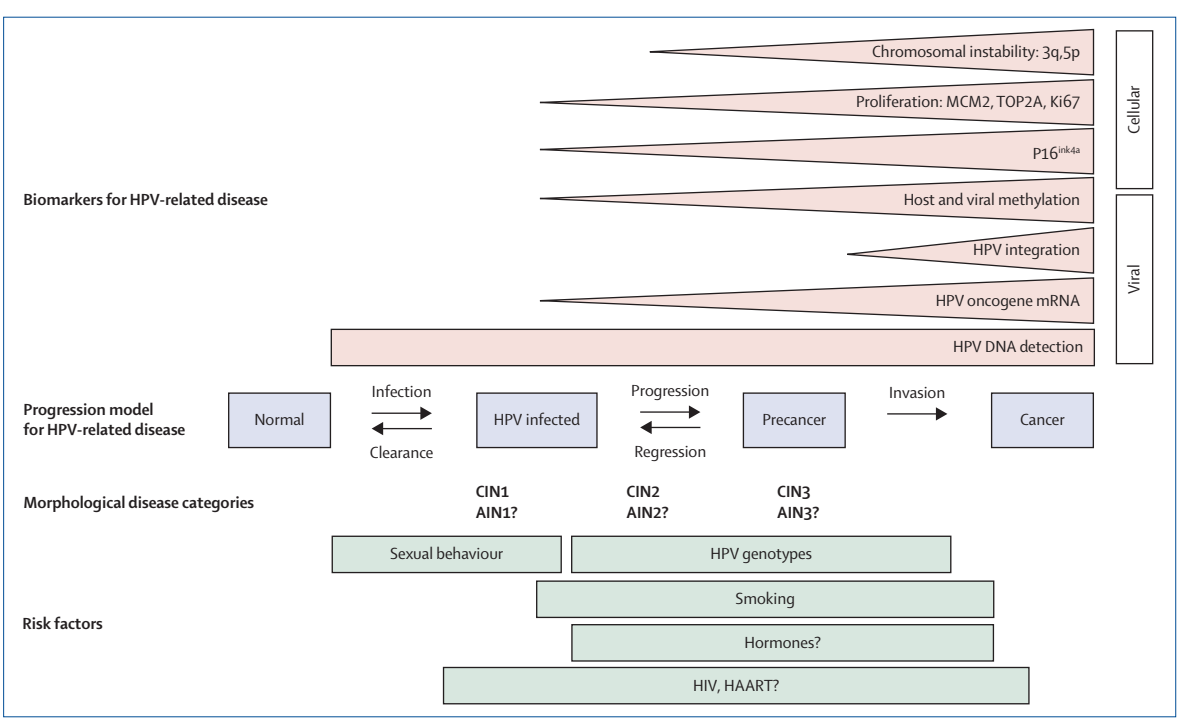

Figure: **Progression model of human papillomavirus (HPV)-related cancers**
The morphological disease categories (cervical intraepithelial neoplasia [CIN], anal intraepithelial neoplasia [AIN]) do not fully translate to the established functional disease progression model. Anal disease categories are less well-defined than cervical disease categories. Important established and presumed risk factors and biomarkers for cervical and anal carcinogenesis are shown below and above the progression model, respectively. HAART=highly active antiretroviral therapy.

is possible—anal cytology and high-resolution anoscopy have been successfully implemented at specialised centres. Localised treatment options are available, but need further assessment of efficacy and safety.

Epidemiological studies have shown that sexual behaviour is the major risk factor for anal HPV infection in MSM.[3] Findings from a randomised trial showed that HPV vaccination can prevent anal HPV infection and AIN lesions in MSM, suggesting that the early steps of anal carcinogenesis are similar to those in the cervix.[4] An important question is whether the risk of progression from high-grade AIN to cancer is similar to that of cervical precancers, thus warranting treatment rather than expectant management. Available evidence suggests that oestrogen promotes cervical carcinogenesis, an exposure that is different in men and women and at the two anatomic sites.[5] Also, not much is known about how HIV and antiretroviral therapy modify the natural history of HPV-related disease.

On the basis of high-grade AIN progression estimates, Machalek and colleagues conclude that substantial differences exist between the natural history of anal HPV infection and cervical HPV infection, meaning that cervical cancer screening strategies cannot simply be transferred to screening for anal cancer.

However, this statement is largely based on a comparison with a study by McCredie and co-workers that described progression of cervical intraepithelial neoplasia (CIN)3 to cancer in women who were left untreated.[6] Machalek and colleagues could not separate out AIN2 and AIN3 in their analysis. By analogy, CIN2 is a poorly reproducible category that includes transient infections and some precancers; a large proportion of CIN2s regress spontaneously.[7] Even within adjudicated and confirmed CIN3, there is biological heterogeneity. The progression estimates from McCredie and co-workers were based on large lesions that had persisted over a long time in women who were poorly screened. Thus, the progression estimates for cervical precancer will be much lower if CIN2 and small incipient CIN3s seen in highly screened populations are included in the denominator.

CIN3 has been widely accepted as a surrogate of cervical cancer risk, and historical comparisons have shown that treatment of CIN3 has led to substantial decreases of cervical cancer incidence.[2] Intentions to combine AIN2 and AIN3 into one category will be counter-productive for the establishment of a better surrogate endpoint for anal cancer, as evidenced by Machalek and colleagues' meta-analysis.[1] Various biomarkers are available to improve classification of HPV-related disease. The availability of HPV genotyping, HPV mRNA, proliferation markers, or P16 might improve the precision of anal disease categories to capture progression risk compared with use of morphological assessment alone (figure).[8]

Implementation of screening for anal cancer in high-risk populations needs more data to estimate the trade-off between benefits (prevention of cancer) and harms (complications related to screening and treatment, cost). The screening of anal cancer in HIV-positive MSM is done at highly specialised centres, but most providers of such screening caution against widespread introduction of screening without standardisation of diagnosis and treatment. Definition of a good surrogate endpoint for anal cancer risk is a crucial first step. Molecular characterisation of anal precancers identified at sites that do close surveillance of HIV-positive MSM populations and disease identified in natural history and biomarker studies will provide invaluable data to define anal precancers, before moving towards trials of screening and management modalities to screen for anal cancer.

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I declare that I have no conflicts of interest.

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