Who should be targeted for vaccination against anal cancer?

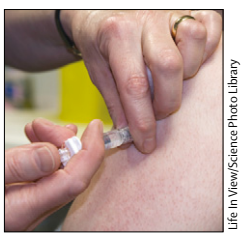
Although cervical cancer occurs 35 times more frequently than anal cancer in unscreened women and is the focus of prophylactic HPV vaccines, anal cancer, while unequally distributed in the population, is another HPV-associated cancer. Women have twice the incidence of anal cancer as men, participate in receptive anal intercourse (an independent risk factor for anal cancer) 2–10 times more frequently than do heterosexual men, and are predisposed to anal HPV infection if they already have cervical neoplasia, irrespective of anal intercourse.[1,2] For these reasons, the work presented by Aimee Kreimer and colleagues[3] in *The Lancet Oncology*, which shows that the bivalent vaccine (Cervarix, GlaxoSmithKline, Rixensart, Belgium) prevents infection with four oncogenic anal HPV genotypes, is extremely important for additional extracervical coverage.

However, the yearly incidence of anal cancer, at two per 100 000 individuals in the general population, is an order of magnitude higher for HIV-negative men who have sex with men (40 per 100 000) and in HIV-positive men who have sex with men (80 per 100 000).[4] Few explanations exist for the large differences in incidence rates of anal cancer in these population groups since the natural history of anal dysplasia remains incompletely described. Because immunosuppression is also an independent risk factor for anal cancer,[2] many studies of the natural history of anal intraepithelial neoplasia (AIN) have been done in men with HIV or in those receiving transplants.

The natural history studies adopted similar histology grades for AIN as for cervical intraepithelial neoplasia (CIN). AIN1 is an indication of active HPV infection, not a cancer precursor, as is CIN1. Mimicking CIN2, AIN2 is highly unreliable among pathologists and unpredictable for cancer progression.[5] AIN3 lesions, by contrast, have a nearly complete association with HPV infection,[6] but, unlike CIN3, have a relatively low rate of malignant transformation in the immunocompetent patient.[7] Many people with AIN3 die with it, not of it. The natural history differs in immunosuppressed men or those with HIV infection,[8] in these populations, high-grade AIN is defined as a combination of AIN2 and AIN3. AIN2/3 is associated with multiple HPV genotypes, high HPV 16 viral load, and is deemed a precursor to an eventual anal cancer.[9]

With the natural histories of AIN2/3 progressing to anal cancer in different time frames for distinct populations, the public health benefit of prophylactic HPV vaccines for anal cancer is an open question. Would resources be better spent in developing therapeutic vaccines for the general male population? In men, the only evidence of efficacy is in the population of HIV-negative men who have sex with men,[10] a higher risk population than the general heterosexual male population. In the trial of men who have sex with men,[10] no significant efficacy was shown for AIN2/3 associated with HPV 16 and HPV 18 in any analytical dataset; additionally, no cancers occurred in either the placebo or vaccine groups in the 2·7 years of the trial.[10] Only an efficacy against the composite endpoint of AIN2 and AIN3 associated with HPV 6, 11, 16, and 18 was established, with most of the efficacy seen for HPV 6-related AIN1. Despite US regulatory approval for broad labelling, this level of efficacy is insufficient to claim prevention of anal cancer in the general population since HPV 16 and HPV 18 are the dominate causes of anal cancer and AIN3 is often benign in hosts other than men who have sex with men or immunosuppressed populations.

Finally, the cost effectiveness of prophylactic HPV vaccines must be considered. The additional protection against four oncogenic anal HPV types in women increases their benefits from vaccination. For men who have sex with men, HPV vaccination for anal cancer prevention is very cost effective,[11] but, cost-effectiveness analyses for women and for men who have sex with men pivot on the duration of vaccine efficacy. Without duration of efficacy of at least 15 years, cancers will not be prevented for women or men who have sex with men, only postponed.[11,12] The benefit of prophylactic HPV vaccines against anal cancer in the heterosexual male population is unknown: efficacy trials are lacking and anal cancer incidence is rare. Let's use our resources wisely.



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