Studies Shed Light on Anal Precancer Progression

Abnormal anal screening results are common, but they often do not to lead to invasive cancer.

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Studies of gay and bisexual men in Australia and Spain found that while high-grade precancerous cell changes are common, in many cases these do not progress to invasive anal cancer—and the risk may not be much higher for those living with HIV. These findings, presented at the recent 17th European AIDS Conference in Basel, Switzerland, leave open the question of whether routine anal cancer screening and treatment is beneficial for this population.

Most anal and cervical cancer is caused by high-risk human papillomavirus (HPV), especially types 16 and 18; HPV is also a growing cause of oral cancer. HPV is one of the most common sexually transmitted infections, and most people acquire one or more types soon after they become sexually active. Risk factors include receptive anal intercourse and having multiple sex partners.

Although anal cancer is rare overall—about 8,300 new cases in 2019, according to the American Cancer Society—it is one of the most common cancers in gay and bi men living with HIV. Past studies have shown that HIV-positive people carry more HPV types, on average, and are less likely to clear the virus than HIV-negative people.

People with cancer-causing HPV typically first develop precancerous cell changes known as dysplasia or squamous intraepithelial lesions (SIL). But the course of the disease can be quite variable. Low-grade changes (LSIL) may not progress to high-grade lesions (HSIL), and HSIL does not always progress to invasive cancer.

Although routine screening with Pap smears has dramatically reduced deaths from cervical cancer, most guidelines do not recommend the equivalent screening for anal cancer. Some clinicians who see many men who have sex with men and people with HIV offer such screening, but it is not clear how best to proceed if HSIL is detected.

Various methods may be used to destroy or remove abnormal cells before they spread, but adverse outcomes are common. While a substantial amount of abnormal cervical tissue can be removed without complications, removing anal tissue can have a negative impact on quality of life. What's more, dysplasia may improve or resolve on its own, suggesting that routine treatment may not be necessary.

David Templeton, MD, of the University of New South Wales in Sydney, and colleagues with the Study of the Prevention of Anal Cancer (SPANC) assessed the natural history of anal HSIL in HIV-positive and HIV-negative gay and bi men.

This prospective analysis included 617 men who have sex with men age 35 or older recruited from community-based settings in Sydney between 2010 and 2018. Of these, 220 (36%) were HIV positive. The mean age was about 50, and they had been living with HIV for about 15 years on average. Almost all were on antiretroviral therapy with an undetectable viral load, but about 45% had a lowest-ever (nadir) CD4 count below 200, indicating a history of serious immune suppression.

The participants received anal Pap smears or high-resolution anoscopy and biopsy, which involves examination and collection of a tissue sample using an anal speculum. These tests were performed at baseline and repeated six months later and then at three annual visits.

At baseline, 47% of HIV-positive men and nearly a third of HIV-negative men already had HSIL. Furthermore, 38% and 25%, respectively, had HSIL plus more extensive anal tissue abnormalities known as Grade 3 anal intraepithelial neoplasia (AIN).

Over the course of the study, 124 new cases of HSIL were diagnosed among men who had no or low-grade SIL at baseline, yielding an incidence rate of about 11 cases per 100 cumulative years of follow-up, or 11%. In most cases, this was first-time HSIL, but some people who had previously had HSIL and experienced regression or clearance progressed to HSIL again.

The main predictor of HSIL was age less than 45 years (incidence rate of 16% versus 10% for older men). In contrast with some prior studies, HIV-positive men had only a marginally increased risk of HSIL compared with HIV-negative men (14% versus 10%, or a 43% increase); this did not reach the threshold for statistical significance, meaning the difference could have been driven by chance. Smoking—often linked to anal dysplasia and cancer in previous studies—was not a significant risk factor.

Presence of HPV-16 was associated with about a threefold higher risk of HSIL (27% incidence for those who tested positive twice). That is, those with two positive tests for HPV-16 were 72% more likely to develop HSIL than those with two negative tests. Those who twice tested positive for other HPV types had an incidence rate of 13%. Those who twice tested negative for any HPV type still had an HSIL incidence of 2%, indicating that precancerous tissue changes may continue to progress even after HPV clearance.

Among men with HSIL, 153 cases cleared spontaneously without treatment, for a clearance rate of 22 per 100 cumulative years of follow-up, or 22% per year. Predictors of HSIL clearance included age less than 45, less extensive anal tissue abnormalities and absence of persistent HPV-16 infection. Being HIV positive, however, was not associated with a lower likelihood of HSIL clearance.

Only one man, who was HIV negative, was newly diagnosed with anal cancer during the study, for

an incidence rate of 0.22 per 100 cumulative years of follow-up.

“These data strongly suggest that not all anal HSIL detected in screening requires treatment,” the researchers concluded. “Men with persistent HPV-16 were less likely to clear HSIL and are more likely to benefit from effective HSIL treatments.”

Another study, however, showed a decrease in the development of anal HSIL among gay and bi men living with HIV after implementation of a screening and treatment program in Spain.

Carmen Hidalgo Tenorio, MD, PhD, of University Hospital Virgen de las Nieves in Granada, and colleagues carried out a study that included 405 HIV-positive men who have sex with men seen at a large Spanish clinic between 2010 and 2018. The average age was 36. They had been diagnosed with HIV for a median of two years, most were on antiretrovirals with an undetectable viral load and the median CD4 count was high. They had no prior history of HSIL or anal cancer.

Men who participated in the program underwent screening to detect anal cell or tissue abnormalities and PCR testing for HPV. Between 2012 and 2014, 66 participants received the original Gardasil vaccine, which protects against four types of HPV, including HPV-16.

Those who had normal cell appearance and tested negative for cancer-causing HPV were rescreened annually with repeat Pap and HPV tests. Those who had abnormal findings (LSIL, HSIL or atypical cells) and tested positive for high-risk HPV underwent anoscopy. If this was normal, they also were rescreened annually. Those with LSIL followed an active monitoring approach, undergoing anoscopy along with Pap and HPV tests every year. Those found to have HSIL or anal cancer were offered treatment—either removal of abnormal tissue with an electric scalpel or imiquimod cream (Aldara or generics).

During follow-up, 353 men (87%) ended up receiving two or more high-resolution anoscopies. A total of 88 new cases of HSIL and three cases of anal carcinoma were detected (incidence rates of 22% and 0.7%, respectively). Risk factors for HSIL included the presence of HPV-16 as well as various other HPV types and a lower nadir CD4 count.

Most men with HSIL underwent treatment, 49 with the electric scalpel and 34 with imiquimod. None of the men who were treated progressed to anal cancer. Two of those with anal carcinoma were successfully treated, but the third died 15 months after diagnosis.

During the course of the study, new cases of HSIL declined significantly, from 43% in 2010 to just 4% in 2018. Based on these findings, the researchers suggested that the declining rate “may be attributable to the bundle of measures adopted at our center.”

In a separate analysis, Hidalgo Tenorio’s team also found that during a three-year period, 43% of the 405 men in the cohort acquired cancer-causing HPV types while 35% cleared these viruses. In other words, it was common for HPV to come and go over time. Those who had been on antiretroviral therapy longer were significantly more likely to clear high-risk HPV. However, HPV acquisition and clearance did not affect the likelihood of developing HSIL or anal carcinoma.

Taken together, these findings indicate that gay and bi men may benefit from regular anal screening, but because anal cancer rates are low with or without treatment, routine therapy may not be necessary. Templeton suggested that active monitoring might be conducted more often in younger men, who appeared more likely to develop anal cell abnormalities in his study.

The ongoing ANCHOR study aims to clarify this issue. HIV-positive men and women diagnosed with HSIL are randomized to either receive immediate therapy or undergo active monitoring to determine whether routine treatment reduces the risk of developing anal cancer.

HPV vaccination for older individuals is also controversial. The newest vaccine, Gardasil 9, protects against nine types of HPV that cause cancer or genital and anal warts. The vaccine is most effective when given before people become sexually active, and the Centers for Disease Control and Prevention (CDC) recommends vaccination for girls and boys at age 11 or 12, with catch-up vaccines for those up to age 26.

In 2018, the Food and Drug Administration approved Gardasil 9 for women and men up to age 45. The CDC advises that those between 27 and 45 should have a discussion with their health care providers about whether they might still benefit from vaccination. The more HPV types included in a vaccine, the greater the odds that an individual will not yet have been exposed to all of them.

Click here to read the SPANC study abstract.
Click here to read the Spanish screening program abstract.

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