Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and can lead to genital warts and anogenital cancers, with the highest prevalence in cervical and anal cancers. Studies have shown an increased prevalence of cervical dysplasia, a precursor to cervical cancer, among women with inflammatory bowel disease (IBD), particularly among women on immunosuppressive medications. Vaccination for HPV has been available since 2006 and is recommended for all individuals ages 11 - 26, including those with IBD. The vaccine is safe for use in immunosuppressed patients. Research has shown that immunosuppressed patients mount an adequate immune response following vaccination for HPV. Screening for cervical dysplasia should continue at regular intervals as the HPV vaccine does not cover all high-risk HPV types and Pap testing is still needed to detect cervical dysplasia. There are currently no screening guidelines for anal cancer.

BACKGROUND

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States with over 6 million new cases each year. There are over 100 types of HPV, over 40 of which are spread through skin-to-skin contact during intercourse and can lead to anogenital infections. Over half of all sexually active individuals will be infected with at least one HPV type during their lifetime. The sexually transmitted types are subdivided into high-risk or low-risk groups based on their oncogenicity. Infection with a low-risk HPV type, such as type 6 or 11, can result in cervical dysplasia or genital warts. Infection with a high-risk type, such as type 16 or 18, increases the risk for developing cancers, particularly cervical and anal cancers. A high-risk HPV type is detected in almost all cases of cervical cancer, with over 70% of all worldwide cases of cervical cancers due to types 16 and 18. High-risk HPV types also are responsible for approximately 90% of all anal cancers. As well, these high-risk HPV types can lead to other cancers such as oropharyngeal, vulvar, vaginal, and penile cancers.
Persistent infection with a high-risk HPV type, particularly type 16, is the most important predictor for developing cervical dysplasia or cancer. Immune suppression is another risk factor that plays a key role in the progression of an HPV infection to cervical cancer. Studies in human immunodeficiency virus (HIV) populations and in women who have undergone organ transplantation confirm an increased incidence of cervical dysplasia among these populations. Because of the prevalence of these infections and the risk of progression to cancer, two vaccines have been developed to help protect patients from HPV. One is a quadrivalent HPV vaccine, which covers HPV types 6, 11, 16 and 18 (HPV4; Gardasil, Merck) while the other is a bivalent HPV vaccine, which covers only HPV types 16 and 18 (HPV2; Cervarix, GlaxoSmithKline). The HPV4 vaccine has been approved by the Food and Drug Administration for use in females and males ages 9 – 26 and the HPV2 vaccine has been approved for use in females ages 9 – 25. The Advisory Committee on Immunization Practices recommends HPV vaccination for all children beginning at age 11 up to 26 years of age.7, 8

HPV in Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory diseases, including Crohn’s disease and ulcerative colitis. These conditions involve inflammation throughout the GI tract and frequently require treatment with immunosuppressive medications. A handful of studies have examined the prevalence of cervical dysplasia, resulting from persistent HPV infection, among women with IBD (Table 1.9,15). The results of the studies are mixed, with some showing IBD brings an independently increased risk of cervical dysplasia, others showing an increased risk associated with medications for IBD, while others found no increased risk. Due to limitations in study design, only one of these prior studies was able to assess for the presence of HPV infection. Kane et al. found an increased incidence of cervical abnormalities in women with IBD and more advanced lesions in those being treated with immunosuppressive therapies. All abnormal Pap results tested positive for HPV types 16 or 18.12

Fewer studies have examined the risk for anal cancer among the IBD population. A population-based case-control study out of Denmark and Sweden evaluated the risk for HPV positive and HPV negative anal carcinoma among subjects diagnosed with anal cancer, rectal cancer and population controls.16 Subjects with IBD made up < 1% of the study population. Despite the lack of power in the analysis, the researchers determined that ulcerative colitis and Crohn’s disease were not associated with an increased risk for anal cancer.

HPV Vaccination Recommendations in Inflammatory Bowel Disease

Over the past several years, there has been an influx of publications reviewing indications for vaccination among patients with IBD. Vaccinations are of particular importance among this population as a large percentage of these patients are currently taking or will be taking immunosuppressive medications to treat their disease, which increases their risk for acquiring certain infections. All vaccination guidelines published since the HPV vaccine has become available have recommended its use for this population.

HPV preferentially infects the epithelial cells and causes inactive cells to actively replicate, resulting in dysplasia. Because these infections are limited to the epithelium, the virus is somewhat shielded from a host immune response. This can lead to persistent infections and also limits the use of antibody testing to assess for previous or current infection. A study of antibody response to incident infection found only 54 - 69% of women with HPV 16, 6, or 18 infection had positive antibodies.17 Current testing requires the presence of HPV DNA or RNA, on cervical smear, to detect an HPV infection. In some cases there is no way to definitively determine prior exposure.

Given the lack of sensitivity of antibody testing to detect prior exposure, HPV vaccination is recommended for all individuals ages 9 - 26, regardless of sexual history or history of cervical dysplasia, as the likelihood of exposure to all HPV types covered by the vaccine is low. In addition, the antigen in the HPV vaccine is a viral L1 capsid protein and is non-infectious. It is safe to give to patients who are already immune suppressed, however it is not recommended during pregnancy.

When vaccinating immunosuppressed individuals, there is some question as to whether they will develop an adequate immunologic response. One study examined

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the immunologic response of 30 female IBD patients on immunosuppressive medications who received the quadrivalent HPV vaccine. They found that over 90% of the subjects became seropositive to all of the 4 HPV types, with their response comparable to a historical control group.\textsuperscript{18} Even with an adequate immune response, HPV vaccines do not include all high-risk types and vaccination does not eliminate the need for regular screening.

Table 1. Cervical Dysplasia in Women with IBD

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatia, 2006</td>
<td>116 with IBD (64 CD, 52 UC), 116 age-matched controls</td>
<td>Abnormal Paps in 18% with IBD vs 5% of controls (p=0.004)</td>
</tr>
<tr>
<td>Venkatesan, 2006</td>
<td>518 with IBD</td>
<td>Abnormal Pap in 25/518 (4.8%). Infliximab use associated with OR 5.0 (2.11 – 11.85, p=0.0001).</td>
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<tr>
<td>Hutfless, 2008</td>
<td>1165 with IBD (427 CD, 738 UC), 12124 age-matched controls</td>
<td>10 (0.85%) cervical cancers (3CD, 7 UC) among IBD, 72 (0.59%) cancers among controls. Adjusted OR for cervical cancer in IBD 1.45 (0.74 – 3.84).</td>
</tr>
<tr>
<td>Kane, 2008</td>
<td>40 with IBD (32 CD, 8 UC) with 134 Paps; age-, race-, and parity-matched controls</td>
<td>42.5% abnormal Paps in IBD vs 7% in controls; higher grade lesions in IBD (p&lt;0.001); exposure to IS more likely to have cervical dysplasia (p&lt;0.001); &gt; 6 months exposures OR 1.5 (1.2 – 4.1; p=0.02).</td>
</tr>
<tr>
<td>Lees, 2009</td>
<td>411 with IBD (204 CD, 107 UC), 1644 controls from same geographic location</td>
<td>No difference in rates of cervical dysplasia; more abnormal Paps among smokers with IBD vs non-smokers and never smokers with IBD 27.4% vs 11.4% (p=0.001; OR 2.95, 1.55 – 5.50).</td>
</tr>
<tr>
<td>Singh, 2008</td>
<td>525 with IBD (292 CD, 233 UC); 19,692 with abnormal Paps matched with 57,898 controls</td>
<td>No association between abnormal Pap and UC; increased risk in CD limited to women exposed to &gt; 10 prescriptions for OCPs (OR 1.66, 1.08 – 2.54); combined exposure to steroids and IS increased risk of cervical abnormality (OR 1.41, 1.09 – 1.81).</td>
</tr>
<tr>
<td>Marehbian, 2009</td>
<td>22,310 CD; 111,550 controls</td>
<td>Monotherapy IS increased risk of cervical dysplasia (HR 1.5, 1.2 – 2.0); use of 2 – 3 IS medications further increased risk (HR 1.8, 1.1 – 3.0).</td>
</tr>
</tbody>
</table>

IDB = inflammatory bowel disease; CD = Crohn’s disease; UC = ulcerative colitis; Pap = Papanicolau testing; IS = immunosuppressive medications, including steroids, immunomodulators, and biologic agents; OCP = oral contraceptive pills.
HPV Screening Recommendations

Updated recommendations for cervical cancer screening were published in March 2012 by the US Preventative Task Force. These include a later onset of screening and a decreased frequency of screening. These recommendations clearly state that they do not apply to women who are immune suppressed as they are at an increased risk for developing cervical cancer. The American College of Obstetrics and Gynecology recommends that women who are immune suppressed undergo cervical cancer screening every 6 months for the first year of immune suppression, then annually thereafter. There is no indication whether HPV testing should be performed at each screening or if cytologic exam is adequate. However, it is becoming common practice for reflex HPV testing to be performed if the cytologic exam is abnormal.

Several studies have found a lower rate of cervical cancer screening among women with IBD. Long et al. showed that women with IBD who are on immunosuppressive medications, i.e. those with the highest risk for developing dysplasia, had cervical cancer screening less frequently than their matched controls.19 Similarly, Selby et al. showed an overall lower rate of receipt of preventative care, including cervical cancer screening, among IBD patients compared to the general population.20

Anal HPV infections and anal cancer precursors are commonly diagnosed in men who have sex with men. At this time, there are no FDA-approved tests for detecting HPV infections in men or screening guidelines for detecting HPV-induced dysplasia or cancer of the anus in this population. A systematic review and meta-analysis from May 2012 determined that the rate of progression from anal HPV to cancer among men who have sex with men was too low for a screening program to be effective.21 Continued research in HPV may yield specific recommendations for men.

In summary, HPV is an extremely prevalent infection, which can lead to genital warts or anogenital cancers. The HPV vaccination is approved and recommended for use in all individuals ages 9 - 26, including immunosuppressed patients. One study in immune suppressed women with IBD has shown an adequate immune response following vaccination. Our center’s practice is to vaccinate women and men with IBD. This approach must be tempered by the fact that available HPV vaccines do NOT cover all high-risk HPV types; regular screening is still recommended.

References