Human Papilloma Virus (HPV)  
What can you do?

- This is Part 2 of the series that deals with HPV. There are steps that you can take that may inactivate or suppress the disease. If you have not read last month's article HPV article, it was Part 1 of the series and has been posted in the medical library.

- There are multiple investigators looking at “natural” substances that can improve the body’s ability to reduce or eliminate the activity of the HPV virus.

- A very dedicated young woman, Jordan Snyder, is our guest contributor. Jordan has completed a curriculum assignment through Custom Rx. It was our combined interest in searching for a possible solution to inactivate or suppress the HPV virus that led to the creation of her presentation. She has been kind enough to share it with us.
Human Papillomavirus

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PharmD Candidate 2016
Objectives

- Understand the pathophysiology of human papillomavirus
- Identify risk factors for acquiring human papillomavirus
- Discuss non-pharmacologic and pharmacologic prevention strategies
- Review treatment options for human papillomavirus and the complications associated with the virus
- Recognize and evaluate the potential use of active hexose correlated compound and curcumin in the treatment of human papillomavirus
Human Papillomavirus (HPV)¹

- HPV is the most common sexually transmitted infection
- Affects nearly all sexually active men and women
- Over 150 strains of HPV
- Spread via skin-to-skin contact
- 79 million Americans currently infected
- Causes 17,000 cancers in women and 9,000 cancers in men yearly
HPV: Virology²

- Non-enveloped, double-stranded DNA virus
- 55 nanometers in diameter
- Capsid composed of 2 encoded proteins, L1 and L2
- Genome contains 3 regions
  - Regulatory region
  - Early region
  - Late region

Adapted from:
HPV: Life Cycle

- Virus enters skin through cut or open sore
- Productive infection and hyperproliferation are initiated when virus enters basal epithelial cells
- Binding to cell receptors dependent upon L1 capsid protein
- Virus can enter cell and begin replication
- As virus moves up the epithelial layers:
  - Viral genome amplification begins
  - Virus assembly occurs
  - Shedding of the virus
HPV: Life Cycle

Adapted from:http://img.medscape.com/article/732/740/732740-fig1.jpg
HPV: Risk Factors³

- Risk factors for contracting HPV include:
  - High number of sexual partners
  - Unprotected intercourse
  - History of sexually transmitted infections
  - Oral contraceptive use
  - Immunodeficiency
HPV: Signs and Symptoms

- Typically asymptomatic
- Can cause:
  - Genital warts
  - Abnormal pap smear results
  - Increase risk for developing cancer
    - Cervical
    - Vaginal
    - Penile
    - Anal
    - Oropharyngeal
HPV: Diagnosis\textsuperscript{3,4}

- **Genital warts**
  - Typically diagnosed clinically
  - If uncertain, can perform biopsy
  - Acetowhitening can aid in diagnosis

- **Cervical cancer**
  - HPV tests
    - Indicated for:
      - Following abnormal pap test
      - Cervical cancer screening in women $>30$
      - Primary cervical cancer screening in women $>25$
HPV: Prevention

- Non-pharmacologic:
  - Abstinence
  - Condom use
  - Limiting number of partners

- Pharmacologic:
  - Vaccination
    - Bivalent HPV vaccine (Cervarix)
    - Quadrivalent HPV vaccine (Gardasil)
    - 9-Valent HPV vaccine (Gardasil 9)
Prevention: Non-Pharmacologic

- Abstinence
  - Most reliable method of prevention

- Condom Use
  - Can decrease risk of transmission

- Limiting number of partners
  - Can reduce risk for HPV
  - Can still contract HPV with only one lifetime partner
## Table 1: Available HPV Vaccines

<table>
<thead>
<tr>
<th>HPV Strain</th>
<th>9-Valent Vaccine</th>
<th>Quadrivalent Vaccine</th>
<th>Bivalent Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV Strain</td>
<td>HPV types 16, 18, 6, 11, 31, 33, 45, 52, and 58</td>
<td>HPV types 16, 18, 6, and 11</td>
<td>HPV types 16 and 18</td>
</tr>
</tbody>
</table>
| Population | • Routine vaccination girls/boys 11 or 12 years old  
• Catch-up for teen girls/women, immunocompromised, gay, or bisexual men: through age 26  
• Catch-up for teen boys/men: through age 21 | | • Routine vaccination for girls 11 or 12 years old  
• Catch-up for teens/women: through age 26 |
Prevention: Vaccines

- HPV vaccination schedule:
  - 3 shot series
  - Second dose given 1-2 months after the first
  - Third dose administered 6 months following the first dose

- Adverse events:
  - Pain, redness, or swelling at injection site
  - Fever
  - Headache, nausea, fatigue
  - Muscle or joint pain
  - Syncope
HPV: Treatment$^7$-10

- Genital warts
  - Imiquimod
  - Podofilox
  - Sinecatechins

- Cancer
  - Surgery
  - Radiation
  - Chemotherapy

- Alternative Therapies
  - Active hexose correlated compound (AHCC)
  - Curcumin
Genital Warts: Treatment

- Primary Goal of therapy:
  - Removal of symptomatic/visible warts

Table 2: Treatment Options for Genital Warts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose/Duration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod 3.75% or 5% Cream*</td>
<td>Apply at bedtime 3x/week for 16 weeks</td>
<td>Redness, irritation, pigmentary changes</td>
</tr>
<tr>
<td>Podofilox 0.5% Solution or Gel</td>
<td>Apply 2x/day for 3 days then 4 days without treatment</td>
<td>Burning, swelling, redness, pain</td>
</tr>
<tr>
<td>Sinecatechins 15% Ointment*</td>
<td>Apply 3x/day for up to 16 weeks</td>
<td>Redness, irritation, pigmentary changes</td>
</tr>
</tbody>
</table>

*Weakens condoms and diaphragms
Cancer: Treatment

- Treatment options dependent upon site and extent of spread

- Can include:
  - Surgery
    - Potential complications
    - Inability to fully resect
  - Radiation/Chemotherapy
    - Wide array of side effects
    - Potential for secondary malignancies
Alternative Therapies: AHCC\textsuperscript{9,10}

- Japanese mushroom extract derived from medicinal mushroom mycelia
- Modifies innate and adaptive immunity by:
  - Increases production of cytokines
  - Increases natural killer cell activity
  - Increases macrophages
  - Increases dendritic cells
  - Increases T-cells
- Enhances the body’s ability to respond to infections and block the proliferation of tumors
Evaluation of AHCC for the Eradication of HPV Infections\textsuperscript{11,12}

- Smith JA, et al.

**Methods:**
- HPV (+) females over the age of 30 (N=10)
- 3 grams AHCC by mouth daily for up to 5 months

**Purpose:**
- To determine if AHCC is effective in eradicating cervical HPV infections
Evaluation of AHCC for the Eradication of HPV Infections\textsuperscript{11,12}

- **Results:**
  - 5 women achieved a negative HPV test result
    - 2 confirmed eradication after 3 months
    - 1 confirmed eradication following 5 months of therapy
    - 2 continuing treatment for additional 2 months in order to assess eradication status
  - 1 patient experienced treatment failure

- **Authors’ Conclusion:**
  - Determined at least 3 months of therapy is necessary
  - Further investigation via a phase II randomized, placebo-controlled study is planned
Alternative Therapies: Curcumin

- Yellow pigment from the root of *Curcuma longa linn*
- Present in the Southeast Asian spice turmeric
- Oral administration is safe and well-tolerated
- Low oral bioavailability
- Currently being investigated for its antitumor, anti-inflammatory, and anti-viral properties
Curcumin-based Vaginal Cream Eliminates Apposed Human Cervical Cancer Cells

- Debata PR, et al.

**Methods:**
- Tested selectivity and potency of curcumin against four HPV (+) cervical cancer cell lines and normal fibroblasts
- Evaluated efficacy of curcumin-based vaginal cream, Vacurin-20
  - Vacurin-20 formulation: curcumin powder in topical oil-in-water cream base, Vanicream

**Purpose:**
- To test the possibility of developing a curcumin-based therapy for cervical cancer
Curcumin-based Vaginal Cream Eliminates Apposed Human Cervical Cancer Cells\textsuperscript{13}

- Results:
  - Cultured human cervical cancer cells were eliminated by curcumin/Vacurin-20
    - Suppressed epidermal growth factor receptor (EGFR)
    - Induction of p53
    - Inhibits serine-780 phosphorylation of the retinoblastoma protein (Rb)
  - Mice treated with Vacurin-20 did not result in increased vaginal inflammation

- Authors’ conclusion:
  - Vacurin-20 eliminates cervical cancer cells and intravaginal application is safe
Clearance of HPV by Topical Curcumin and Curcumin Polyherbal Cream\textsuperscript{14}


- Methods:
  - HPV (+) women between 30-60 years old (N=287)

- Purpose:
  - To evaluate efficacy of *Basant* polyherbal vaginal cream and curcumin vaginal capsules to eliminate HPV infection

### Table 3: Treatment Arms and Dosing of Curcumin

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Treatment</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 (n=72)</td>
<td><em>Basant</em> vaginal cream</td>
<td></td>
</tr>
<tr>
<td>Arm 2 (n=54)</td>
<td>Placebo vaginal cream</td>
<td>One application daily at bedtime for 30 days</td>
</tr>
<tr>
<td>Arm 3 (n=79)</td>
<td>Curcumin vaginal capsule</td>
<td></td>
</tr>
<tr>
<td>Arm 4 (n=82)</td>
<td>Placebo vaginal capsule</td>
<td></td>
</tr>
</tbody>
</table>
Clearance of HPV by Topical Curcumin and Curcumin Polyherbal Cream

Results:

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>HPV Elimination</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basant Cream</td>
<td>57/65 (87.7%)</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Placebo Cream</td>
<td>36/48 (75.0%)</td>
<td>p=0.19</td>
</tr>
<tr>
<td>Curcumin Capsule</td>
<td>61/75 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>Placebo Capsule</td>
<td>58/80 (72.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Authors’ Conclusion:
- Women treated with *Basant* cream and curcumin capsule had higher rates of HPV elimination.
Discussion

- **AHCC:**
  - Resulted in eradication of HPV in select women

- **Curcumin:**
  - Suppressed pro-cancer signaling pathways
  - Vaginal application was found to be safe and generally well tolerated

Table 5: Strengths and Limitations of selected AHCC and Curcumin Studies

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate endpoints</td>
<td>Small sample size</td>
</tr>
<tr>
<td><em>Basant</em> was placebo-controlled</td>
<td>Short treatment duration</td>
</tr>
<tr>
<td>--</td>
<td>Excluded men</td>
</tr>
</tbody>
</table>
Summary

- HPV is the most common sexually transmitted infection
- Typically asymptomatic and self-limiting
- Prevention methods include abstinence, condom use, and HPV vaccination
- Current commercial treatments only treat complications of the virus
- AHCC, derived from mushroom, has shown to be effective in HPV eradication
- Curcumin suppresses pro-cancer signaling pathways and results in HPV negative tests


References


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