Penile Carcinoma: From Anatomy to Molecular Biology
Antonio Cubilla
And
Gustavo Ayala, M.D.

Penis-Cross Section

Demographics
- Sporadic/familial
- Age: 7th decade
  - Verruciform, basaloid and low grade papillary carcinomas appear a decade before SCC,NOS
  - Young individuals as isolated cases or in clusters
- Race: no preference
  - Secondary tumors more frequent in AA

Geographic Distribution Patterns
**Causes**

**Major causes**
- Circumcision
- HPV
- Tobacco
- BXO
- PUVA

**Minor causes**
- Hailey-Hailey
- Lichen planus
- Burns
- Asbestos
- Sinus tracts
- Hypoplasia
- Mineral oil injection
- Sexual activity
- Zoo’s plasmacellular balanitis

**Not associated:** Herpes virus, Epstein Barr virus, Syphilis

**Circumcision**

- The risk for PeCA was 3.2 times greater among men who were never circumcised than the risk in men circumcised at birth
- 88% of Kenyan patients with PeCA were uncircumcised and 12% had late circumcision
- Late circumcision does not seem to have the same preventive effect.
  - Often performed because of early penile lesions or penile diseases associated to the development of PeCA. Bissada found 15 patients that developed PeCA post adult circumcision in circumcision scars
- Penile cancers do occur in circumcised males

<table>
<thead>
<tr>
<th>Type</th>
<th># of cases</th>
<th>Circumcision</th>
<th>Late circumcision</th>
</tr>
</thead>
<tbody>
<tr>
<td>PeCA</td>
<td>189</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>PeIN</td>
<td>118</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>0/29</td>
<td></td>
<td>3 of 32</td>
</tr>
</tbody>
</table>

**Circumcision and HPV**

- Circumcision also has a protective effect against HPV infection, urinary tract infections and HIV.
- The foreskin provides a permissive microenvironment for infectious organisms and for the progression of HPV lesions.
- Penile cancers do occur in circumcised males

**HPV**

- Invasive PeCA: HPV in 40-60%
- PeIN: HPV in 90-100%
- Condylomas and low grade PeIN: HPV 6 & 11
- High grade PeIN and PeCA: HPV 16 and 18
- HPV also found in normal mucosa (to the eye)
- HPV in PeCA is associated with histologic subtypes
**HPV DNA detection in penile condyloma, dysplasia and carcinoma.**

Gregoire et al. - HPV associated with SCC at areas showing basaloid and/or warty changes. HPV was found in a very low percentage of typical SCC of the penis (11.1%). Stepwise logistic regression analysis revealed that only tumor histopathology was a significant predictor of an HPV association.

**HPV Regional Differences**

<table>
<thead>
<tr>
<th>HPV PHYLOGENETIC TYPES*</th>
<th>PENILE CARCINOMA PARAGUAY</th>
<th>PENILE CARCINOMA USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANY HPV POSITIVE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A10:HPV 6,11,31,33,52</td>
<td>0</td>
<td>15.0</td>
</tr>
<tr>
<td>A7: HPV 18,39,45,68,70</td>
<td>4</td>
<td>17.3</td>
</tr>
<tr>
<td>A6: HPV 51,69</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>OTHER HPVs</td>
<td>3</td>
<td>13.8</td>
</tr>
</tbody>
</table>

**HPV- Oncogenic Mechanisms**

- Mostly integrated in primary DNA
- Metastasis and primary have same integration
- Background HPV infection in population
- Regional differences in oncogenic potential: Enhancer region of Ugandan HPV with greater transformation potential
- Permissive factors: Foreskin

**Causes**

- **Tobacco**
  - Case control study: Association with smoking, chewing and use of snuff
  - Odds ratio of developing PeCA for smokers: 2.8
  - 80% PeCA patients are heavy smokers

- **PUVA**
  - Dose-dependent correlation
  - 14 patients followed for 12 yr. developed 30 genital CA
  - Incidence of PeCA 2.56 general population and 16.3 times lower levels of exposure
  - Risk of genital tumors with UVB is 4.6 higher than controls

- **BXO**
  - Anecdotal reports
  - 5.8% patients with BXO developed PeCA (lag time 17 yr.)

- **Radiation**
  - Secondary post radiation PeCA
  - Malignant progression post radiation

- **Chronic Irritation**

**Growth Patterns**

- Growth
  - Cancer DNA
  - Metastasis and primary have same integration
  - Background HPV infection in population
  - Regional differences in oncogenic potential: Enhancer region of Ugandan HPV with greater transformation potential
  - Permissive factors: Foreskin
Growth Patterns

- Superficially Spreading

- Verruciform

- Multicentric PeCA

- Vertical Growth

Growth Patterns
Growth Patterns

Histologic Subtypes

SCC, NOS
(not otherwise specified)

Basaloid Carcinoma

Basaloid Penile Carcinoma

Verruciform Tumors
Verruciform Tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Papillae</th>
<th>Fibrovascular cores</th>
<th>Koilocytic atypia</th>
<th>Base</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warty Carcinoma</td>
<td>Long</td>
<td>Prominent</td>
<td>Prominent and diffuse</td>
<td>Rounded or irregular</td>
<td>I/II</td>
</tr>
<tr>
<td>Giant Condyloma</td>
<td>Undulating</td>
<td>Prominent</td>
<td>Present at surface</td>
<td>Regular, broad and pushing</td>
<td>I</td>
</tr>
<tr>
<td>Verrucous Carcinoma</td>
<td>Arborizing</td>
<td>Rare</td>
<td>Absent</td>
<td>Irregular and jagged</td>
<td>I</td>
</tr>
<tr>
<td>Papillary Carcinoma, NOS</td>
<td>Variable</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>I</td>
</tr>
</tbody>
</table>

- HPV 16
- HPV 6 and 11
- Yes
- No
- Yes

Buschke-Lowenstein Giant Condyloma

- HPV Absent
- No

Verrucous Carcinoma

- Glassy
- Keratohyaline granules
- Low nuclear grade
- Centrally located vesicular
- Absence or paucity of koilocytes
- Intracellular edema
- Well-formed cellular bridges
- Necrofibrovascular cores
- Pushing border

Papillary carcinoma

- Mixed Warty/Basaloid Carcinomas
**Rare Variants**
- Small cell
- Adenosquamous
- Sarcomatoid

**Foreskin Carcinoma**
- Associated to Lichen sclerosis
- Low grade
- More superficial

**Penile Intra-epithelial Neoplasia**
- Warty PeIN
- Basaloid PeIN
- PeIN, NOS
- Hyperplastic-hypertrophic PeIN
- Micaceous PeIN
- Pseudoepitheliomatous PeIN

**Prognostic factors**
- Primary Tumor Site
- Anatomic site
- Morphologic Patterns
- Histologic subtypes
- Histologic grade
- Anatomic level & depth of infiltration in mm.
- Mitosis index
- Vascular invasion
Molecular Changes

Molecular Anatomy

- P21
  - 40% of PeCA have p21
- DNA ploidy
  - Prognostic significance questionable
  - Small nuclear size-bad prognosis (basaloid?)
- Ki-67
  - Growing edge of verrucous carcinoma
- Telomerase
  - 55% of PeCA/80% of normal epithelium and corpora
- Cytogenetics
- C-RAS
  - Found only in second metastasis of one case-Progression?
- ABO
  - Lost in most PeCA
- SCRA
  - 54% of PeCA
  - Lost most frequently (91%) in metastatic PeCA
- Glucose transporter -1
  - Present in proliferating areas of tumor
- C-RAS
- ABO
- SCRA
- Glucose transporter -1

Prognostic Index

Penis-Cervix
- Marital Clusters
  - Some males more prone to have spouse with cervical cancer
- Male-Female HPV transmission
- Estradiol/progesterone receptors
- Immune response
Micro-environmental Relationships

- **Penile carcinoma - Cervix carcinoma**
  - Anecdotal reports of concurrent cancers
  - Puerto Rican couples: no correlation
  - Risk of female developing preinvasive or invasive cervical cancer: 1.05/1.75

- **Penile carcinoma - Vulva carcinoma**
  - Histologic and demographic similarities: most similar cancers
  - Same relation to HPV in invasive (basaloid/warty) and in situ lesions
  - Anecdotal reports of concurrent cancers
  - However no established link

- **Penile carcinoma - Anal canal carcinoma**
  - More common in women and homosexual men
  - Similar to cervix
  - Strong relation to HPV

- **Penile carcinoma - Perianal skin carcinoma**
  - More common in heterosexual men
  - Similar to vulva and penis
  - Not related to HPV

---

HPV Male/Female

- **Sexual transmission:**
  - Increased incidence of lesions

- **Straight transmission:**
  - 6/11 - condyloma
  - 16/18 - CIN

<table>
<thead>
<tr>
<th>HPV type</th>
<th>Male partners</th>
<th>Female partners</th>
<th>Male with PeCA</th>
<th>Female with PeCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/11</td>
<td>11.1%</td>
<td>17.7%</td>
<td>20%</td>
<td>18.6%</td>
</tr>
<tr>
<td>16/18</td>
<td>5.6%</td>
<td>11.9%</td>
<td>22%</td>
<td>14.5%</td>
</tr>
</tbody>
</table>

---

HPV Relationship Male-Female

Case control studies

- Differences according to populations:
  - Colombia vs Spain

---

Micro-environmental Relationships

- **Progression Factors**
  - Foreseen PeCA
  - Foreskin PeCA

- **Non progression or regression**
  - Bowenoid papulosis

- **ER/PR**
  - HPV has progesterone response elements
  - Cervix tendency to HPV progression
  - Penis and PeCA lack ER/PR

- **Immune response**

---

Penile Carcinoma

- **Basaloid carcinoma**
- **Warty carcinoma**
- **SCC, NOS**
- **Chronic irritation**
- **Dysplastic hyperplasia**
- **Verrucous carcinoma**
Penile Carcinoma