PRE-MALIGNANT AND MALIGNANT NEOPLASMS OF THE CERVIX
Cervix

• The cervix consists of the ectocervix and endocervical canal
• Ectocervix - covered by mature squamous cells
• Endocervix – lined by columnar, mucus-secreting epithelium
• “Transformation zone” - The area of the cervix where the columnar epithelium abuts the squamous epithelium
Transformation zone

Figure 22-16 In the diagram (upper), reserve cells in the transformation zone are continuous with the basal cells of the ectocervix (right) and may undergo columnar squamous differentiation (metaplasia). Photomicrographs at bottom depict (from left to right) quiescent subcolumnar reserve cells, reserve cells undergoing columnar differentiation (second from left), reserve cells undergoing squamous metaplasia (second from right) and ectocervical squamous epithelium (right).
Cervix

• The unique epithelial environment of the cervix renders it highly susceptible to infections with HPV → leading cause of cervical cancer

• Immature squamous metaplastic epithelial cells in the transformation zone are most susceptible to HPV infection
  – This is where cervical precursor lesions and cancers develop.
Cervical cancer

• 3rd most common cancer in women worldwide (530,000 new cases in 2008, half fatal)
• USA: ↓ incidence due to effective screening (12,410 new cases in 2008; 4,000 deaths)
• Pathogenesis: high-risk HPV types
• HR HPV types (16, 18, 31, 33, 35, 51, 52, 56, 58, 59, and 68): squamous cell carcinoma of vagina, vulva, penis, anus, tonsil, oropharynx
• LR HPV types (6, 11): vulvar, perineal, perianal warts (condyloma acuminatum)
HPV infection sequence
HPV infection of cell

- Even though HPV has been firmly established as a common cause of cervical cancer, it is not sufficient to cause cancer
  - A high percentage of young women are infected with one or more HPV types during their reproductive years, but only a few develop cancer.
- Other factors, such as exposure to co-carcinogens and host immune status, influence whether an HPV infection regresses or persists and eventually progresses to cancer.
SIL/CIN Cytology (Pap test)
## Classification of Cervical Intraepithelial Neoplasia

**TABLE 22-1** Classification Systems for Squamous Cervical Precursor Lesions

<table>
<thead>
<tr>
<th>Dysplasia/Carcinoma in Situ</th>
<th>Cervical Intraepithelial Neoplasia (CIN)</th>
<th>Squamous Intraepithelial Lesion (SIL), Current Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dysplasia</td>
<td>CIN I</td>
<td>Low-grade SIL (LSIL)</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>CIN II</td>
<td>High-grade SIL (HSIL)</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>CIN III</td>
<td>High-grade SIL (HSIL)</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>CIN III</td>
<td>High-grade SIL (HSIL)</td>
</tr>
</tbody>
</table>

CIN, Cervical intraepithelial neoplasia; SIL, squamous intraepithelial lesion.
SIL/CIN histology
Natural History of Squamous Intraepithelial Lesion

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Regress</th>
<th>Persist</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL</td>
<td>60%</td>
<td>30%</td>
<td>10% to HSIL</td>
</tr>
<tr>
<td>HSIL</td>
<td>30%</td>
<td>60%</td>
<td>10% to carcinoma</td>
</tr>
</tbody>
</table>

HSIL, High-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
Invasive squamous cell carcinoma
Invasive squamous cell carcinoma
Adenocarcinoma of the cervix
Cervical Cancer Staging

Cervical cancer is staged as follows:

**Stage 0**—Carcinoma in situ (CIN III, HSIL)

**Stage I**—Carcinoma confined to the cervix

  * Ia—Preclinical carcinoma, that is, diagnosed only by microscopy
  * Ia1—Stromal invasion no deeper than 3 mm and no wider than 7 mm (so-called microinvasive carcinoma)
  * Ia2—Maximum depth of invasion of stroma deeper than 3 mm and no deeper than 5 mm taken from base of epithelium; horizontal invasion not more than 7 mm
  * Ib—Histologically invasive carcinoma confined to the cervix and greater than stage Ia2

**Stage II**—Carcinoma extends beyond the cervix but not to the pelvic wall. Carcinoma involves the vagina but not the lower third.

**Stage III**—Carcinoma has extended to the pelvic wall. On rectal examination there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina.

**Stage IV**—Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. This stage also includes cancers with metastatic dissemination.
Clinical Features

• More than half of invasive cervical cancers are detected in women who did not participate in regular screening

• Treatment:
  – Invasive Carcinoma:
    • May be treated with cervical cone excision if micro invasive
    • If > microinvasive, then treated with hysterectomy with lymph node dissection, +/- radiation if advanced.

• Prognosis and Survival:
  – Depends on the stage of the cancer at diagnosis and degree of histologic subtype
Cervical Cancer Screening

- HPV screening younger than 30 is not recommended because of the high incidence of infection.
- First Pap smear should be at age 21 or within 3 years of sexual activity, and thereafter every 3 years.
- After age 30, women with normal cytology and negative HPV can be screened every 5 years.
  - Normal cytology and + HPV test = every 6-12 months.
- Abnormal Pap test:
  - Colposcopy to identify lesion + biopsy.
  - LSIL - conservative management.
  - HSIL - LEEP/Cone.
HPV Vaccine

• Vaccination against oncogenic HPV – recommended for all girls and boys age 11 – 12 years, and young men and women up to age 26 years

**INFORMATION ABOUT GARDASIL 9**

GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) helps protect girls and women ages 9 to 26 against cervical, vaginal, vulvar, and anal cancers and genital warts caused by 9 types of HPV. GARDASIL 9 helps protect boys and men ages 9 to 26 against anal cancer and genital warts caused by those same HPV types.

GARDASIL 9 may not fully protect everyone, nor will it protect against diseases caused by other HPV types or against diseases not caused by HPV.

GARDASIL 9 does not prevent all types of cervical cancer, so it’s important for women to continue routine cervical cancer screenings. GARDASIL 9 does not treat cancer or genital warts.

<table>
<thead>
<tr>
<th>AGE</th>
<th>DOSES</th>
<th>SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>9–14 years</td>
<td>2*</td>
<td>1st shot: Today 2nd shot: 6–12 months after the first shot</td>
</tr>
<tr>
<td>15–26 years</td>
<td>3*</td>
<td>1st shot: Today 2nd shot: 2 months after first shot 3rd shot: 6 months after the first shot</td>
</tr>
<tr>
<td>15–26 years</td>
<td>3</td>
<td>1st shot: Today 2nd shot: 2 months after first shot 3rd shot: 6 months after the first shot</td>
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