Screening, diagnosis and management of cervical cancer

Gyula Richárd Nagy MD, PhD
Cervical cancer incidence and mortality by region

Cervical Cancer Incidence and Mortality Worldwide in 2008

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>530</td>
<td>275</td>
</tr>
<tr>
<td>More developed regions</td>
<td>76</td>
<td>32</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>453</td>
<td>242</td>
</tr>
<tr>
<td>WHO Africa region (AFRO)</td>
<td>75</td>
<td>50</td>
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<tr>
<td>WHO Americas region (PAHO)</td>
<td>80</td>
<td>35</td>
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<tr>
<td>WHO East Mediterranean region (EMRO)</td>
<td>18</td>
<td>11</td>
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<tr>
<td>WHO Europe region (EURO)</td>
<td>61</td>
<td>28</td>
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<tr>
<td>WHO South-East Asia region (SEARO)</td>
<td>188</td>
<td>102</td>
</tr>
<tr>
<td>WHO Western Pacific region (WPRO)</td>
<td>105</td>
<td>46</td>
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<tr>
<td>IARC membership (21 countries)</td>
<td>162</td>
<td>98</td>
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<tr>
<td>United States of America</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>China</td>
<td>75</td>
<td>33</td>
</tr>
<tr>
<td>India</td>
<td>134</td>
<td>72</td>
</tr>
<tr>
<td>European Union (EU-27)</td>
<td>31</td>
<td>13</td>
</tr>
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</table>
2007

12,280 women in the United States were diagnosed with cervical cancer.

4,021 women in the United States died from cervical cancer.
ETIOLOGY AND HISTOLOGY

- Etiology: virus induced tumor (HPV)
- Histology:
  - 85-90% carcinoma planocellulare
  - 10-15% adenocarcinoma
  - 1-2% other rare types such as mucinous, endometrioid, clear-cell, serosus, glassy, carcinoid, small-cell
HPV

- DNA-virus (Papovaviridae family)
- Capsid (72 capsomers + circular DNA genome)
- More than 100 biotypes
- Classified based on DNA-test (not serology)
HPV

• **HPV-types**
  - High risk (for malignancy): 16, 18, 31, 33, 35, 39, 45, 52, 53, 56, 58, 59, 66, 67, 68, 70
  - Intermediate risk: 40, 42, 43, 51, 54, 61, 62, 69, 71, 72, 73, 77, 82, 83, 84, 86, 87
  - Low risk: 6, 11, 44, 55, 74

• High risk types — HPV types 16 and 18 are considered high-risk types because they may cause cervical cancer in some women.

• Low risk types — HPV types 6 and 11 can cause genital warts and are low-risk types because they rarely cause cervical cancer.
HPV

• HPV is spread by direct skin-to-skin contact, including sexual intercourse, oral sex, anal sex, or any other contact involving the genital area (eg, hand to genital contact). It is not possible to become infected with HPV by touching an object, such as a toilet seat.

• Most people who are infected with HPV have no signs or symptoms.

• Key determinants of HPV prevalence among women
  • Age at which sexual intercourse was initiated
  • Number of sexual partners (Likelihood that each of her sexual partners was an HPV carrier)
• Higher persistent infection among smokers!

• Condom doesn’t provide proper prevention against infection (60-70%)
HPV

- 80% of women (in the US) are infected at least once during life
- Prevalence is highest among 20-25 years (30-40 %)
- Most cases spontaneously eradicated by the immune system
- When the virus persists (in 10 to 20 percent of cases), there is a chance of developing cervical precancer or cancer. However, it usually takes many years for HPV infection to cause cervical cancer.
HPV

• 3 stages of HPV-infection;
  • *Latent* (DNA-test +, but cytology and histology are normal)
  • *Subclinical* (CIN)
  • *Clinical* (anogenital warts and carcinomas, praecarcinomas, condylomas, newborns laryngeal papillomatosis)
Genital warts
HPV

- Structure of the HPV genome
- Double-stranded DNA
- Genome could be divided into 3 regions:
  - Long Control Region (LCR) without coding potential
  - Region of early proteins (E1-8)
  - Region of late proteins (L1-2) → codes capsid proteins

- E6 oncprotein key action is p53 inhibition
- E7 oncprotein acts by binding Rb gene
- E2 downregulates E6, E7
- Integration to the host DNA → E2 injures → without down regulation abnormal cell proliferation, immortalisation → carcinogenesis

Cell proliferation
Prevalence of the most common HPV types by region

Fig 1. Prevalence of the eight most common HPV types in 14,595 cases of invasive cervical cancer by region. Originally published in the Int J Cancer. 2007;121:621-32.
Human papillomavirus infection & replication in cervical epithelial cells

Expert Reviews in Molecular Medicine
Cervical cancer prevention

• Primary
  • Stable sexual relationship ↔ promiscuity
  • Condom
  • HPV vaccination
  • Education

• Secondary
  • CIN screening and treatment

• Tertiary (prevent cancer related death)
  • Proper treatment of cancer
Vaccination strategies

• **Prophylactic vaccines**
  • Recombinant DNA VLP (Virus Like Partikules) induces virus neutralising IgG antibodies
    • Nonavalent (Gardasil 9) HPV 6, 11, 16, 18, 31, 33, 45, 52, 58
    • Quadrivalent (Silgard/ Gardasil) HPV 6, 11, 16, 18
    • Bivalent (Cervarix) HPV 16, 18 (*monophosphoril lipid adjuvant*)
    • Optimal time for vaccination before first sexual intercourse

• **Therapeutic vaccines**
  • Block the carcinogenesis
  • Causes regression
  • Induces humoral (IgG) and cellular (cytotoxic T cells) immune response
  • clinical trials
Recommendation guidelines of Gardasil®

- Recommended for young girls at the age 11-14 and for young women at the age 16-26
- Pregnancy is contraindication
- Lactation is not contraindication
- Recommended to prevent genital warts (HPV 6,11)
- Recommended to prevent CIN and invasive cervical cancer caused by HPV 16,18
Questions and problems with Gardasil®

- Duration is questionable (lifelong protection?)
- Vaccination of males?
- Cross-protection against other oncogen types? (YES)
- Ineffective in case of active HPV infection?
- Effective antibody titer is not known!
- Protection against other HPV-related tumours (head and neck cancers)
Secondary Prevention

• Prevent from carcinoma
• Find and treat precancerous lesions

We need:
• Screen the population at risk
• Effective screening method
• Effective therapy
SCREENING TEST

- Cytology (Papanicolau-test or Pap-test)
- Colposcopy?
- HPV-DNA-test?
Cytology
To perform a Pap test, a doctor or other health care provider will perform a pelvic exam and use a small brush or spatula to collect cells from the cervix.

The cells are smeared on a glass slide (called a traditional Pap smear) or added to a preservative fluid (called liquid-based, thin layer testing). Studies that have compared the traditional Pap smear to liquid-based cytology do not prove one test to be more accurate than another.
Cytology - Papanicolau classification

• P0 - Improper sample
• P1 - Negative result
• P2 - Negative for dysplasia, but some benign aberration visible (like metaplasia)
• P3 - Pathologic cells but impossible to tell if it is because of inflammation or dysplasia
• P4 - Suspect of malignancy
• P5 – True malignancy
Cytology - Bethesda classification

General description
- Negative for dysplasia
- Neoplasia
- Others: inflammation, infection, atrophy etc.

Detailed description of atypical cells
- Abnormal squamous cells
  - ASC-US, Atypical squamous cells of undefined significance
  - ASC-H, Atypical squamous cells - HSIL not excluded
  - LSIL, Low-grade squamous intraepithelial lesion (CIN 1)
  - HSIL, High-grade squamous intraepithelial lesion (CIN 2, CIN 3, suspect of invasion)
  - Carcinoma planocellulare

- Atypical glandular cells
  - AGC
  - AIS
  - Adenocarcinoma

I. Quality of the slide
II. General description
III. Detailed description of atypical cells
IV. Suggestions
# Cytology

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Infection Reactive Repair</th>
<th>Cytology Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Bethesda System</td>
<td>ASCUS</td>
<td>Squamous Intraepithelial Lesion (SIL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low Grade (LSIL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High Grade (HSIL)</td>
</tr>
<tr>
<td>Richart</td>
<td></td>
<td>Cervical Intraepithelial Neoplasia (CIN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condyloma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade III</td>
</tr>
<tr>
<td>Reagan (WHO)</td>
<td>Normal</td>
<td>Atypia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild Dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate Dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe Dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In situ Carcinoma</td>
</tr>
<tr>
<td>Papanicolaou</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive Carcinoma</td>
</tr>
</tbody>
</table>
Colposcopy
HPV testing

• An HPV test can be done along with a Pap test or as a separate test.
• Like a Pap test, the HPV test is done during a pelvic exam, using a small brush to collect a sample from the cervix.
• HPV tests do not test for all different types of HPV. They test for the strains of HPV that are the highest risk to cause cervical cancer.
<table>
<thead>
<tr>
<th>Agency/Organization</th>
<th>Age to get Screened</th>
<th>Screening Interval</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG)</td>
<td>Start screening no earlier than age 21 and continue until age 65-70</td>
<td>Women age 30-69 get screened every 2 years; after 3 consecutive negative Pap smears (or abnormal cell changes), a woman can get screened every 3 years</td>
<td>Cervical cell abnormalities are common before age 21 and can lead to unnecessary treatments and problems such as preterm delivery (premature birth) and low birth weight.</td>
</tr>
<tr>
<td>National Cancer Institute (NCI)</td>
<td>Screening is effective starting at age 25, but of little value after age 69</td>
<td>Women should get screened at least every three years. If a woman’s last Pap smear was normal, she should wait at least 2 years before having another Pap smear</td>
<td>According to a number of studies, Pap smear was more effective after age 25; one study showed that two years after a negative Pap smear a woman had a small chance of developing cervical cancer.</td>
</tr>
<tr>
<td>United States Preventive Services Task Force/Agency for Healthcare Research and Quality</td>
<td>Start screening within three years of onset of sexual activity or age 21, whichever comes first. Women over 63 with recent normal Pap smears should not get screened</td>
<td>Women should get screened at least every three years. The Task Force concludes there is no evidence to support more frequent screening</td>
<td>Screening was not used in a woman who has been sexually active for three years. A 21-year-old woman who has never had sexual relations does not need screening but the assumptions are that by 21 sexually active women. The Task Force found no direct evidence to recommend annual screening.</td>
</tr>
</tbody>
</table>

**Diagram:**

- **Primary Pap and HPV Test**
  - Pap LSIL or HSIL: Any HPV result
    - Colposcopy
  - Pap ASCUS: HPV positive
    - Repeat Pap in 12 mo
  - Pap ASCUS: HPV negative
    - Repeat both tests in 6–12 mo
    - Repeat in 3 yr
  - Pap negative: HPV positive
    - Repeat Pap and HPV in 12 mo
    - Routine screening every 3 yr
  - Pap negative: HPV negative
    - Colposcopy
Cone biopsy (Conisation)

Conisation
• with a scalpel (cold-knife)
• with Loop Electrosurgical Excision Procedure (LEEP)
and fractional abrasion

**DIAGNOSIS OF CERVICAL CANCER IS BASED ON THE HISTOLOGICAL RESULT!**
Cervical cancer
Cervical cancer - staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)</td>
</tr>
<tr>
<td>IA</td>
<td>Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion $\leq 5$ mm and largest extension $\geq 7$ mm</td>
</tr>
<tr>
<td>IA1</td>
<td>Measured stromal invasion of $\leq 3.0$ mm in depth and extension of $\geq 7.0$ mm</td>
</tr>
<tr>
<td>IA2</td>
<td>Measured stromal invasion of $&gt;3.0$ mm and not $&gt;5.0$ mm with an extension of not $&gt;7.0$ mm</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*</td>
</tr>
<tr>
<td>IB1</td>
<td>Clinically visible lesion $\leq 4.0$ cm in greatest dimension</td>
</tr>
<tr>
<td>IB2</td>
<td>Clinically visible lesion $&gt;4.0$ cm in greatest dimension</td>
</tr>
<tr>
<td>II</td>
<td>Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina</td>
</tr>
<tr>
<td>IIA</td>
<td>Without parametrial invasion</td>
</tr>
<tr>
<td>IIA1</td>
<td>Clinically visible lesion $\leq 4.0$ cm in greatest dimension</td>
</tr>
<tr>
<td>IIA2</td>
<td>Clinically visible lesion $&gt;4.0$ cm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>With obvious parametrial invasion</td>
</tr>
<tr>
<td>III</td>
<td>The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydrenephrosis or non-functioning kidney **</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor involves lower third of the vagina, with no extension to the pelvic wall</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension to the pelvic wall and/or hydrenephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IV</td>
<td>The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of bladder or rectum. A bullos edema, as such, does not permit a case to be allotted to Stage IV.</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread of the growth to adjacent organs</td>
</tr>
<tr>
<td>IVB</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>
Cervical cancer staging

Figure 1. Staging of uterine cervix carcinoma according to FIGO(3).
STAGING I.

TNM and FIGO staging are basically the same

- I/A₁ microinvasive:
  - stromal invasion <3 mm.
  - horizontal invasion <7 mm
- I/A₂
  - depth of infiltration 3-5 mm
- I/B
  - macroscopic tumor confined to the cervix
- I/B₁ - tumor < 4 cm
- I/B₂ - tumor > 4 cm
- II/A - upper third of the vagina
- II/B - parametrium is infiltrated
SPREADING OF CARCINOMA CERVICIS UTERI

- **DIRECT INFILTRATION** → (especially endophytic tumours, so-called barrel-shaped tumours parametrium, vagina, along sacrouterin ligaments to pararectal tissues)

- **LYMPHATIC SPREAD** → to pelvic lymph nodes

- **HAEMATOGEN SPREAD** → (rare, especially small-cell and neuroendocrin types)
STAGING II.

- III/A  lower third of the vagina
- III/B  whole parametrium is infiltrated until the pelvic side wall
- IV/A   bladder or rectum is involved
- IV/B   distant metastasis
Lymphatic spread

Figure 1. Lymph node anatomy in the pelvis. A color diagram outlines the major nodal chains seen in the pelvis. Reprinted with permission, Magnetic Resonance Imaging Clinics of North America © 2004.
Survival statistics

### Stage by Percent and Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percent</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>24</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>70-80%</td>
</tr>
<tr>
<td>III</td>
<td>55</td>
<td>20-30%</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Overall</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT OF CERVICAL CARCINOMA

• I/A1 ➔ Transabdominal hysterectomy (TAH)
  
  Fertility preservation ➔ Cone biopsy

• I/A2-1/B-II/A ➔ Radical hysterectomy (TARH)+ pelvic lymphadenectomy (PLND)
  
  Young patients ➔ conservation and transposition of the ovaries
  
  Fertility preservation (I/A2, I/B1) ➔ Radical trachelectomy + PLND

• II/B, III ➔ Chemoirradiation

• IV ➔ Palliative chemo, RT, surgery
Radical hysterectomy (Wertheim op.)
Radical trachelectomy

- Aim: proper tumor control, fertility preservation
- Removed tissues:
  - Cervix
  - Parametrium
  - Vaginal cuff
- Pelvic lymphadenectomy
- Suture the uterine corpus to the vagina
- Possible in IA2, IB1 st.
Pelvic lymphadenectomy

The most common drainage routes, usually when the lymphatic trunks cross over the obliterated umbilical ligament; the most common locations of sentinel lymph nodes after a cervical injection are medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator space.
Complications of surgical treatment

• Acute
  • Bleeding
  • Pain

• Subacute
  • Urinary bladder dysfunction (innervation!)
  • Lymphocyst

• Chronic
  • Urinary bladder atony
  • Lymphoedema
  • Ureter obstruction
INDICATIONS OF RADIATION THERAPY

• The issue of preoperative irradiation (both cervical and endometrial cancers) is under debate!
  (usually NOT RECOMMENDED!)
• Postoperative radiation therapy is generally indicated
  (if histologic specimen contained tumours)
• CHEMOIRRRA DIATION
  (indicated for locally-advanced cervical cancers)
HDR-AFTER-LOADING BRACHYTHERAPY
EXTERNAL BEAM RADIATION THERAPY
LINEAR ACCELERATOR
EXTERNAL BEAM RADIATION THERAPY
3D PLAN FOR PELVIS
# TREATMENT OF CERVICAL CARCINOMA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>I/A1</td>
<td>Transabdominal hysterectomy (TAH)</td>
</tr>
<tr>
<td></td>
<td>Fertility preservation → Cone biopsy</td>
</tr>
<tr>
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<td></td>
<td>Young patients → conservation and transposition of the ovaries</td>
</tr>
<tr>
<td></td>
<td>Fertility preservation (I/A2, I/B1) → Radical trachelectomy + PLND</td>
</tr>
<tr>
<td>II/B, III</td>
<td>Chemoirradiation</td>
</tr>
<tr>
<td>IV</td>
<td>Palliative chemo, RT, surgery</td>
</tr>
</tbody>
</table>
Cervical cancer and pregnancy

- Precancerous lesion
  - Before pregnancy
    - Cone biopsy
  - During pregnancy
    - Cone biopsy during pregnancy
      - Possible, for diagnostic purpose

- Cervical cancer
  - Pregnancy desire
    - Fertility preservation (Trachelectomy)
  - During pregnancy
    - Management depends on the age of pregnancy
SUMMARY

• Cervical cancer is still a great problem especially in developing countries

• Introduction of prophylactic HPV vaccines is a cornerstone in human cancer prevention!

• However cervical cancer screening must continue!
SUMMARY

• HPV (low risk: 6, 11; high risk: 16, 18)

• HPV vaccination (primary prevention)

• Screening:
  • Cytology (Papanicolau classification, Bethesda classification)
  • Colposcopy

• Diagnosis: conisation (and fractional abrasion) HISTOLOGY

• Radical hysterectomy – Wertheim operation
THANK YOU FOR YOUR ATTENTION!