Global perspectives on HPV and cervical cancer
Edward L. Trimble, MD, MPH
Director, Center for Global Health
National Cancer Institute
National Institutes of Health
US Department of Health and Human Services
Overview of cervical cancer

- Disease burden
- Epidemiology and risk factors
- Primary prevention
- Secondary prevention
- Treatment
- Symptom management
- End-of-life care
World population
Global burden of cervical cancer
Cervical Cancer Incidence and Mortality Estimates by Region

Global cancer statistics

• Third most common cancer in women
• IARC estimates (2008): 530,000 new cases; 275,000 deaths
• Mortality: incidence ratio: 52%
• www.globocan.iarc.fr
History

- Symptom control
- Epidemiology and risk factors
- Treatment of invasive disease
- Screening and treatment of preinvasive disease
- Virology and biology
- Epidemiology and risk factors
- Primary prevention
- Symptom control
Friedrich Sertunen

- Isolated morphine from opium in 1804
- Named after Greek god of sleep (Morpheus)
- First sold by Merck in 1827
Domenico Rigoni-Stern, 1842

- Cancer epidemiology: Verona, Italy
- Breast cancer more common among nuns than among lay women
- Cervical cancer more common among lay women than nuns
- Cervical cancer more common among commercial sex workers
Radical hysterectomy

- John Goodrich Clark, abdominal radical hysterectomy, Baltimore, 1895
- Friedrich Schauta, vaginal radical hysterectomy, Vienna, 1898
- Ernst Wertheim, abdominal radical hysterectomy, Vienna, 1900
Who is this person?
Marie Curie (1867-1934)
George Papanicolaou

- Born in Athens, trained in Munich, worked at Cornell/ New York Hospital
- 1928: report that cervical cancer could be detected by Pap smear
- 1943: Publication of book, *Diagnosis of Cervical Cancer by the Vaginal Smear*
Normal and abnormal Pap smears
Mrs. Andromahi Papanicolaou

- Worked with her husband in pathology laboratory at Cornell
- Underwent daily Pap smears for 20 years
- Receiving award from King of Greece
Persistent Human Papillomavirus (HPV) infection -> cervical cancer

Normal cervix → HPV → CIN3 (pre-cancer) → Invasive cancer
Treatment of preinvasive disease

• Destroy or remove abnormal cervical cells
  • Destruction
    – Freezing
    – Burning
    – Laser
  • Removal
    • Portion of cervix
    • Hysterectomy
Surgical treatment of invasive disease

A hysterectomy removes the uterus and may also remove the cervix (total) and the vagina (radical).
External radiation for invasive disease
Combined external and internal radiation therapy

• External beam: daily treatment M-Friday for 4-6 weeks

• Internal radiation
  – Low-dose rate, requires hospitalization and immobilization for 24 hours
  – High-dose rate; can be given as outpatient
HPV and Harald zur Hausen

- 1976: Harold zur Hausen reported finding HPV in warts and cervical cancer
- Family of 120+ papillomaviruses which can infect skin or mucous membranes in mammals
- HPV 6,11: genital warts
- HPV 16,18: most carcinogenic
- E6 protein (p53) & E7 protein (Rb) block normal cellular control mechanisms
HPV-induced cancers

Annual number of cases worldwide

- Cervix
- Anus
- Vagina/Vulva
- Penis
- Mouth
- Throat
Worldwide Incidence of Cancers Attributable to Infectious Agents

- Infectious agents cause about 17% of all cancers worldwide
- 26% of cancers in developing world, 8% of cancers in developed world

Adapted from Parkin, Int J Cancer 118:3030, 2006
Risk factors

• Chronic HPV infection
  – Most women and men clear HPV infection without adverse events

• High-risk HPV subtypes
  – Subtypes 16 & 18

• Cigarette smoking
  – Current and former smokers have 2-3 times the incidence of CIN and cancer compared to non-smokers

• Immunosuppression (HIV+ and chronic steroid use)
Reproductive risk factors:

• High parity
  – Women with 7+ full term pregnancies have 4 times the incidence of cancer compared with nulliparous women; 2-3 time risk compared to women with 1-2 full-term pregnancies

• Long-term use of oral contraceptives
  – Women who use OCPs for 5-9 years have 3 times the incidence of cancer compared to non-users; women who use OCPs for 10+ years have 4 times the risk compared to non-users
Primary prevention

- Abstinence from sexual activity
- Barrier protection during sexual intercourse
  - Relative risk 0.4
- Development of prophylactic HPV vaccination
  - Four academic laboratories: Georgetown University, National Cancer Institute, University of Rochester, University of Queensland
  - Non-exclusive license to Merck and GSK
Doug Lowy & John Schiller, US NCI
Prophylactic HPV vaccine

- Empty viral capsid (L1)
- Gardasil: HPV 6,11,16,18
- Cervarix: 16,18 +adjuvant
- Efficacy of reduction of incident infection: 91.6%
- Efficacy of reduction of persistent infection: 100%
- 3 doses over 6 months; given before start of sexual activity
HPV vaccination

• US FDA approved quadrivalent HPV vaccine in 2006; bivalent vaccine in 2009
• HPV vaccination recommended for girls and boys in US by American Committee on Immunization Practice (advisory to US CDC)
• HPV vaccination recommended by WHO Strategic Advisory Group on Immunization
• HPV vaccination recommended by Global Alliances for Vaccines and Immunization
Challenges to HPV vaccination

• Cost of vaccine ($150/dose for doses + administration)

• Infrastructure for vaccinating adolescents
  – School versus clinic; other adolescent vaccines (tetanus, whooping cough, meningococcus, etc)

• Societal and parental acceptance of vaccine

• Ongoing research: 2\textsuperscript{nd} generation prophylactic vaccines, therapeutic HPV vaccines, etc
Screening & secondary prevention

• Regular Pap smear screening reduces cervical cancer incidence and mortality by 80%

• Screening systems based on Pap smears are expensive and cumbersome
  – Need for recurrent visits; colposcopy and biopsy; referral to specialists
  – Need to train cytotechnicians, cytopathologists, colposcopists, gynecologists
  – Need for quality control at all levels
System failures leading to cervical cancer diagnosis

- Health care providers do not screen women at visits
- Women do not come in for screening
- Colposcopy for abnormal screen not done
- Patient gets cervical cancer
- Patient does not get appropriate therapy

Source: P Pronovost
How to reduce cost: I

• Pap smear screening is not recommended among women younger than age 25 or those older than age 60 years (if they have a history of recent negative tests)

• Space out screening from yearly to every 3-5 years

• Improve accuracy of Pap?
  – Computer-assisted review; liquid-based Pap
How to reduce cost: II

• Use expression of HPV to find chronic HPV infection with Pap as triage
  – Cost-of-HPV diagnostics?
  – Point-of-care HPV diagnostics?
• Use community health workers to screen with visual inspection following acetic acid application
• See-and-treat with freezing
Reducing toxicity of treatment

• Both surgery and radiation can lead to abnormal bowel, bladder, and sexual function through damage to nerves, fibrosis of tissue, and removal of normal tissue

• Fertility-sparing treatment
  – More conservative surgery
    • Conization rather than hysterectomy; total hysterectomy rather than radical hysterectomy
    • Nerve-sparing radical hysterectomy
  – Neoadjuvant chemotherapy-> surgery?
Improving efficacy of treatment

• Platinum-based chemoradiation
  – Platinum sensitizes cancer cells to radiation
  – On the basis of 5 NCI-sponsored trials, NCI issued Clinical Announcement in 1999 recommending consideration of platinum-based chemoradiation

• Use of PET-CT to evaluate response to radiation

• Intensity-modulated radiation to decrease treatment of normal tissue?

• Image-guided placement of brachytherapy?
Symptom management & end-of-life care

• Side-effects of treatment
  – Bowel function
  – Bladder function
  – Sexual function
  – Body image & intimacy

• End-of-life care
  – Pain control; access to morphine; hospice care
  – Management of cancer-related symptoms
Overview of cervical cancer

- Disease burden
- Epidemiology and risk factors
- Primary prevention
- Secondary prevention
- Treatment
- Symptom management
- End-of-life care
CGH Contact Information

**Website:**
www.cancer.gov/globalhealth

http://www.cancer.gov/aboutnci/globalhealth/lowcosttech

**Telephone number:**
+1-240-276-5810

**Office street address:**
9609 Medical Center Drive, Rockville, MD
(near Shady Grove Adventist Hospital)

**Email:**
NCIGlobalHealth@mail.nih.gov

**Twitter Handle:**
@NCIGlobalHealth
@NCITedTrimble