



Global perspectives on HPV and cervical cancer

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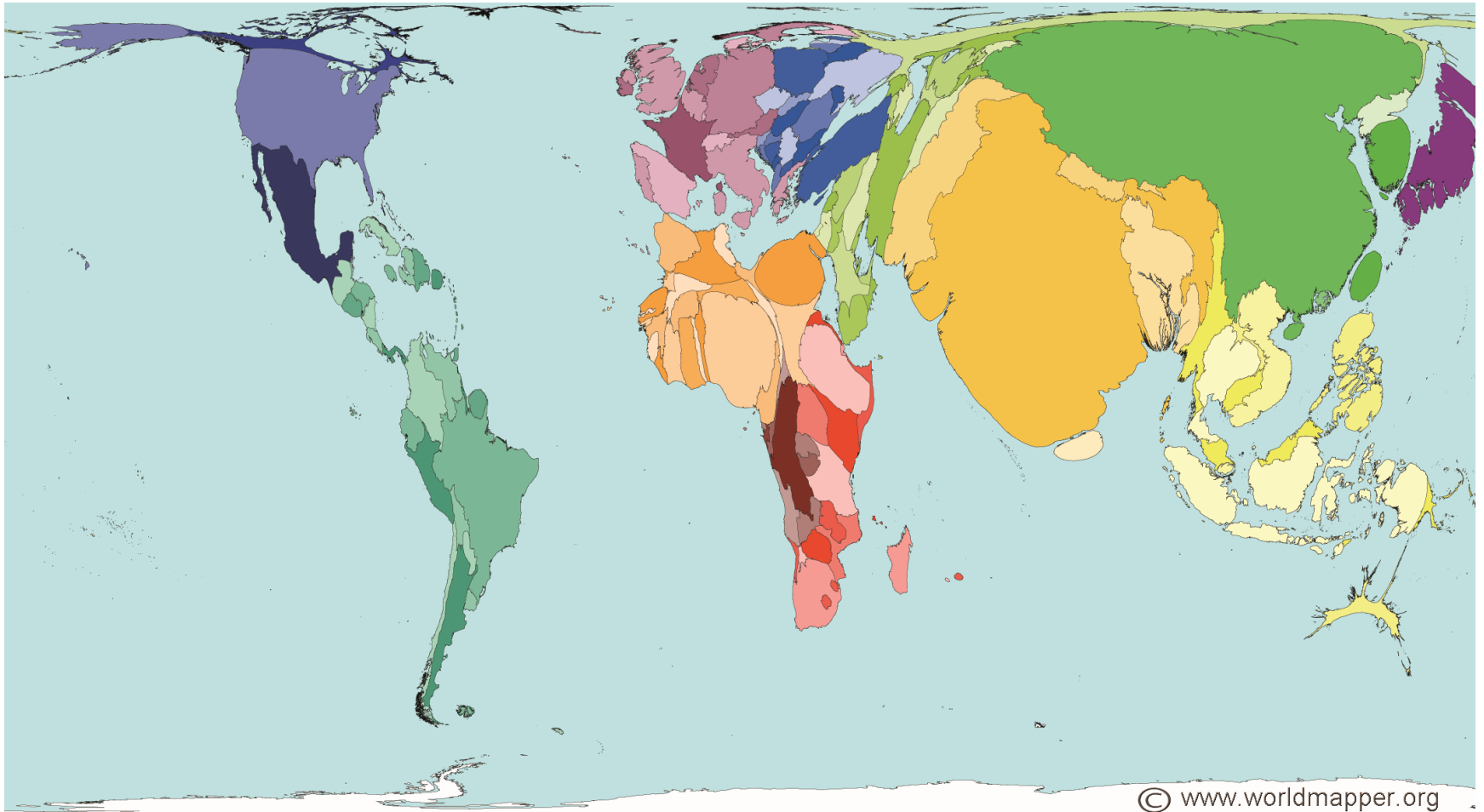
National Institutes of Health

US Department of Health and Human Services

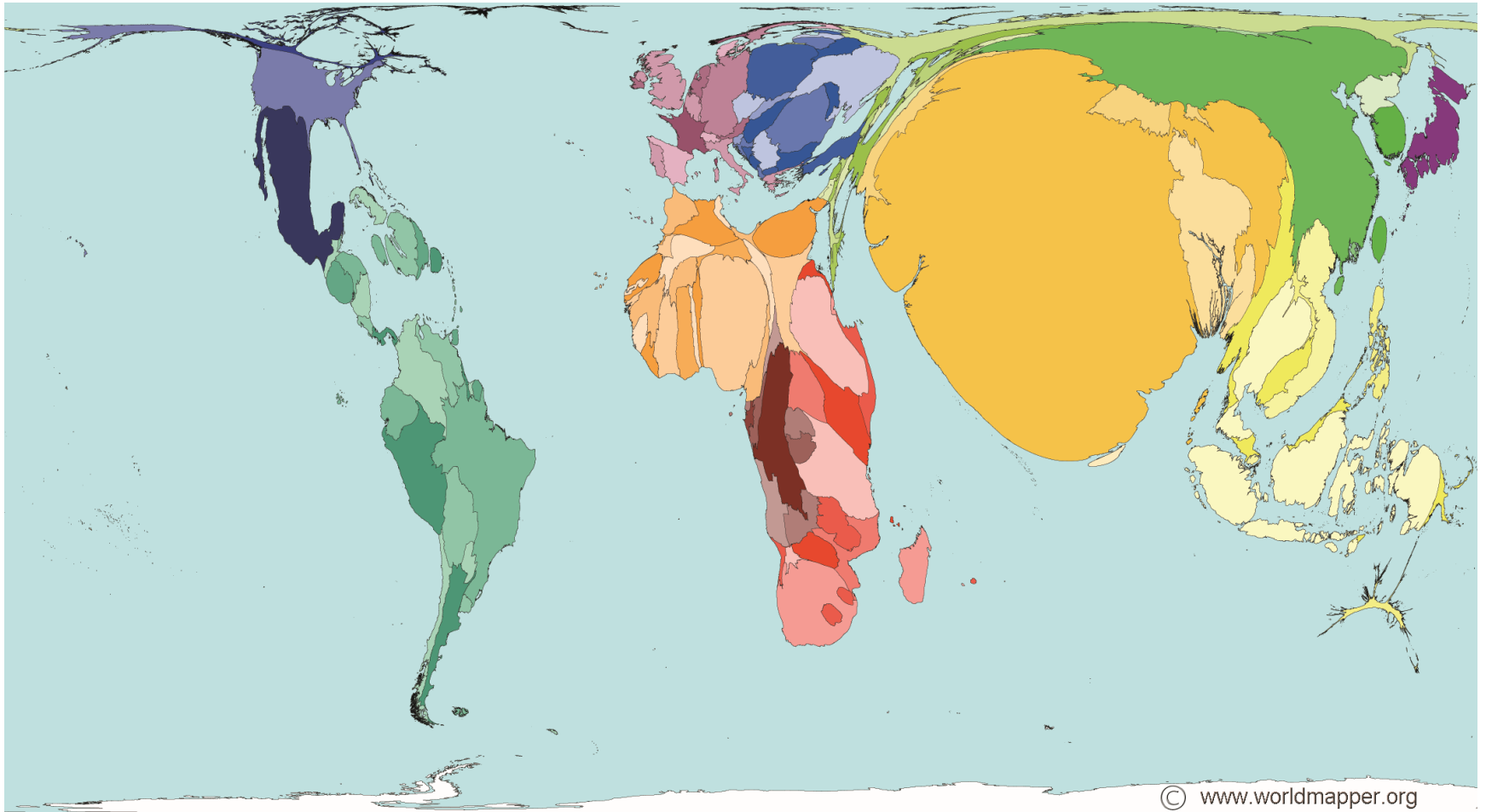
Overview of cervical cancer

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

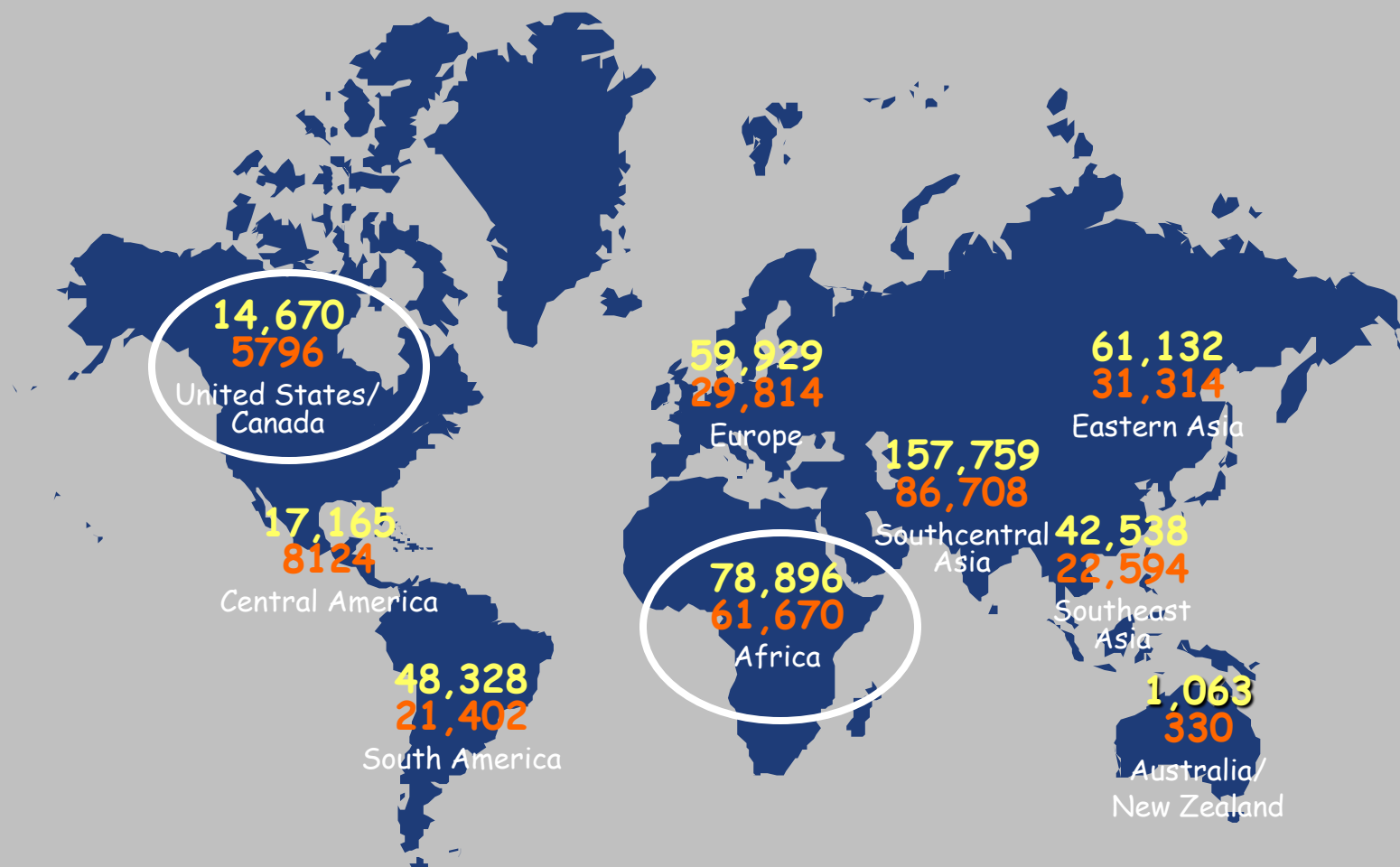
World population



Global burden of cervical cancer



Cervical Cancer Incidence and Mortality Estimates by Region



1. Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004.

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 Sertuner



- 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)

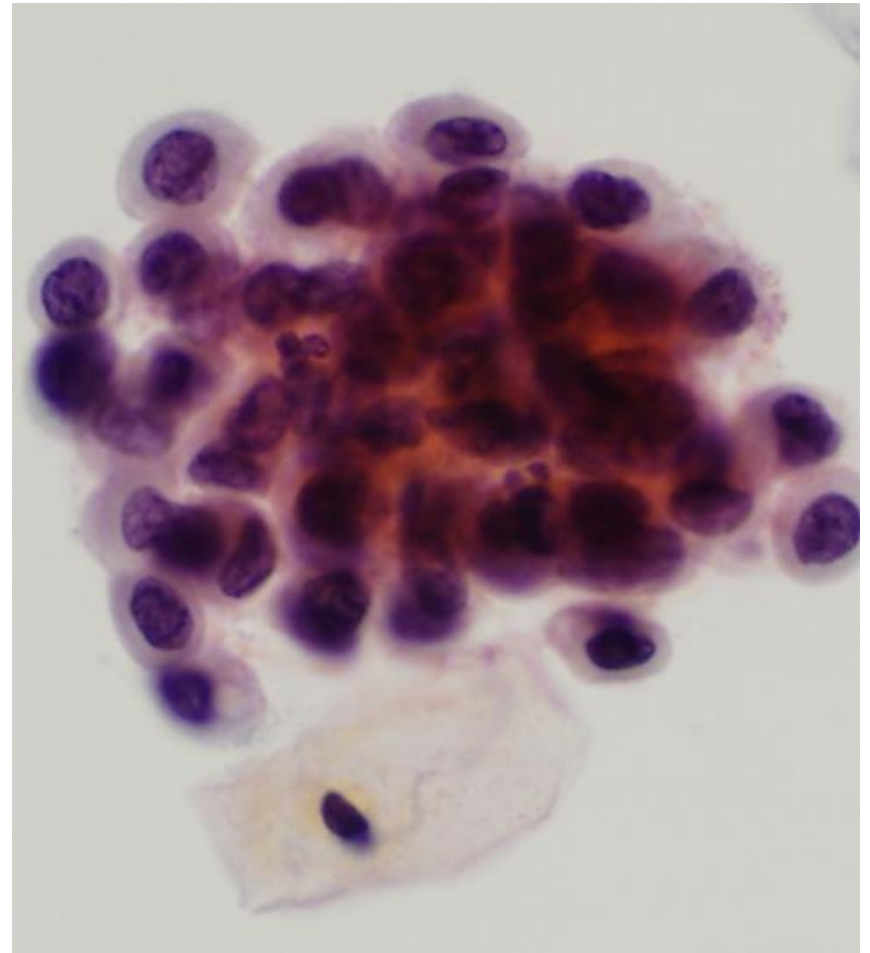
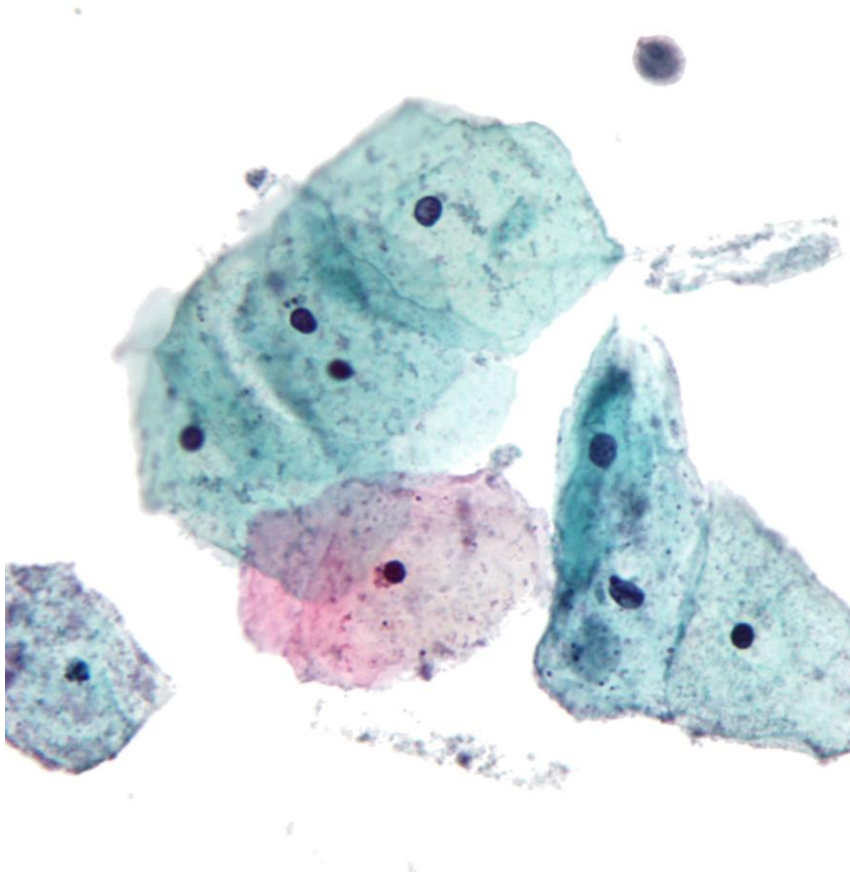


George Papanicolaou



- 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

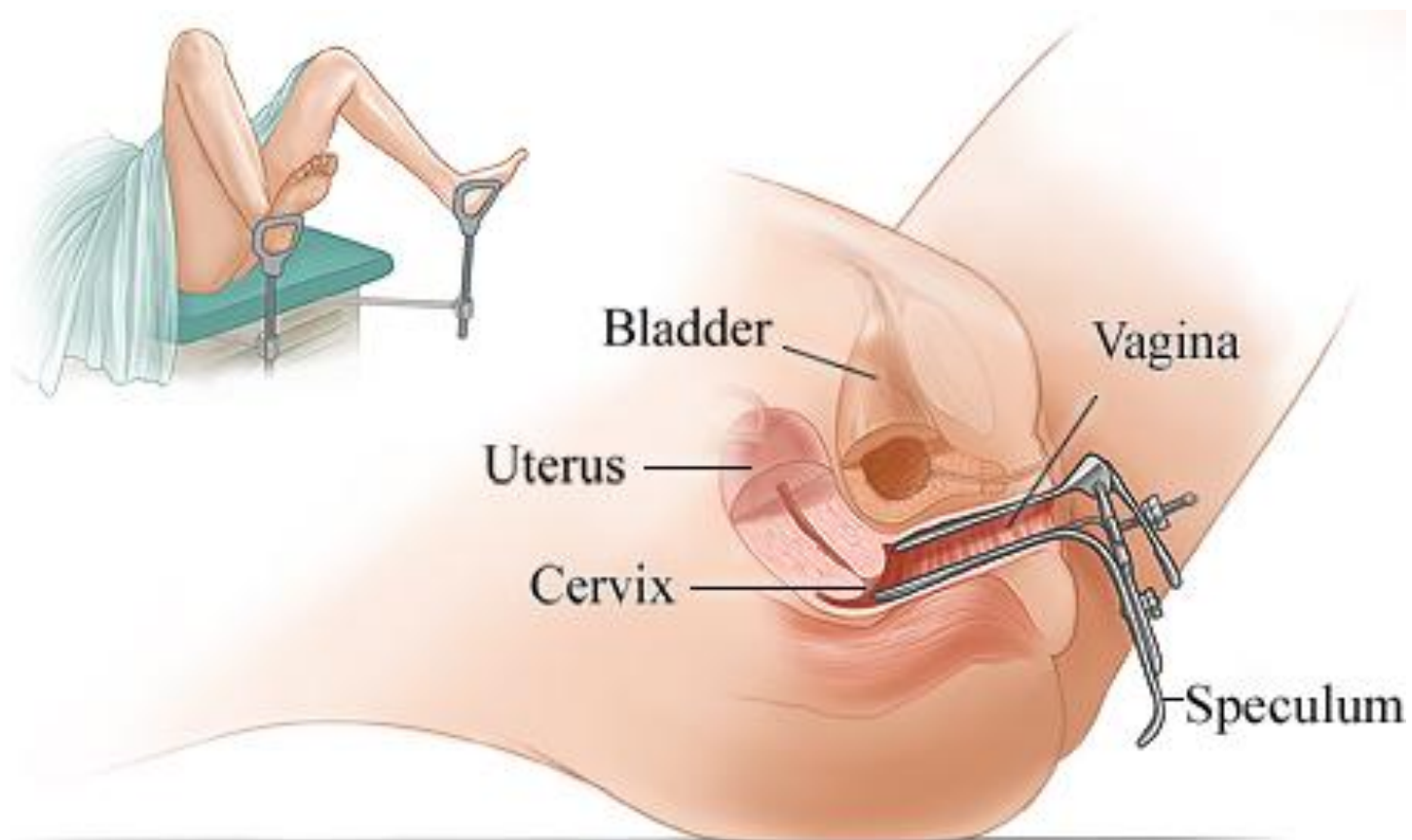
Normal and abnormal Pap smears



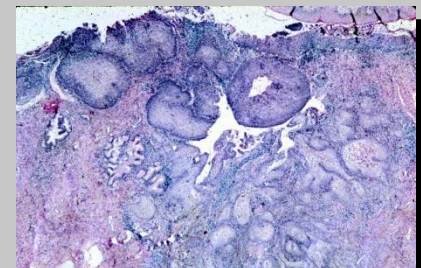
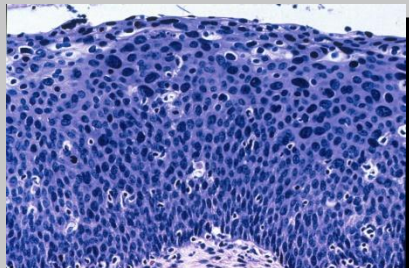
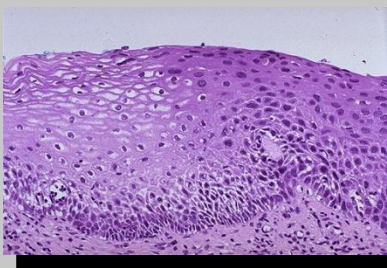
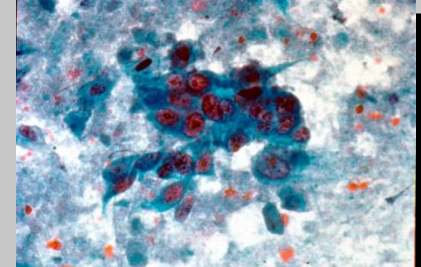
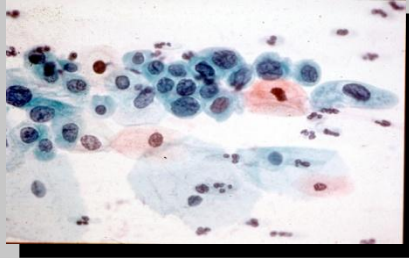
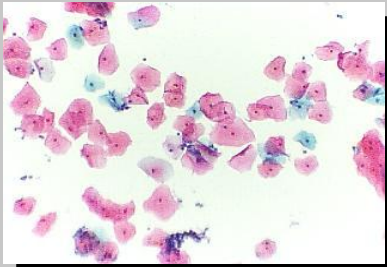
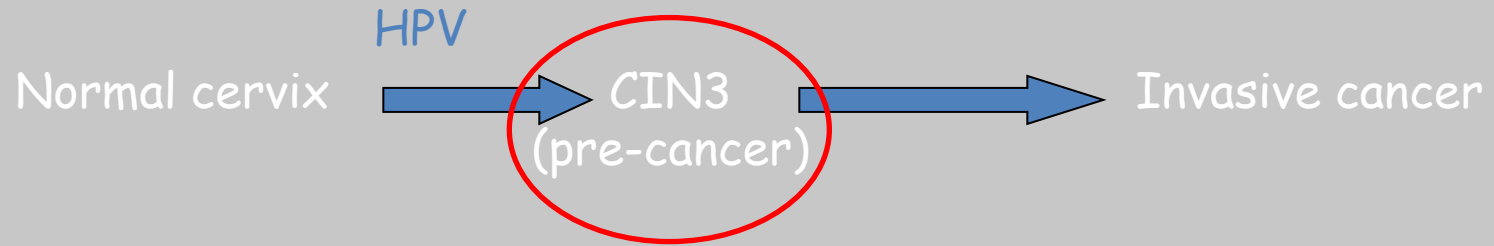
Mrs. Andromahi Papanicolaou



- Worked with her husband in pathology laboratory at Cornell
- Underwent daily Pap smears for 20 years
- Receiving award from King of Greece

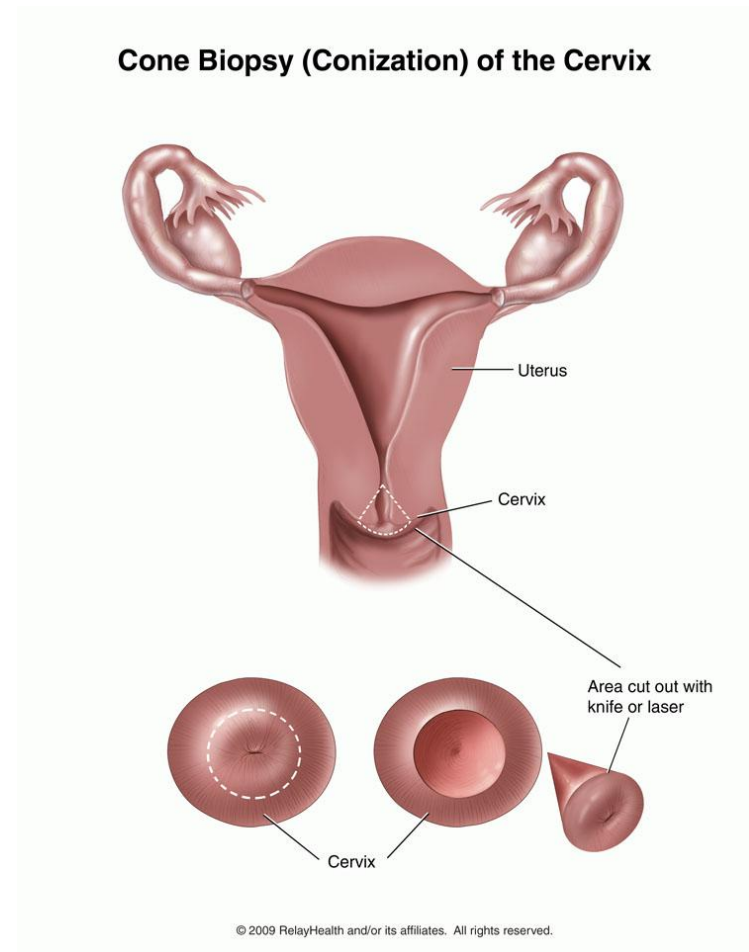


Persistent Human Papillomavirus (HPV) infection-> cervical cancer

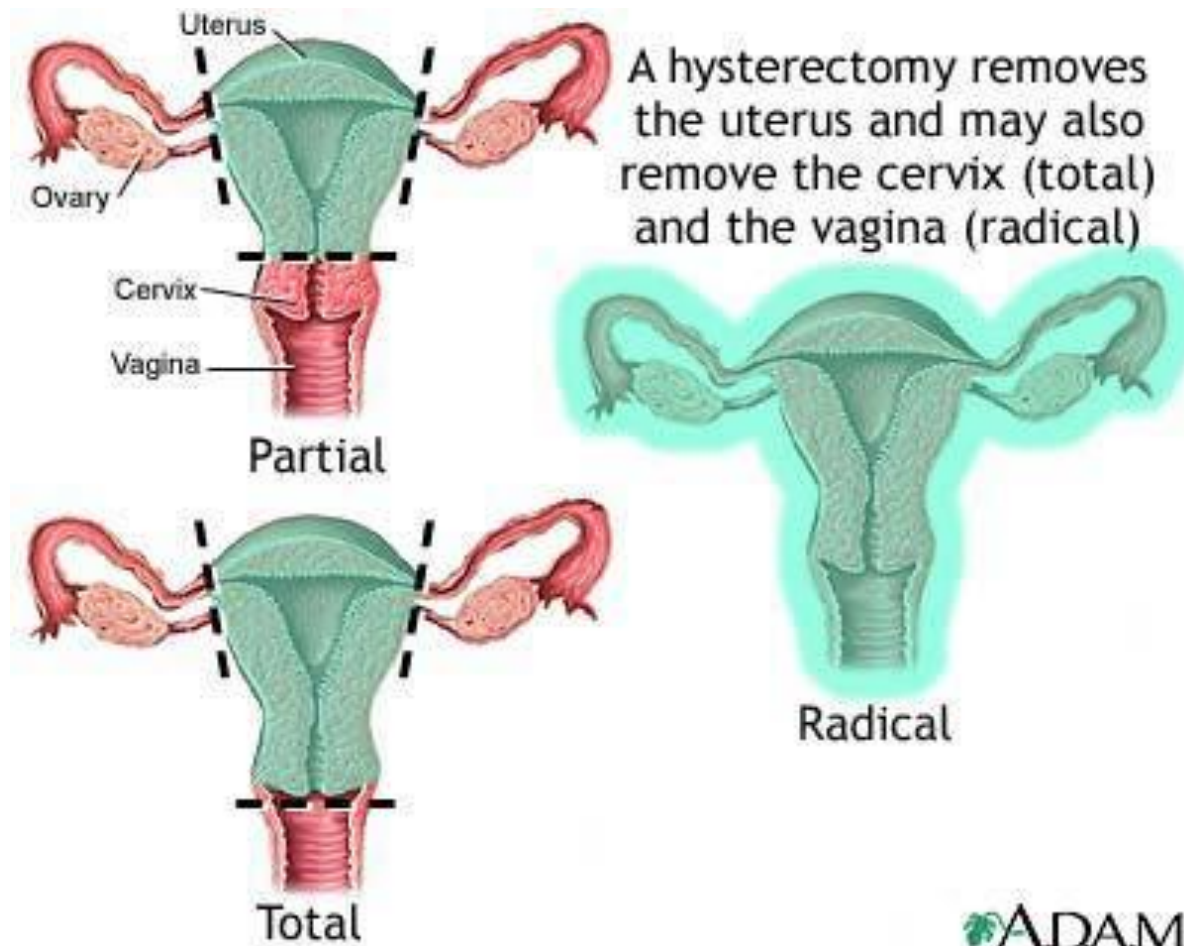


Treatment of preinvasive disease

- Destroy or remove abnormal cervical cells
- Destruction
 - Freezing
 - Burning
 - Laser
- Removal
 - Portion of cervix
 - Hysterectomy



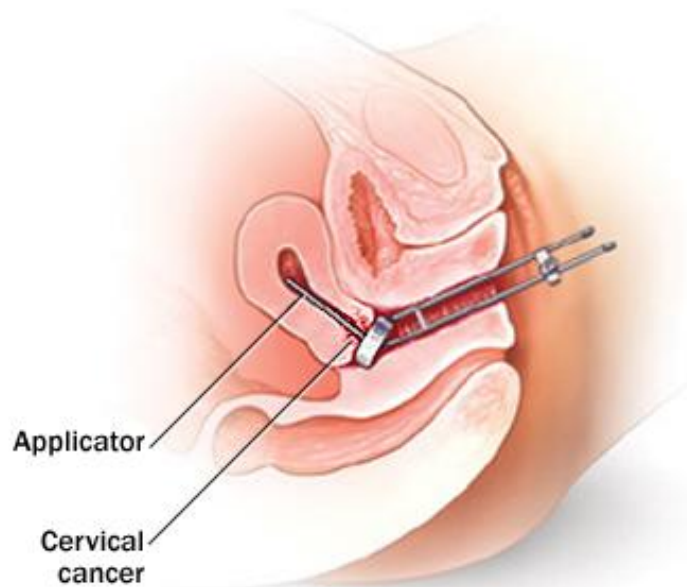
Surgical treatment of invasive disease



External radiation for invasive disease

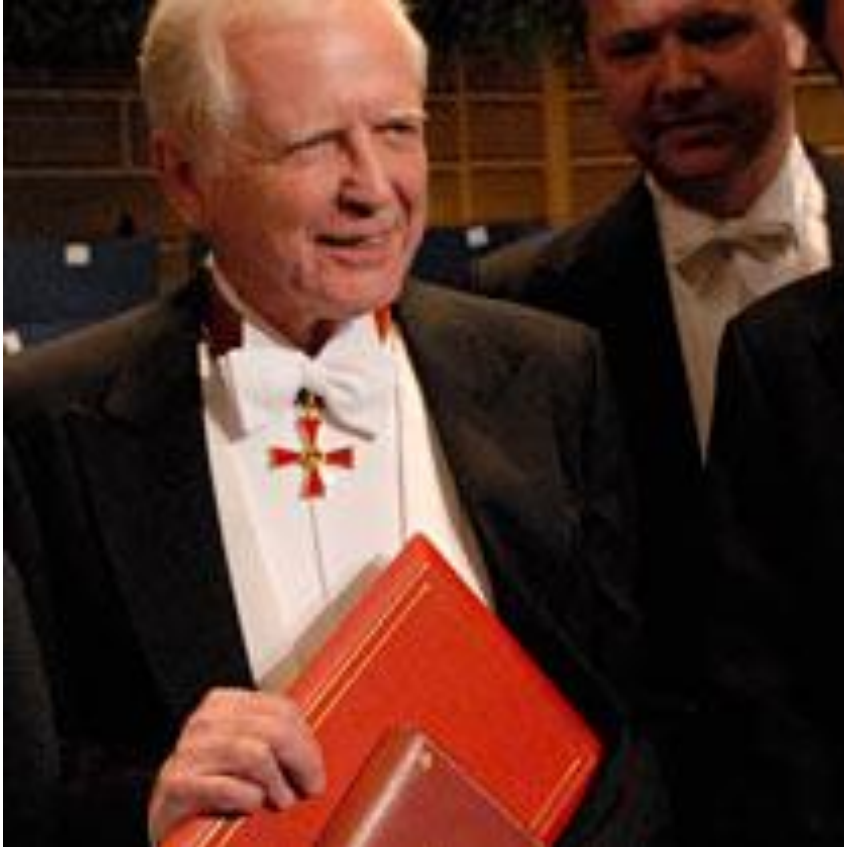


Combined external and internal radiation therapy



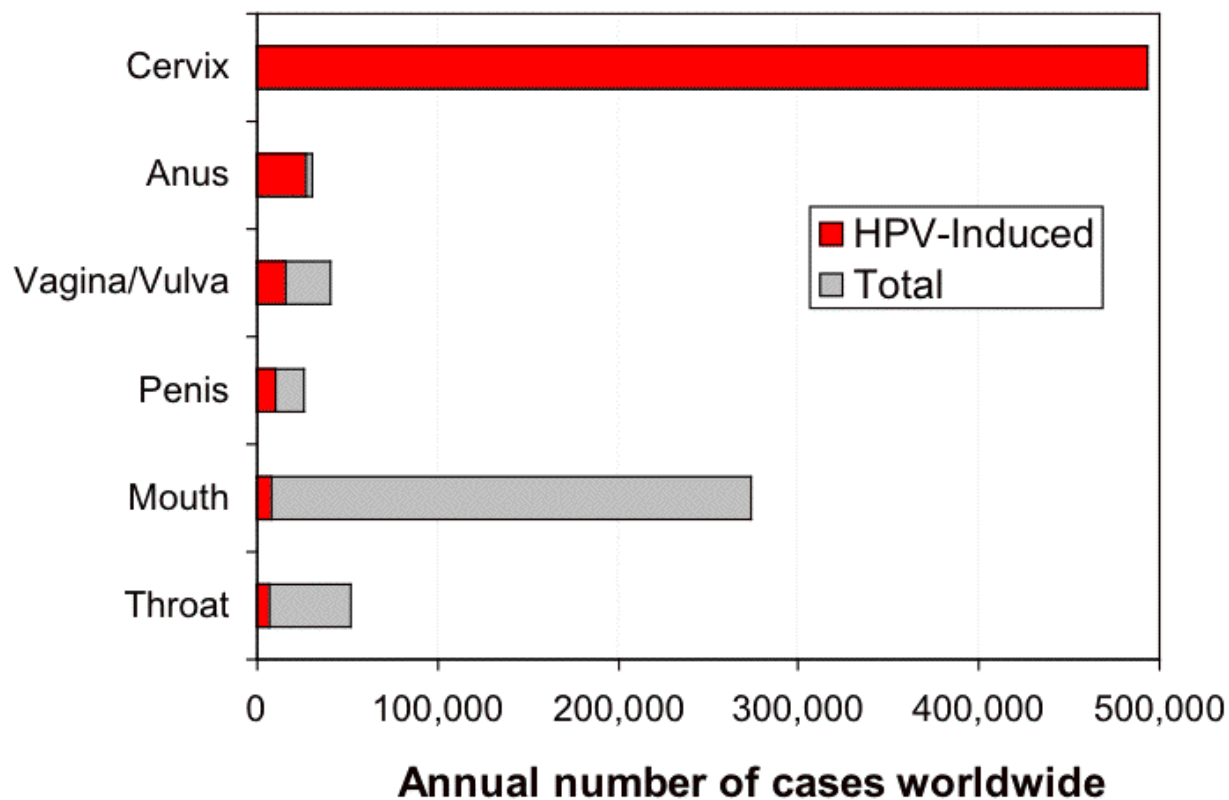
- External beam: daily treatment M-Friday for 4-6 weeks
- Internal radiation
 - Low-dose rate, requires hospitalization and immobilization for 24 hours
 - High-dose rate; can be given as outpatient

HPV and Harald zur Hausen

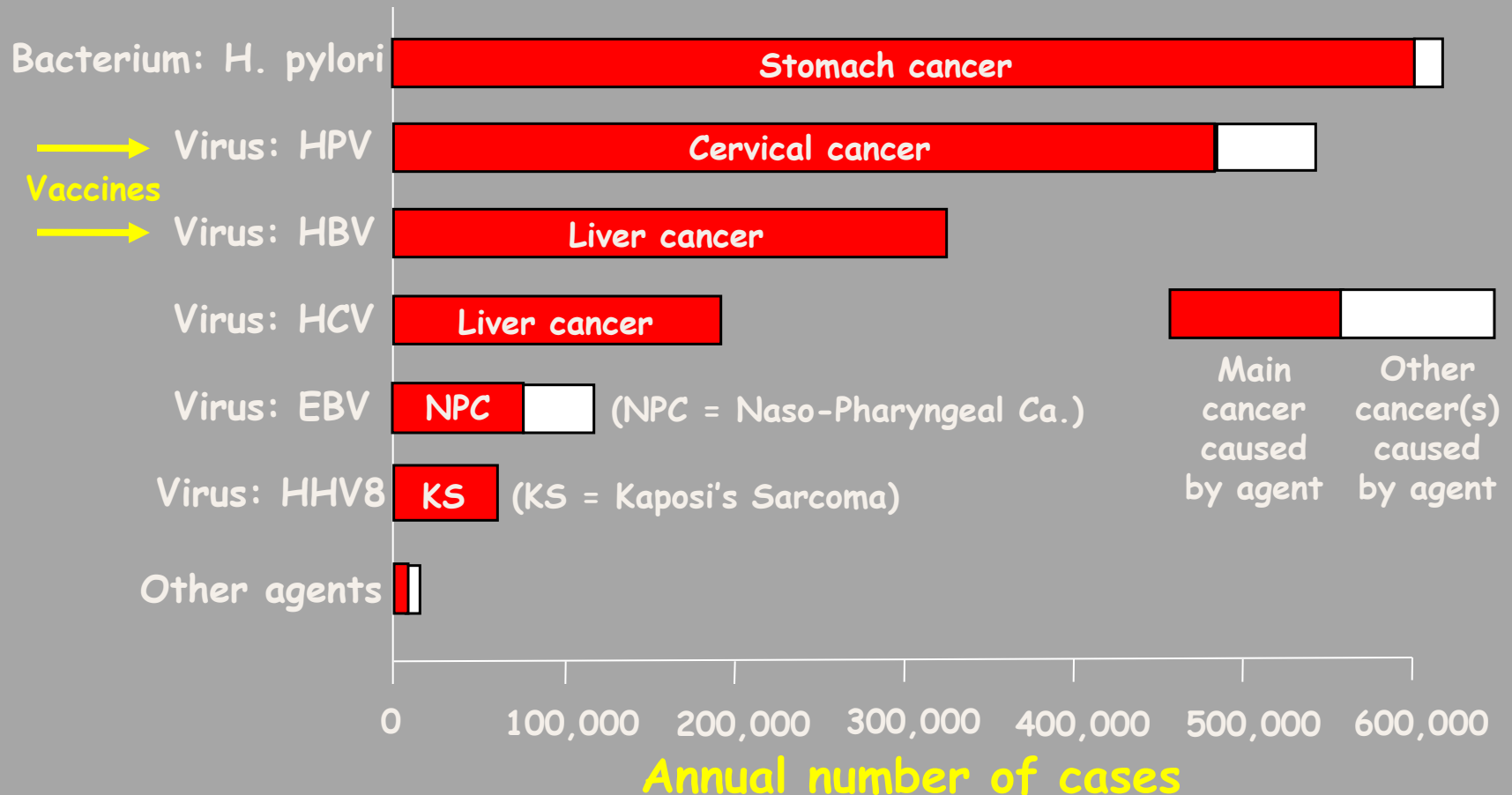


- 1976: Harold zur Hausen reported finding HPV in warts and cervical cancer
- Family of 120+ papillomaviruses which can infect skin or mucous membranes in mammals
- HPV 6,11: genital warts
- HPV 16,18: most carcinogenic
- E6 protein (p53)& E7 protein (Rb) block normal cellular control mechanisms

HPV-induced cancers



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

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)

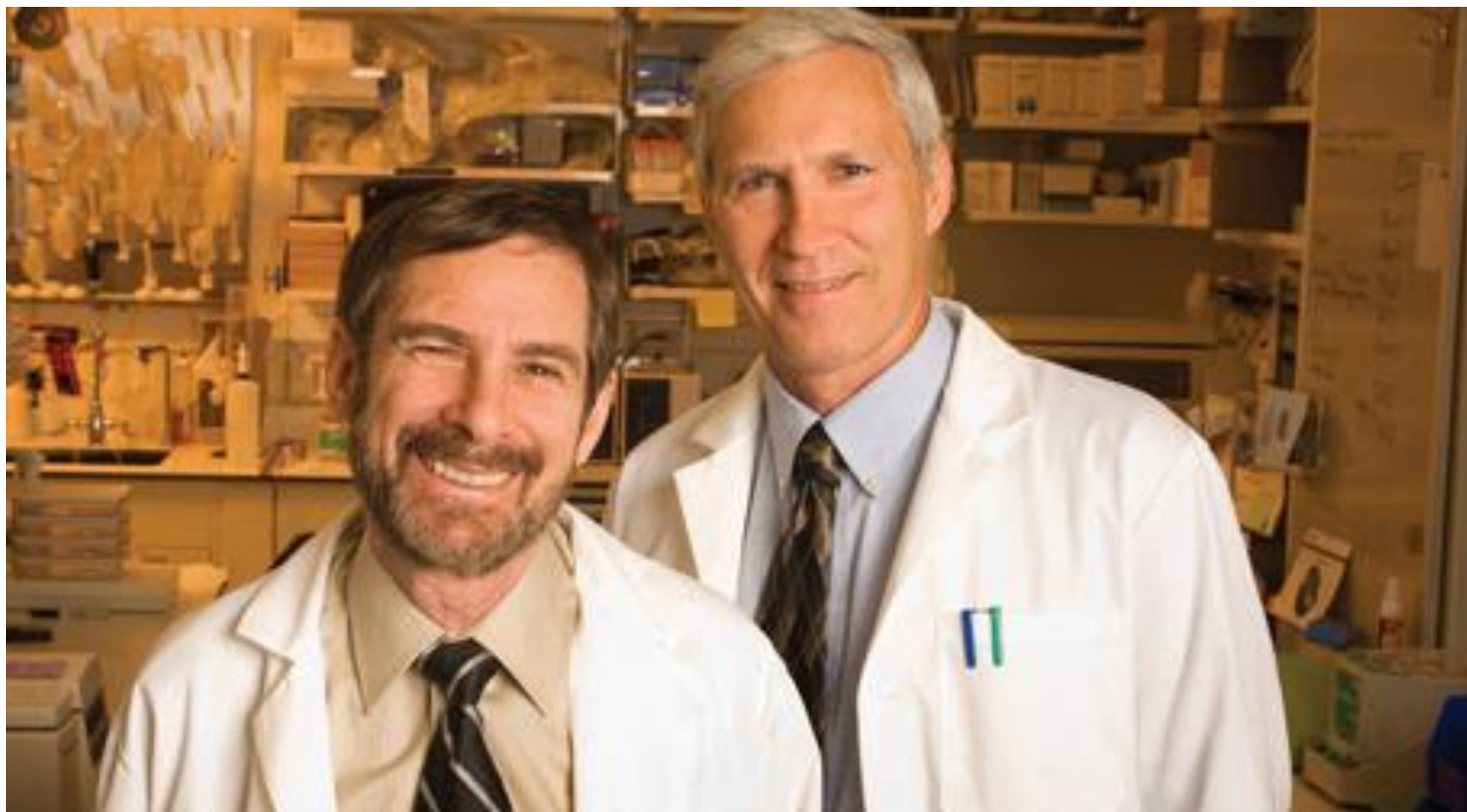
Reproductive risk factors:

- 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

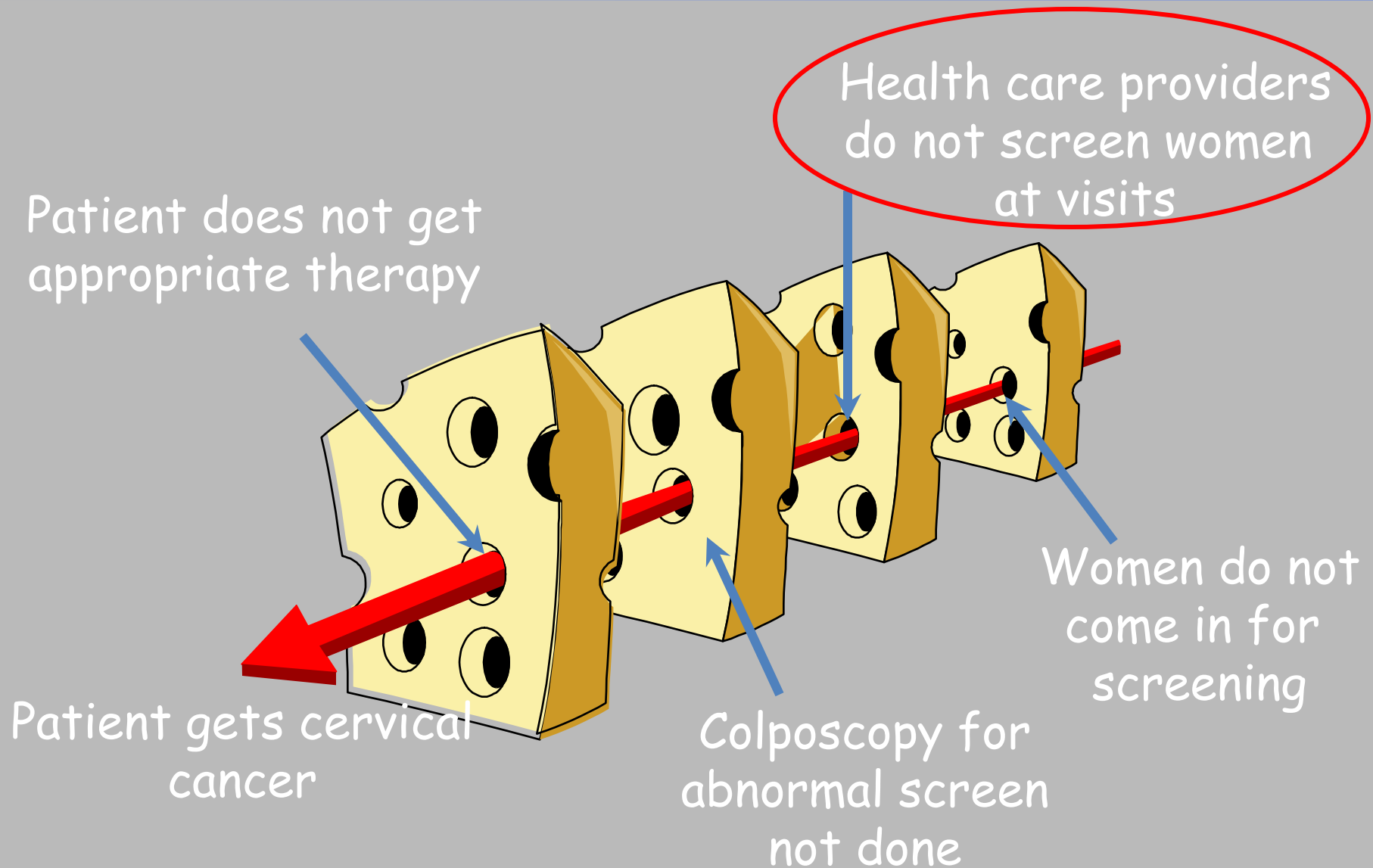
Challenges to HPV vaccination

- 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: 2nd 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



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

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CGH Contact Information

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

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