Cervical Cancer

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Why do I find cervical cancer incredibly interesting?

- Biology is fascinating
- Nothing short of a miracle to go from not knowing what caused it to a vaccine that can prevent 90% of cervical cancer in 22 years
- A public health challenge
- Has been a disease without a voice – societal issues

Published the first paper on HPV causing cervical cancer

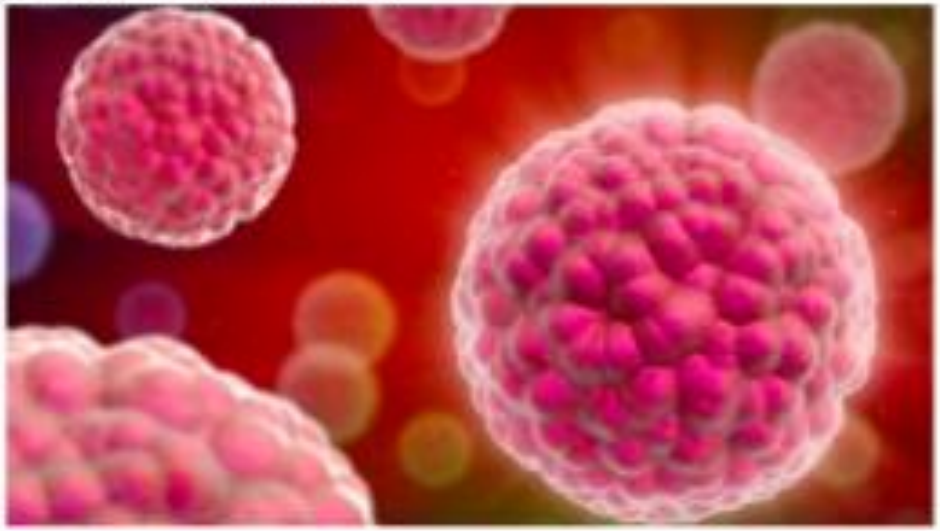
Discovered the proteins made by HPV which cause cancer in 1984

Won the Nobel prize in medicine in 2008

What is HPV?

HPV = Human Papillomavirus

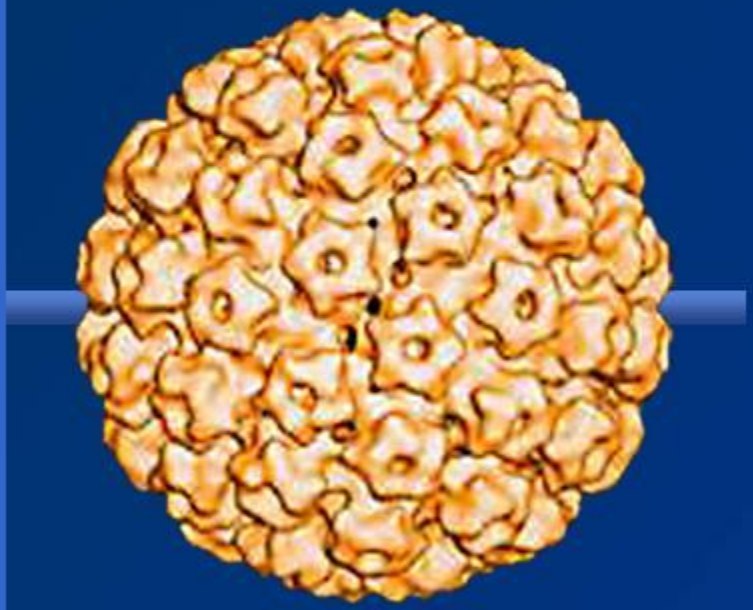
HPV is a very common virus; nearly 80 million people—about one in four—are currently infected in the United States.



Most HPV infections don't lead to cancer but certain types of HPV infection cause cancers. More than 100 varieties of human papillomavirus (HPV) exist.

HPV

Nonenveloped double-stranded DNA virus[1]



Reprinted from Hagensee ME, Olson NH, Bakers TS, Galloway DA. *J Virol.* 1994;68:4503–4505, by permission of the American Society for Microbiology and Dr. Michael Hagensee.

- >100 types identified[2]
- 30–40 anogenital[2,3]
  - 15–20 oncogenic*[,2,3] types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58[4]
    - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.[5]
  - Nononcogenic† types include: 6, 11, 40, 42, 43, 44, 54[4]
    - HPV 6 and 11 are most often associated with external anogenital warts.[3]

*High risk; †Low risk

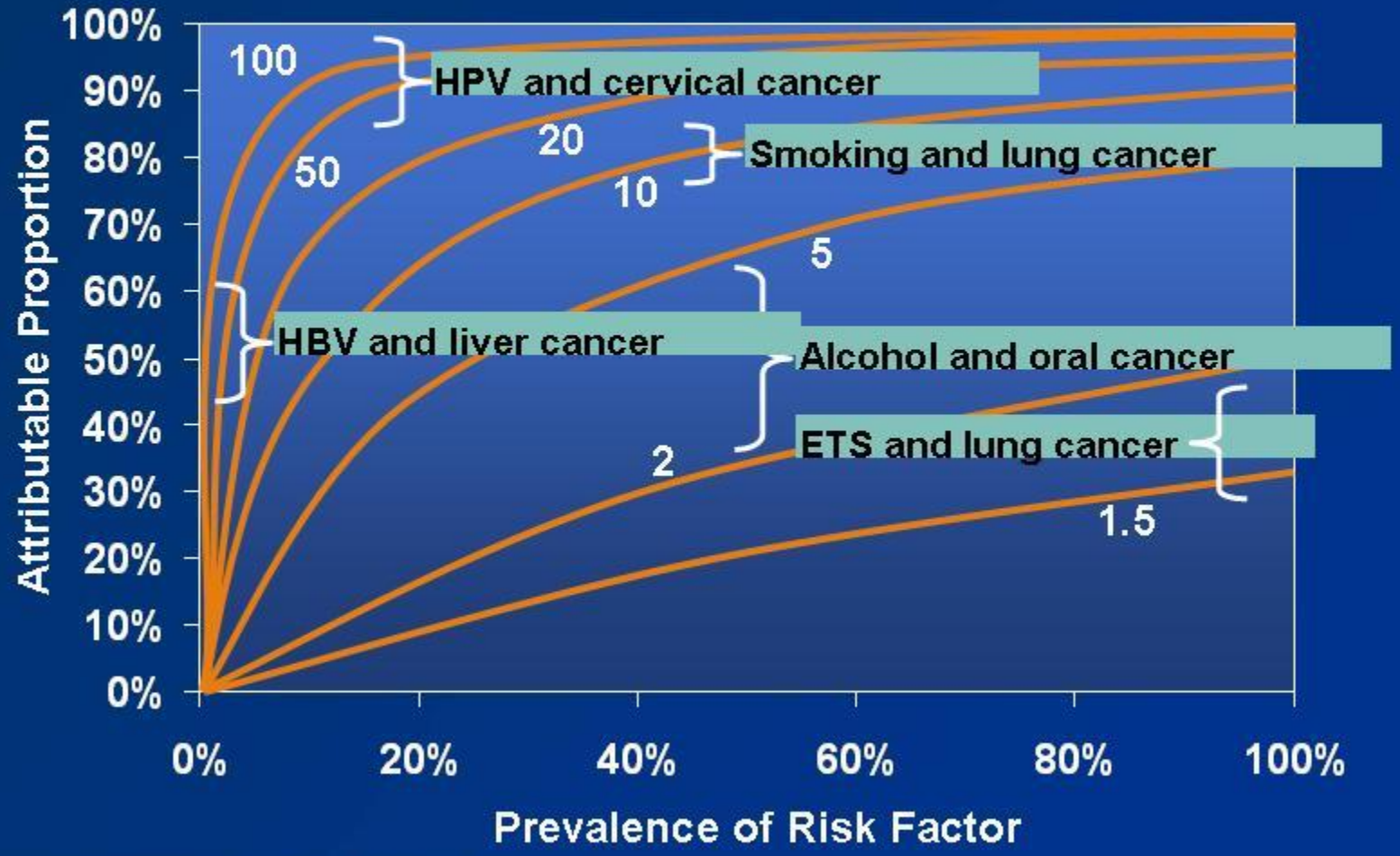
1. Howley PM. In: Fields BN, Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 2002:2197–2229. 2. Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, de Sanjosé S, et al. *N Engl J Med*. 2003;348:518–527. 5. Clifford GM, Smith JS, Aguado T, Franceschi S. *Br J Cancer*. 2003:89;101–105.

Oncogenic HPV Types Are a Necessary Cause of Cervical Cancer

- First ever identified necessary cause of cancer.[1]
- Persistent infection with oncogenic HPV types precedes the development of cervical cancer and is the most significant risk factor in its etiology.[1]
  - Peak incidence of HPV infection in the United States, 2000: 15–24 years of age[2]
  - US peak incidence of cervical cancer, 1998–2002: 35–44 years of age[3]
- An analysis of 932 specimens from women in 22 countries indicated that the prevalence of HPV DNA in cervical cancers worldwide was 99.7%.[4]

1. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. *J Clin Pathol*. 2002;55:244–265. 2. Weinstock H, Berman S, Cates W Jr. *Perspect Sex Reprod Health*. 2004;35:6–10. 3. Ries LAG, Eisner MP, Kosary CL, et al, eds. *SEER Cancer Statistics Review, 1975–2002*. National Cancer Institute. Bethesda, Md; 2005. 4. Walboomers JMM, Jacobs MV, Manos MM, et al. *J Pathol*. 1999;189:12–19.

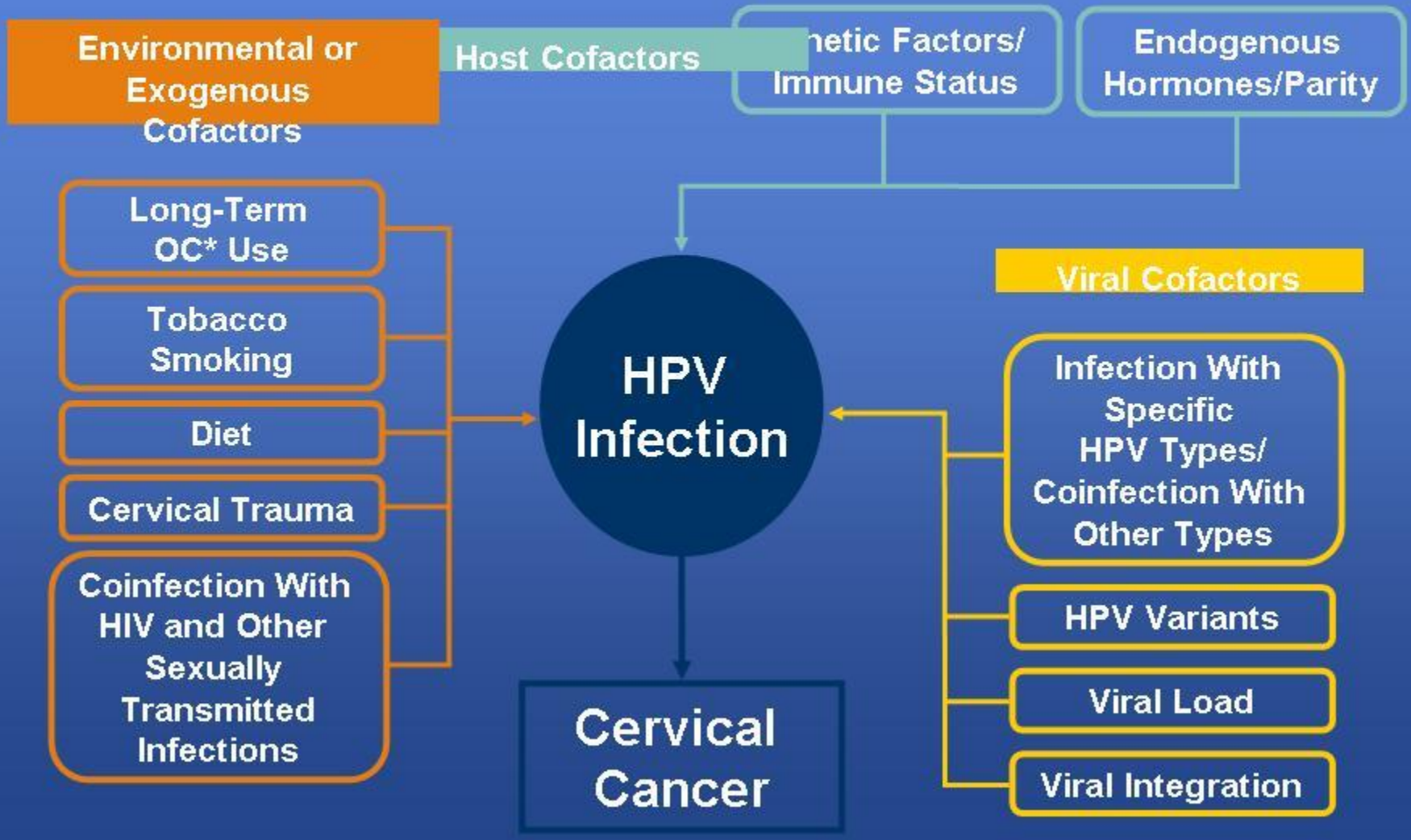
Projected Attributable Proportions of Prevention Targets in Cancer Control[1]



*ETS = Environmental tobacco smoke (passive smoking)

1. Reprinted from Franco EL, Harper DM. *Vaccine*, 2005;23:2388–2394, Copyright © 2005, with permission from Elsevier.

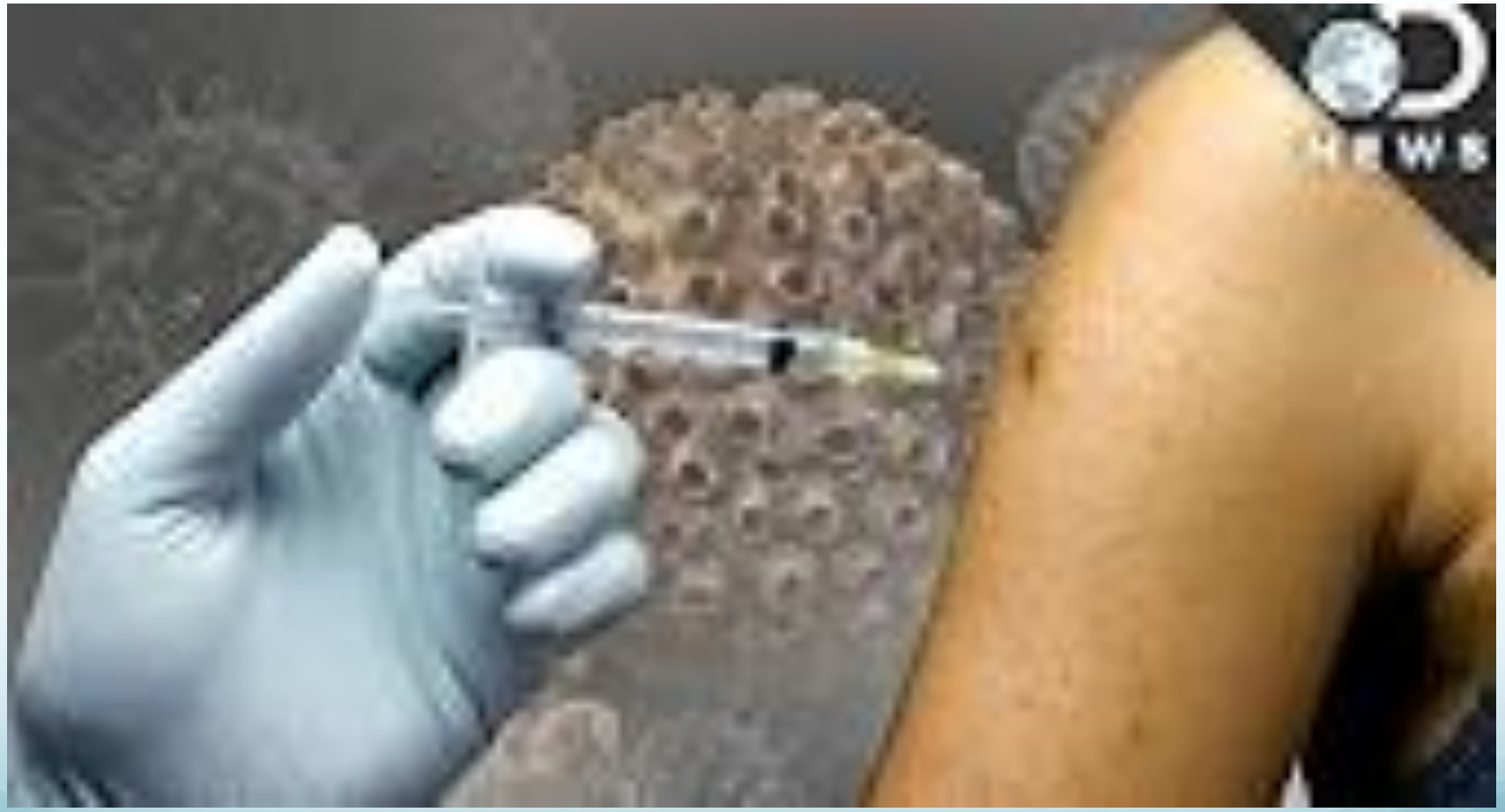
Established and Potential Cofactors Involved in HPV Carcinogenesis[1]



*OC = oral contraceptive

1. Castellsagué X, Muñoz N. *J Natl Cancer Inst Monogr*. 2003;31:20–28.

Ask about the HPV vaccine



HPV vaccines

	Bivalent (Cervarix)	Quadrivalent (Gardasil)	9-valent (Gardasil 9)
Manufacturer	GSK	Merck	Merck
HPV Types	16, 18	6,11,16,18	6,11,16,18,31,33,45,52,58
Recommended for	Girls ages 11-12 (can be started at 9) Females 13-26 who were not adequately vaccinated	• Females and males ages 11-12 (can start at age 9 years) • Females ages 13 through 26 and males ages 13 through 21 who were not adequately vaccinated previously • Males ages 22	• Females and males ages 11-12 (can start at age 9 years) • Females ages 13 through 26 and males ages 13 through 21 who were not adequately vaccinated previously • Males ages 22

HPV vaccine can safely be given to…

- ☒ Patients with minor acute illnesses, such as diarrhea or mild upper respiratory tract infections, with or without fever.
- ☒ Women who have had an unclear or abnormal Pap test, a positive HPV test, or genital warts. However, these patients should be advised that the vaccine may not have any therapeutic effect on existing Pap test abnormalities, HPV infection, or genital warts.
- ☒ Patients with immunocompromising conditions, including certain diseases or medications. However, the immune response to vaccination and effectiveness of the vaccine might be less than in people with a normally functioning immune system.
- ☒ Women who are breastfeeding.

Why is HPV vaccine important?

- Every year in the United States, 31,000 women and men are diagnosed with a cancer caused by HPV infection. Most of these cancers could be prevented by HPV vaccination.

- HPV vaccination prevents more than just cervical cancer. Vaccination can prevent uncomfortable testing and treatment even for cervical precancers. Each year in the U.S. more than 300,000 women endure invasive testing and treatment for lesions (changes in the cells) on the cervix that can develop into cancers. Testing and treatment for these "precancers" can have lasting effects.

- However cervical cancer only accounts for 1 in 3 cancers caused by HPV infection. While there is screening for cervical cancer, there is no routine screening for the other 20,000 cancers caused by HPV infections each year in the United States. Often these cancers—such as cancers of the back of the throat (oropharynx) and cancers of the anus/rectum—aren't detected until later stages when they are difficult to treat.

HPV VACCINE

- CDC now recommends 11 to 12 year olds get two doses of HPV vaccine—rather than the previously recommended three doses—to protect against cancers caused by HPV. The second dose should be given 6-12 months after the first dose.

HPV vaccines should not be given to...

- ☒ Patients with a history of allergies to any vaccine component. Quadrivalent vaccine (4vHPV) and nine-valent vaccine (9vHPV) are not recommended for people with immediate hypersensitivity to yeast. Bivalent vaccine (2vHPV) is not recommended for people with anaphylaxis caused by latex.
- ☒ Patients with moderate or severe acute illnesses. In these cases, patients should wait until the illness improves before getting vaccinated.
- ☒ Pregnant women. However, HPV vaccines have not been shown to cause any adverse pregnancy outcomes or adverse events for the mother or her developing fetus.

HPV Vaccine Effectiveness

- HPV vaccines work extremely well. HPV vaccine was first recommended in 2006 in the United States, and by 2010, quadrivalent type HPV infections in teen girls decreased by 56%, and decreases in prevalence were also observed in women in their early 20s. Research has also shown that fewer U.S. teens are getting genital warts since HPV vaccines have been in use. Also, decreases in vaccine-type prevalence, genital warts, and cervical dysplasia have been observed in other countries with HPV vaccination programs.

- There are no data to suggest HPV vaccines will treat existing diseases or conditions caused by HPV. However, people who already have HPV-associated diseases or conditions can still get protection from other HPV types covered by the vaccines.

- Cervical cancer screening is recommended for women beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women. Women who have received any HPV vaccine should still be screened for cervical cancer beginning at age 21 years, in accordance with currently published cervical cancer screening guidelines. There are no screening recommendations for other cancers caused by HPV.

Duration of vaccine protection

- Studies suggest that HPV vaccines offer long-lasting protection against HPV infection and therefore disease caused by HPV infection. Studies of the bivalent and quadrivalent vaccines have followed vaccinated individuals for around ten years, and so far have found no evidence of protection decreasing over time. Duration of protection provided by HPV vaccination will continue to be studied.

HPV Vaccine Dosing Schedules

- If the first dose of any HPV vaccine is given before the 15th birthday, vaccination should be completed according to a 2-dose schedule. In a 2-dose series, the second dose is recommended 6–12 months after the first dose (0, 6–12 month schedule).
- If the first dose of any HPV vaccine is given on or after the 15th birthday, vaccination should be completed according to a 3-dose schedule. In a 3-dose series, the second dose is recommended 1–2 months after the first dose, and the third dose is recommended 6 months after the first dose (0, 1–2, 6 month schedule).
- In a 2-dose schedule of HPV vaccine, the minimum interval is 5 months between the first and second dose. If the second dose is administered at a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose.
- In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose. If a vaccine dose is administered at a shorter interval, it should be re-administered after another minimum interval has been met since the most recent dose.

- There is no ACIP recommendation regarding additional 9-valent HPV vaccine doses for persons who have been adequately vaccinated with bivalent or quadrivalent HPV vaccine.
- HPV vaccine can safely be administered at the same visit as other vaccines recommended for adolescents at ages 11 or 12 years, such as tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine, quadrivalent meningococcal conjugate (MenACWY) vaccine, and influenza vaccine. Administering all indicated vaccines at a single visit at ages 11 or 12 years increases the likelihood that patients receive their vaccinations on schedule.

FDA Approves HPV Vaccine for Adults Over 26

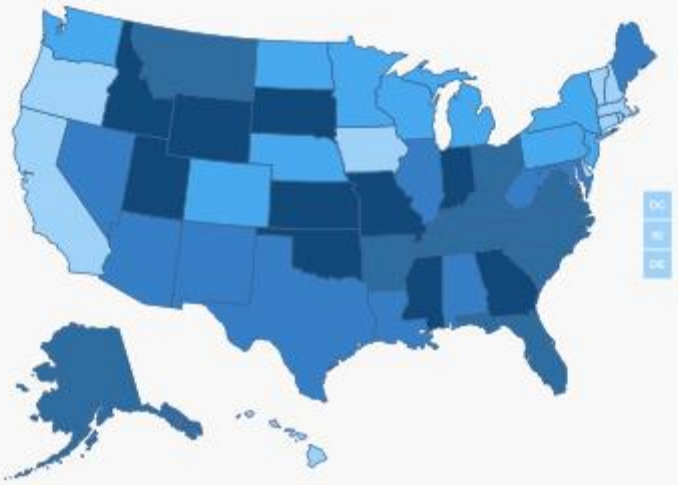
- On October 5, 2018 the FDA approved use of the Gardasil 9 HPV vaccine in males and females ages 27-45, expanding the previous indication that covered from ages 9-26. Gardasil 9 prevents infections with the “high-risk” HPV types most commonly found in a number of cancers worldwide, including cervical cancer. The vaccine also protects against “low-risk” HPV types associated with most cases of genital warts.

HPV vaccine after LEEP excision may decrease recurrent CIN

- • Re-analysis of PATRICIA and FUTURE studies have found vaccination after LEEP to be prevent 65-88% of HSIL/AIS recurrence (Joura 2012; Garland, 2016)

2016 ANIMATE

Percentage of females aged 13 to 17 years who received =3 doses of human papillomavirus (HPV) vaccine, either quadrivalent or bivalent

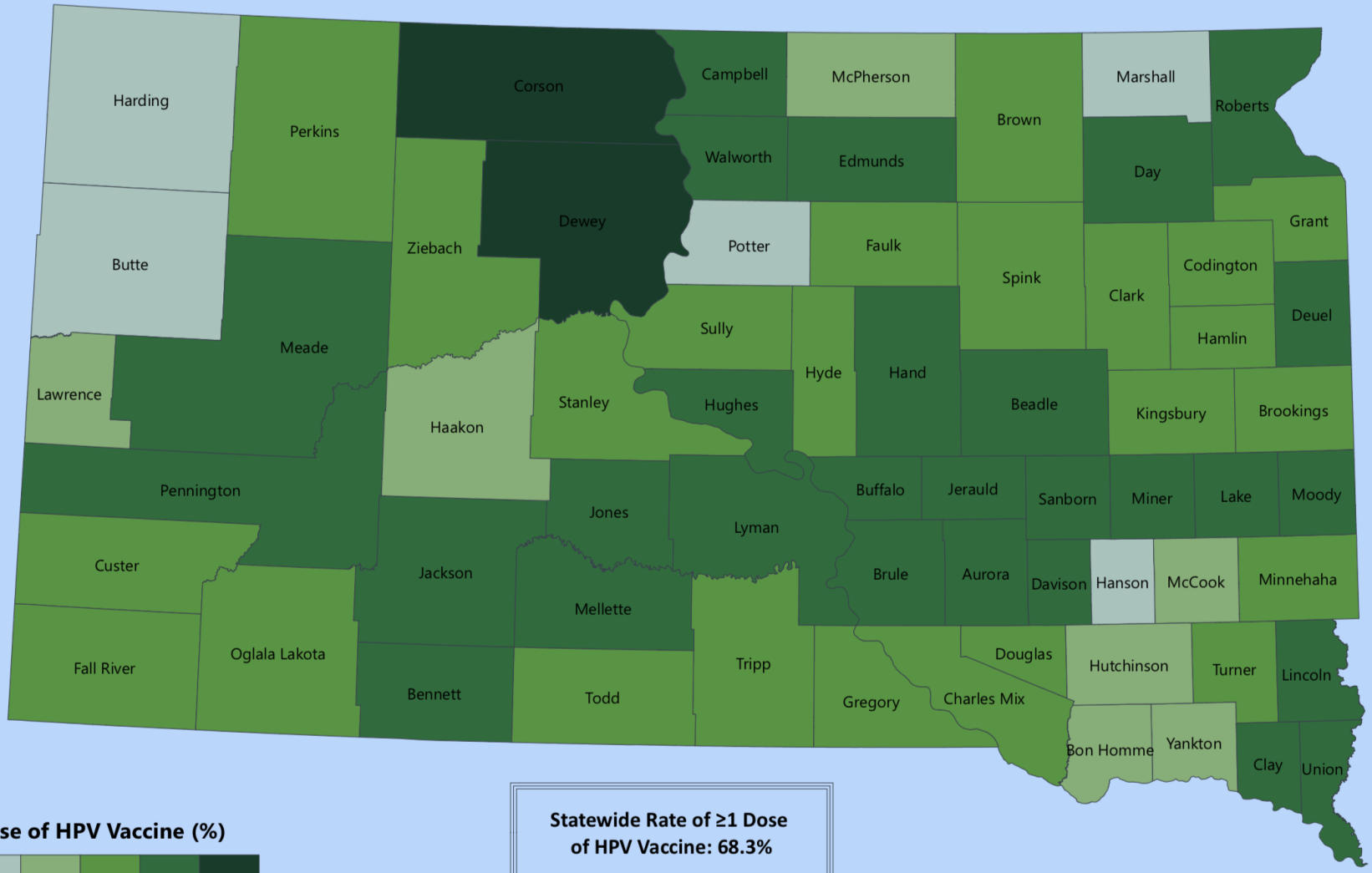


>= 48.4%	44.5% - 48.3%	39.2% - 44.4%
34.0% - 39.1%	<= 33.9%	

Source:

- CDC, National Immunization Survey

Rates of ≥1 Dose of HPV Vaccine Among Adolescents Ages 13-17 by County, South Dakota, August 2019



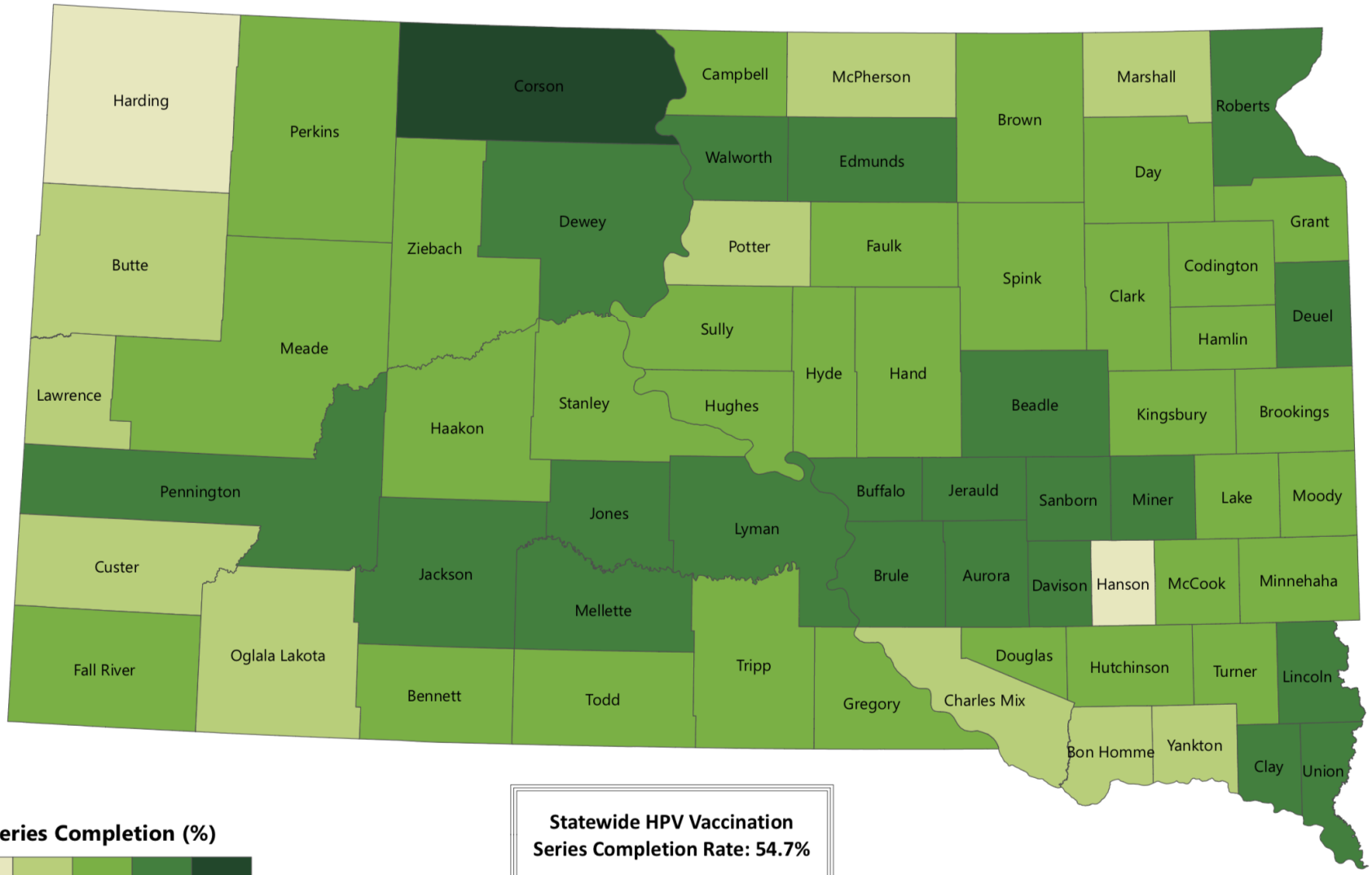
≥1 Dose of HPV Vaccine (%)

24-40 | 41-55 | 56-70 | 71-85 | 86-100

Statewide Rate of ≥1 Dose of HPV Vaccine: 68.3%

Data from the South Dakota Immunization Information System as of August 31, 2019

HPV Vaccination Series Completion* Rates Among Adolescents Ages 13-17 by County, South Dakota, August 2019



HPV Series Completion (%)

0-20 | 21-40 | 41-60 | 61-80 | 81-100

Statewide HPV Vaccination Series Completion Rate: 54.7%

Data from the South Dakota Immunization Information System as of August 31, 2019

*A completed HPV vaccination series includes 2 doses separated by at least 5 months (minus 4 days) for adolescents who initiated the series before their 15th birthday and 3 doses for all others

SCREENING

CHANGES ALL THE TIME

USPSTF RECOMMENDATIONS

Women 21 to 65 (Pap Smear) or 30-65 (in combo with HPV testing)

- recommends screening for cervical cancer in women age 21 to 65 years with cytology (Pap smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years.

Women younger than 30 years, HPV testing

- recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years.

Women younger than 21

- recommends against screening for cervical cancer in women younger than age 21 years.

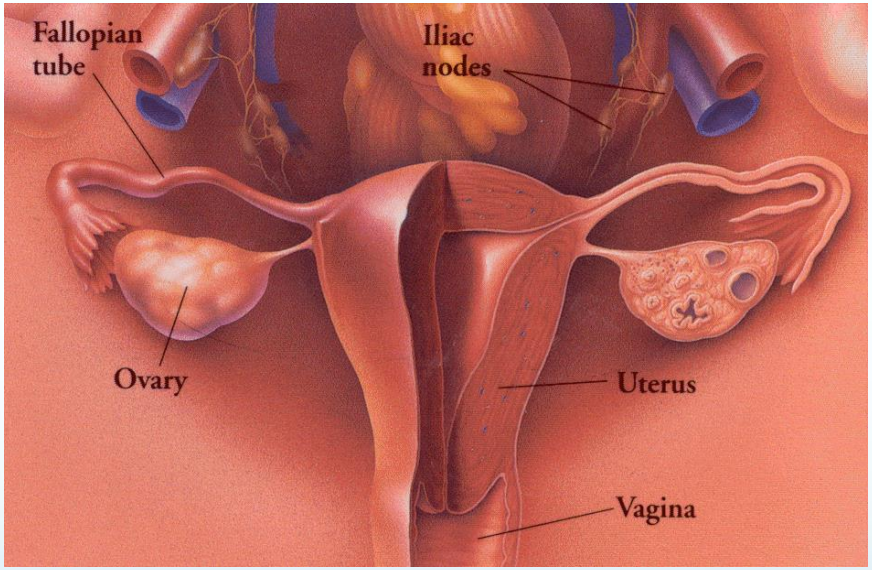
Women Older than 65, who have had adequate prior screening

- recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.

Women who have had a hysterectomy

- recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer

Cervical Cancer



Epidemiology - “who gets it”

- World-wide – 2nd most common cause of cancer death in women
- prevalent in developing countries
  - lack of screening
- Advent of Pap smear - decrease in invasive cervical cancer, but increase in diagnosing preinvasive disease.

All Women Count!

BREAST & CERVICAL CANCER
EARLY DETECTION PROGRAM

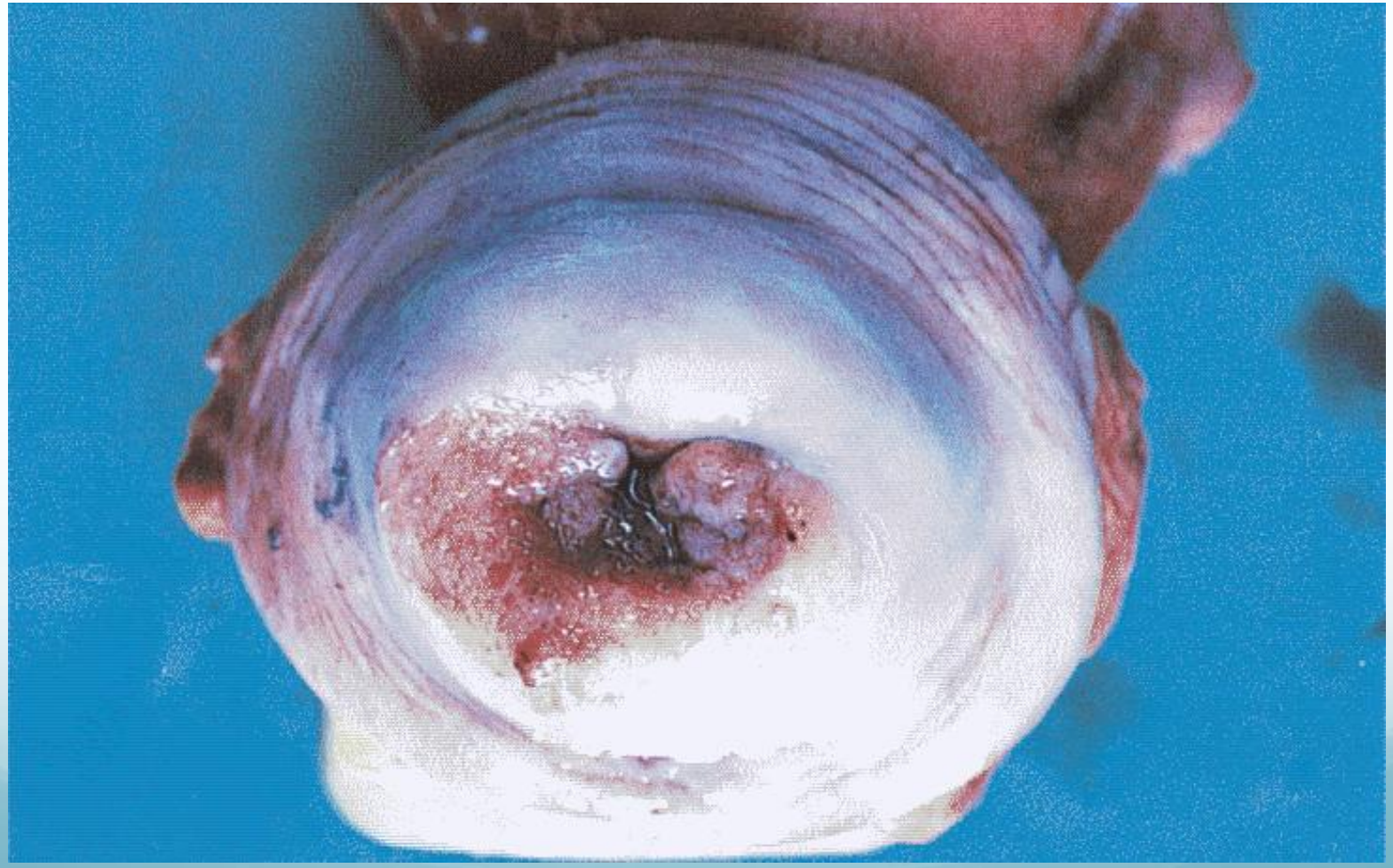
Clinical Features of invasive cervical carcinoma

- 80% present with abnormal vaginal bleeding
  - intermittent, postcoital
- foul vaginal discharge
- pain - associated with advanced disease
- leg edema - advanced disease

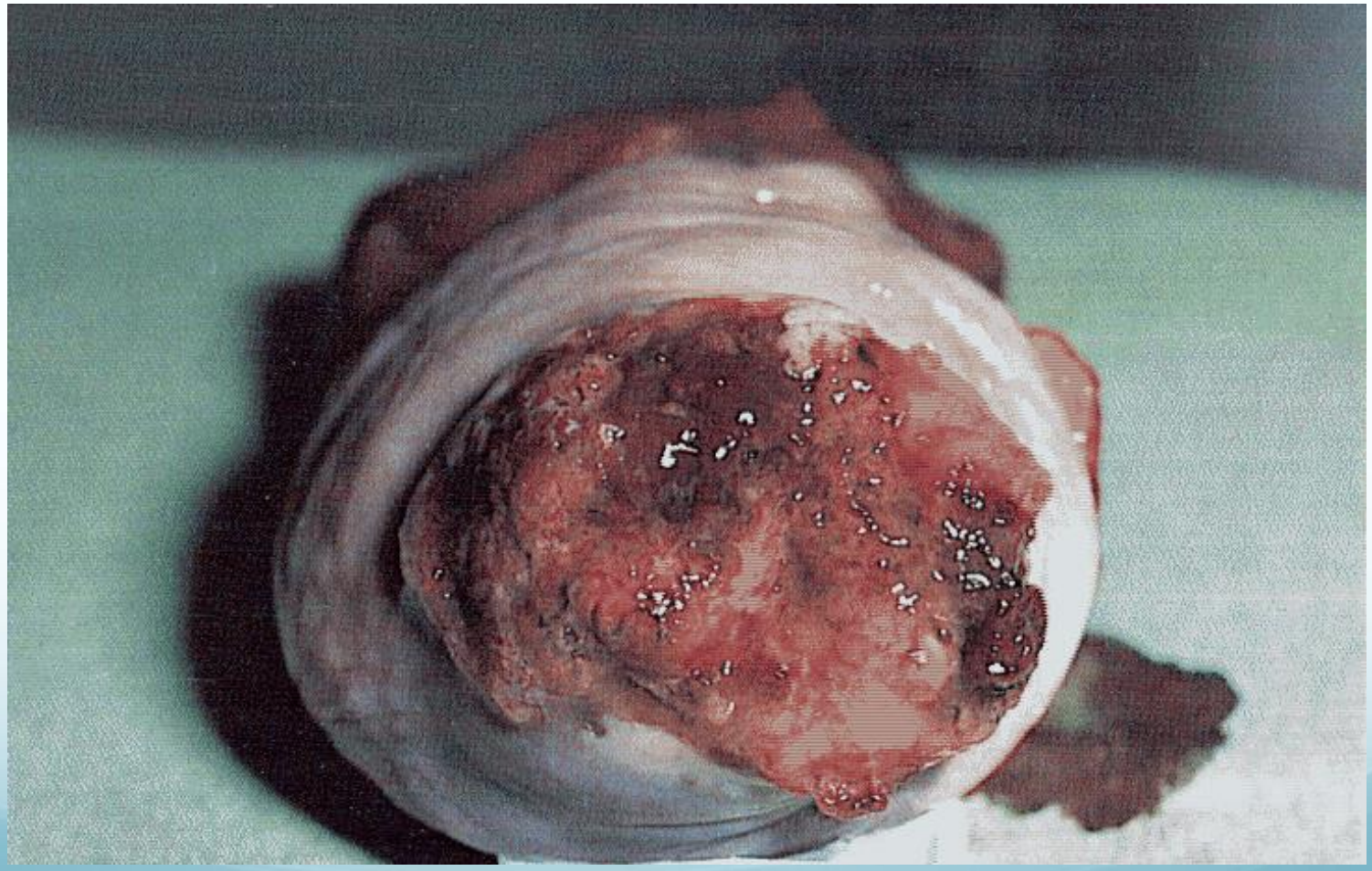
Physical signs

- Anemia
- cachexia - indicative of advanced disease
- tumor may be exophytic or endophytic, may extend to vagina or pelvis
- Distinct odor

Endophytic lesion



Exophytic lesion



Treatment

- Surgery - for early stage cancer
  - good for young women
    - may preserve the ovaries (transposition)
  - Conization (Ia1) in women who wish to preserve fertility
  - extrafascial hysterectomy (Ia1)
  - radical hysterectomy
- Radiation and chemotherapy for poor surgical candidates and advanced disease (IB2 or greater)

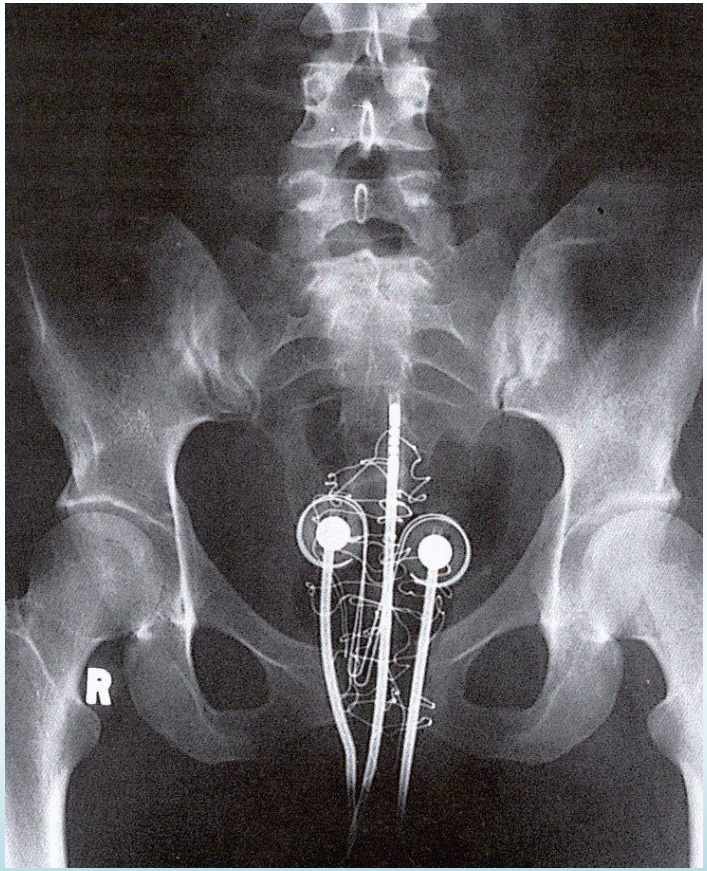
Treatment

- Stage Ia1
  - conization if they wish to preserve fertility
  - extrafascial hysterectomy
    - vaginal
    - abdominal
  - may leave ovaries

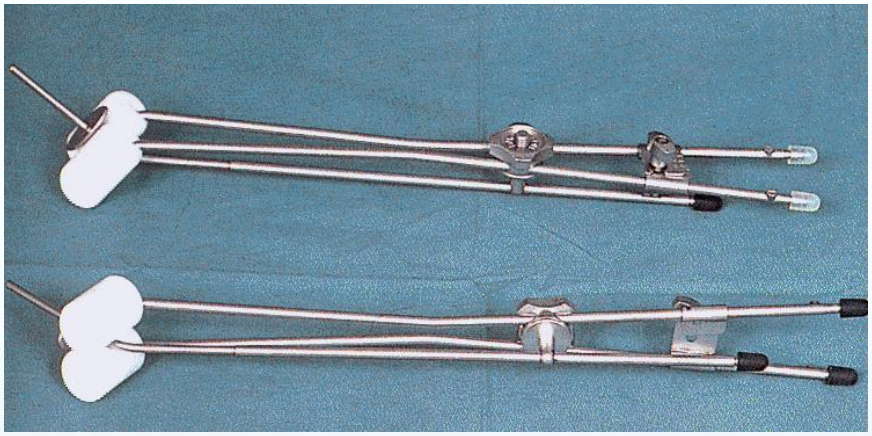
Treatment

- Stage IB1
  - radical hysterectomy
  - pelvic and para-aortic lymphadenectomy
  - adjuvant radiation if positive nodes/margins
- Stage IB2-IVa
  - concurrent chemo/radiation
  - cisplatin 40 mg/m2 weekly during radiation
- Stage IVb
  - individualization, probably will need radiation to control vaginal bleeding
  - chemotherapy is not curative for metastatic disease

X-ray confirming brachytherapy



Brachytherapy devices



Recurrent cervical cancer

- Difficult to diagnose
- pelvic recurrence
  - offer radiation if previously treated with surgery
  - offer surgery (exenteration) if previously treated with radiation
- Recurrence outside of pelvis
  - chemotherapy - not curative, poor response
  - Immunotherapy is promising

Exenteration

- Anterior
  - remove vagina, uterus, bladder
  - perform urinary conduit
- Posterior
  - remove vagina, uterus, rectum
  - perform colostomy
- Total
  - remove vagina, uterus, rectum, bladder
  - perform urostomy, colostomy

All Women Count! Program:

- http://getscreened.sd.gov/count/

SD Cancer Coalition:

- http://www.cancersd.com/