Female Genital System Part I: Vulva, Vagina, and Cervix



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I've included some questions throughout lecture to encourage active learning! Some of the relevant pages from First Aid are found at the end of these notes.

Goals for today

By the end of today's lecture you should be able to:

- Identify common non-neoplastic diseases of the vulva and vagina based on clinical presentation and pathology
- 2. Recognize and describe the commonly occurring cancers of the vulva, vagina and cervix
- 3. Explain the role of human papilloma virus in cancers of the cervix
- 4. Explain the relationship of cervical dysplasia to cervical cancer
- 5. Describe the role of screening prevention of cervical cancer

Outline of lecture

- 1. Diseases of the Vulva
 - Developmental
 - Inflammatory
 - Infectious
 - Neoplastic
- 2. Diseases of the Vagina
 - Developmental
 - Infectious
 - Neoplastic
- 3. Diseases of the Cervix
 - Infectious
 - Non-neoplastic lesions
 - Neoplasms
 - Carcinoma
 - Dysplasia
- 4. Screening/Pap smears

Diseases of the Vulva

- Developmental
- Inflammatory Diseases
- Infectious
 - STD's, see Dr. Hick's lecture 6/9/11
 - -HPV
- Neoplastic diseases

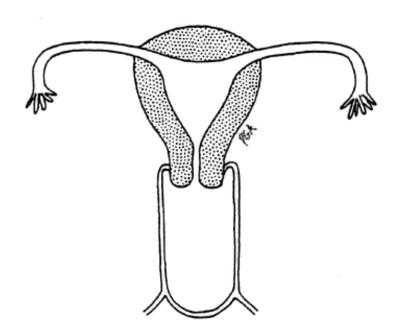
Developmental

- Abnormalities of sexual differentiation

 Beyond scope of lecture, see specialized textbooks for details
- <u>Middlesex: A Novel</u> by Jeffrey Eugenides

Developmental

Imperforate Hymen



Imperforate hymenReproduced with perr Secretory and Adolescent Gynecology, (Fourth Edition MR, Goldstein, DP (Eds), Lippincott William 1998. Copyright © 1998 Lippincott William by perforation. Bartho

Bartholin's glands: normal secretory glands located posteriolaterally on the vulva. Quite large cysts and abscesses can form due to inflammatory plugging of the glands.

Bartholin's cyst

RX: open or remove gland entirely

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Diseases of the Vulva

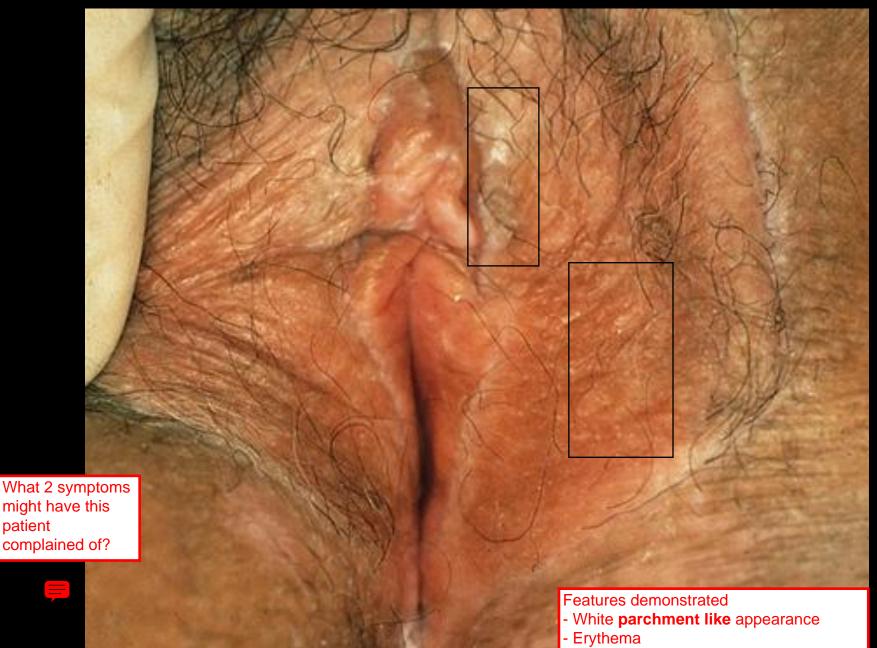
- Developmental
- Inflammatory Diseases
- Infectious
 - STD's, covered elsewhere
 - -HPV
- Neoplastic diseases

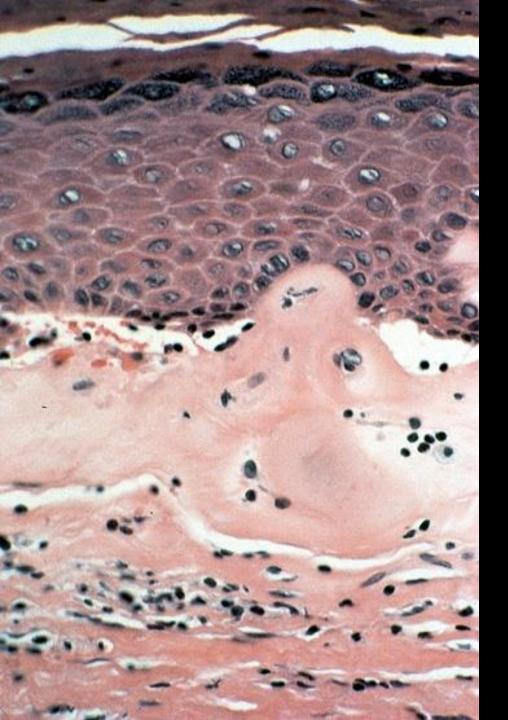
Inflammatory Diseases

- Lichen Sclerosus
 - Clinical
 - Postmenopausal
 - Itching, pain Chief complaint
 - White "parchment paper" like appearance
 - Elevated risk of squamous cell carcinoma
 - 10-15% develop carcinoma on follow-up
 - Treated with topical steroids

Pathophysiology -- unknown

Lichen Sclerosus





Lichen Sclerosus

No rete pegs

Rete pegs: normal extensions of epithelium into dermis

Homogenous, hyalinized layer of collagen

Scant inflammation

Diseases of the Vulva

- Non-neoplastic
- Inflammatory Diseases
- Infectious
 - STD's, covered elsewhere
 - -HPV
- Neoplastic diseases

Vulva-HPV

- Condyloma acuminata = Anogenital warts
 Condyloma lata (syphillis induced vulvar skin lesions)
 Condyloma lata is unrelated (syphillis)
- Usually transmitted sexually
 - Local control problem in immunosuppressed patients (HIV)
 - Can develop dysplasia as in cervix
 - See also lecture from Dr. Cardones 6/22 for additional information on HPV

Can overgrow anogenital region in patients with

depressed cell

HIGH RISK HPV

TYPES ONLY

mediated immunity.

(16, 18)

Features demonstrated

- Verrucous (warty) appearance
- Multifocality

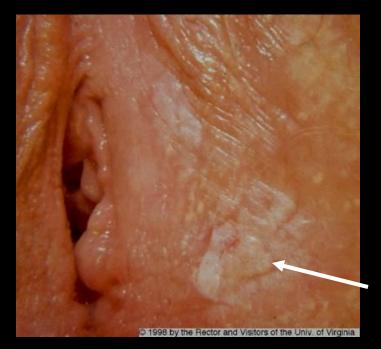
Condyloma Acuminata

Diseases of the Vulva

- Non-neoplastic
- Inflammatory Diseases
- Infectious
 - STD's, covered elsewhere
 - -HPV
- Neoplastic diseases

Neoplasms of the Vulva

- Vulvar Intraepithelial Neoplasia (VIN)
 Aka "Dysplasia"
- Squamous cell carcinoma
- Paget's Disease of the vulva



Based on lecture contents thus far, what is your differential diagnosis for an itchy or painful white area on the vulva?

VIN

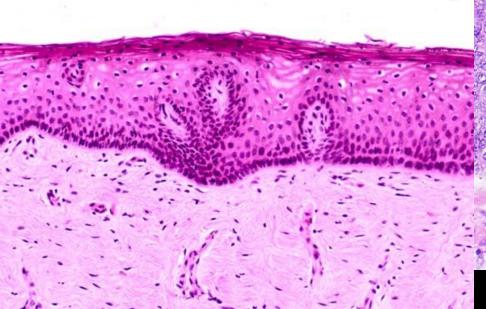
- Dysplasia, aka Bowen's disease
- Graded as VIN-1, 2, or 3 (mild, moderate, severe dysplasia /carcinoma in situ)
 - Oncogenic HPV 16, 18 in high grade
 VIN DO NOT USUALLY CAUSE CONDYLOMA ACUMIINATA!
- Presents with itching or pain
 - 50% asymptomatic
- White patch (leukoplakia), sometimes red or even hyperpigmented
- May remain non-invasive for many years.
- Treatment: Destroy lesion (surgery, laser, chemicals)

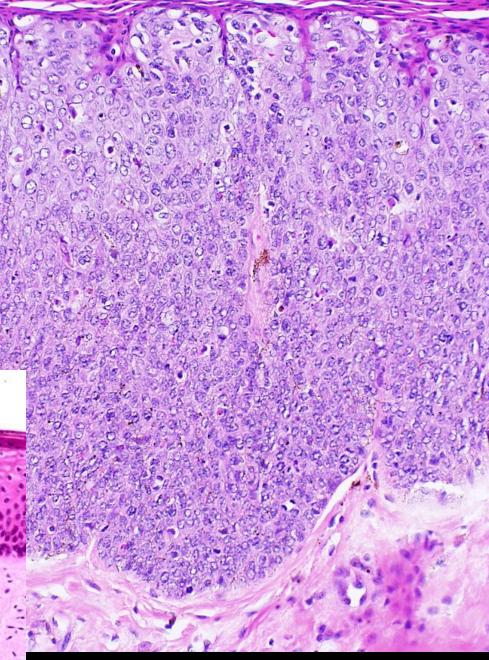


VIN-3

- Features demonstrated
- Full thickness dysplasia
- Koilocytic atypia (indicates HPV infection)
- Lack of basement membrane invasion

Normal





Both images are same magnification

Squamous Cell Carcinoma

- 90% of vulvar cancers
 - 3% genital tract cancers
 - 4000 cases/year, 800 deaths in US
- Risk factors Memorize
 - VIN
 - Lichen sclerosus
 - Smoking
 - History of cervical cancer

Cervical cancer development is promoted by the same high risk HPV strains (16,18) that cause vulvar neoplasia.

Take home1. SCC accounts for the majority of vulvar cancer.2.Vulvar cancer is a relatively uncommon cause of female genitourinary cancer.

Nobody should die of this disease --it should in theory be caught early in everyone considering the accessibility of the vulva for examination and excision.

Squamous Cell Carcinoma

- Spreads first to local superfical groin nodes
- Risk of spread related to size and depth of invasion (i.e. stage)
- Low stage disease cured by local resection only.

Squamous Cell Carcinoma

Features of vulvar SCC demonstrated by this radical vulvectomy specimen:

- Erythematous, raised process

PATHOLOGY CEPT

4

5 6 7 8 9 10 10 11 12

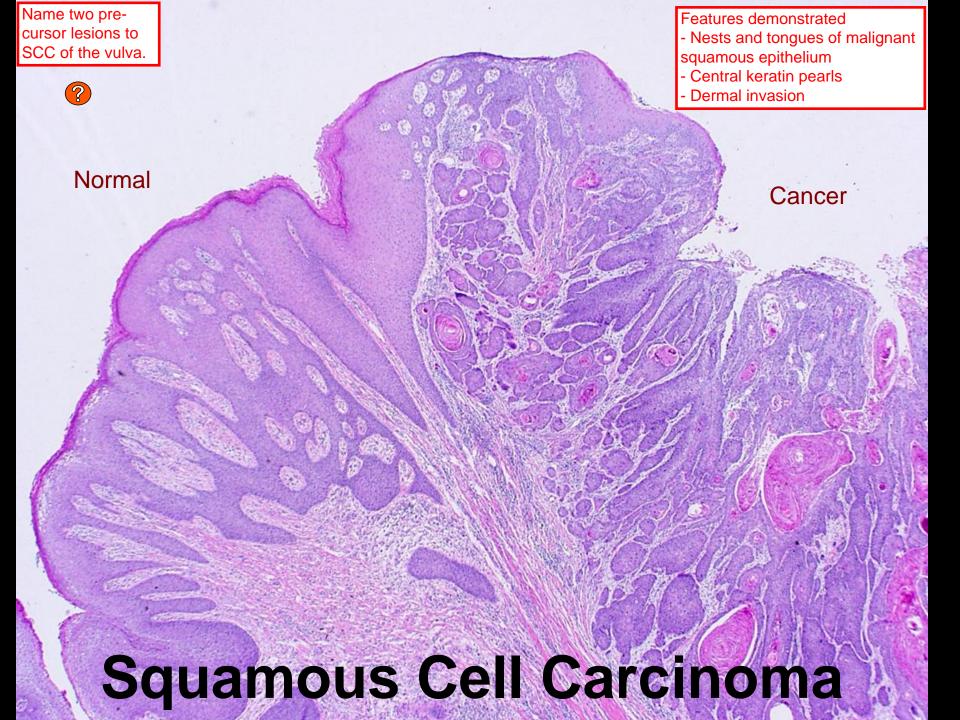
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ETTUC 1

- Large, deeply invasive process

Why is asking your patient about his or her sexual history pertinent to this lesion?



Paget's Disease

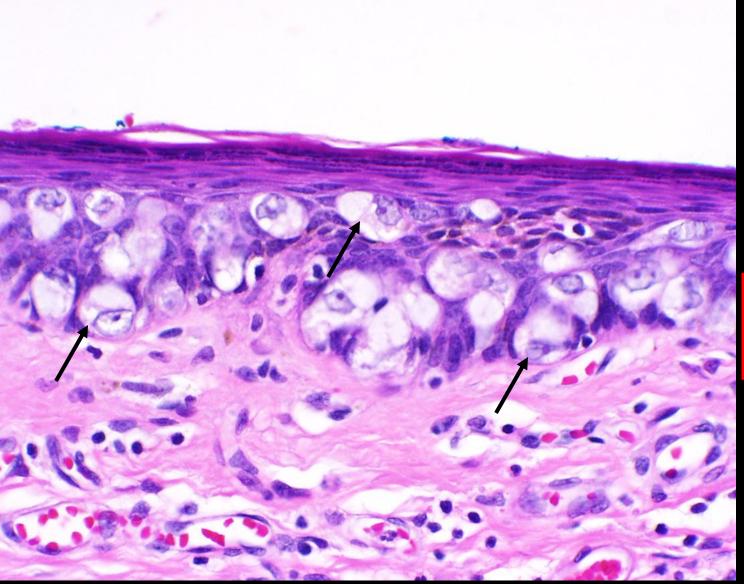
- Aka "Extramammary" Paget's disease
- Unique form of intraepithelial adenocarcinoma
- Red, itchy lesions often mistaken for inflammation clinically

Differential diagnosis (4)

- Lichen sclerosis (has red parts)
- Contact dermatitis
- Vulvar intraepithelial neoplasia (can be red or white)
- Vulvar squamous cell carcinoma

Paget's Disease

- Most (>95%) patients have no invasive component (all tumor cells limited to epidermis)
- Prognosis excellent unless invasive cancer found
- Treatment mostly symptomatic
- Note that although histologically indistiguishable from Paget's disease of the nipple, this has a very different biology



Paget's Disease of the Vulva

Features - Mucinous halos surround nuclei - Small clusters of neoplastic cells confined to epidermis

Large cells with pale cytoplasm (mucin containing), located within the epidermis

At this point in the lecture it was established that Rex Bentley does not rule the world.

Diseases of the Vagina

- Relatively rare site of significant disease
 - Congenital anomalies
 - Infections
 - Cancers

Congenital Anomalies

- Septate or double vagina
- Gartner's duct cyst (mesonephric duct remnants)
 - Located laterally (sidewalls)

Septate or double vagina:

Fusion of the paramesonephric (mullerian) ducts is required to form the normal uterus and upper vagina (recall that the lower vagina is derived from the urogenital sinus). Failure of these paired ducts to fuse can lead to a septate or double vagina. This abnormality is almost always accompanied by a double uterus. Risk factors include DES exposure, genetic syndromes, teratogens. **Gartner's duct cyst:**

Common lesions found on the lateral walls of the vagina. Typically fluid filled cysts that are 1-2 cm in size and localized submocosally. Important to keep these in mind because they are benign but on a differential that includes neoplastic and infectious processes.

- Bacterial vaginosis
 - Most common cause of vaginal discharge,
 - 15-20% prevalence
 - Complex change in vaginal flora with loss of lactobacilli, overgrowth of anaerobes, and increase in pH
 - "Fishy" odor
 - Tx clindamycin or metronidazole

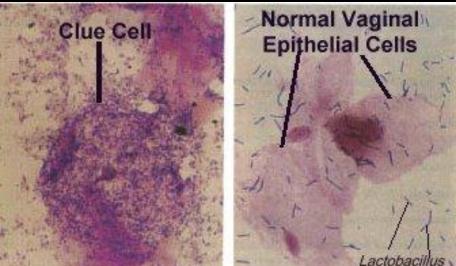
Treatment is indicated by the patient being bothered by odor/ discharge.

Bacterial vaginosis-diagnosis

- (1) Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls,
- (2) Vaginal pH greater than 4.5,
- (3) Positive whiff-amine test, defined as the presence of a fishy odor when 10 percent potassium hydroxide (KOH) is added to a sample of vaginal discharge,
- (4) "Clue cells" on saline wet mount.

"Clue cell"

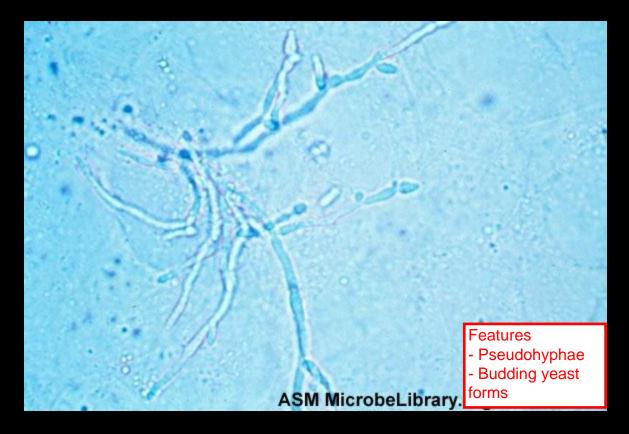
Vaginal epithelial cell coated with adherent bacteria



www.kcom.edu

- Candidiasis
 - Also common, 75% lifetime incidence
 - Itching, "cottage cheese" discharge
 - Associated with recent antibiotic use
 - Treated with oral or intravaginal antifungal agents, many available over the counter. Fluconazole

- Candidiasis
 - Dx: KOH prep, wet mount



Extremely common, but does not cause a lot of *systemic* pathology.

Vaginal Infections

- Bacterial vaginosis
- Candidiasis
- Trichomonas vaginalis
 - Sexually transmitted protozoan
 - 3-5 million cases/year in U.S.
 - Itching, pain, discharge
 - Motile-identified on wet prep!
 - Tx, Metronidazole or tinidazole—partner also should be treated
- Other STD's covered by Dr. Hicks

Trichomonas--diagnosis



Trichomonas vaginalis High power microscopy revealing Trichomonas vaginalis w WET MOUNT flagella. Courtesy of Jack D Sobel,

Motile protozoa

http://www.youtube.com/watch?v=XVNJQZLJRJw

Check this video out and you will never forget Trichomonas is motile.

What drug would you administer to treat this patient's vaginitis?



Vaginal Cancer

- Very uncommon 0.6 per 100,000 women yearly
 - Most common primary tumor squamous cell carcinoma associated with HPV 16,18
 - Secondary spread from adjacent sites more common (gyn tract, colon, bladder)

if you see cancer n the vagina, begin searching for a primary neoplasm elsewhere.

Vaginal Cancer

- Sarcoma botryoides (embryonal rhabdomyosarcoma)
- Occurs in young children (<5 years)
- Rare but important to recognize—can be cured!

Locally invasive, can cause death by penetrating into the peritoneal cavity or obstructing the ureters leading to ARF.

Features demonstrated

- Frequently project out of vagina
- Polypoid, rounded, bulky
- Grapelike clusters (botyroides = grapelike)



Vaginal Cancer

Clear cell carcinoma of vagina

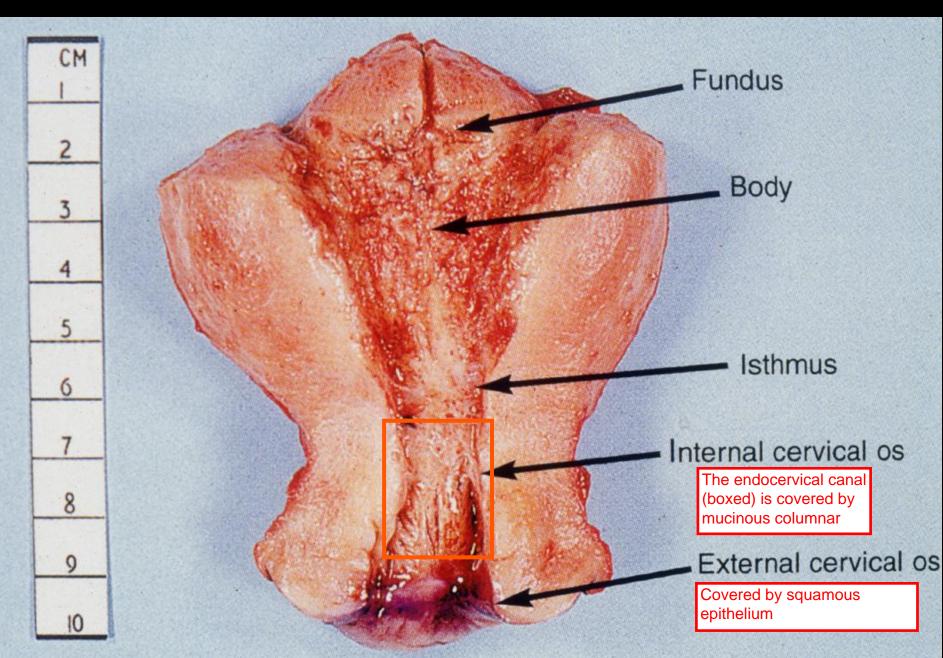
 Rare tumor almost exclusively seen in young women whose mothers took DES (diethylstilbestrol, a synthetic estrogen)

 Important because it established principle of trans-generational teratogenicity for drugs

This cancer is not high yield for the wards, but the fact that it demonstrates the principal of trans-generational teratogencitiy makes it board worthy. I suggest you check out some histologic images of the neoplasm online or on page 1016 in Robbins. http://www.webpathology.com/image.asp?n=17&Case=543



Uterus



Pathology of the Uterus

- Cervix (today)
- Endometrium (gyn part 2)
- Myometrium (gyn part 2)

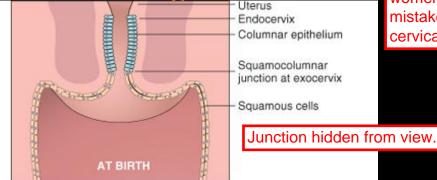


- Infectious
 - STDs
 - Any vaginitis will also involve cervix
- Non-neoplastic lesions
- Neoplasms
 - Dysplasia
 - Cancer

Cervix

- Infectious
- Non-neoplastic lesions
 - Ectropion
 - Squamous metaplasia
 - Nabothian Cysts
 - Endocervical polyp
- Neoplasms
 - Dysplasia
 - Cancer

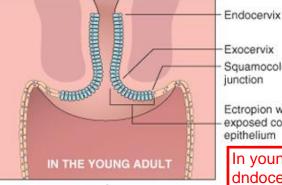
Squamocolumnar junction moves with age



Ectroprion is a completely normal finding in younger women. Often mistaken for cervical neoplasia.

Ectropion: glandular epithelium

Probably a younger women, hopefully they did not think this was cancer.



MANDONDAN

IN THE ADULT

Exocervix Squamocolumnar junction

Ectropion with exposed columnar epithelium

In younger women, the dndocervical epithelium often folds out onto exposed cervix. It may appear red and and inflamed. This is an ectropion.

Exocervix with "restored" squamocolumnar junction at original site

"Transformation zone" with regrowth of squamous epithelium

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The harsh exposures of the exocervix cause squamous metaplasia of any exposed columnar epithelium as women age. Thus, ectropion is not MASS. GENEF normally found in older postmenopausal women.

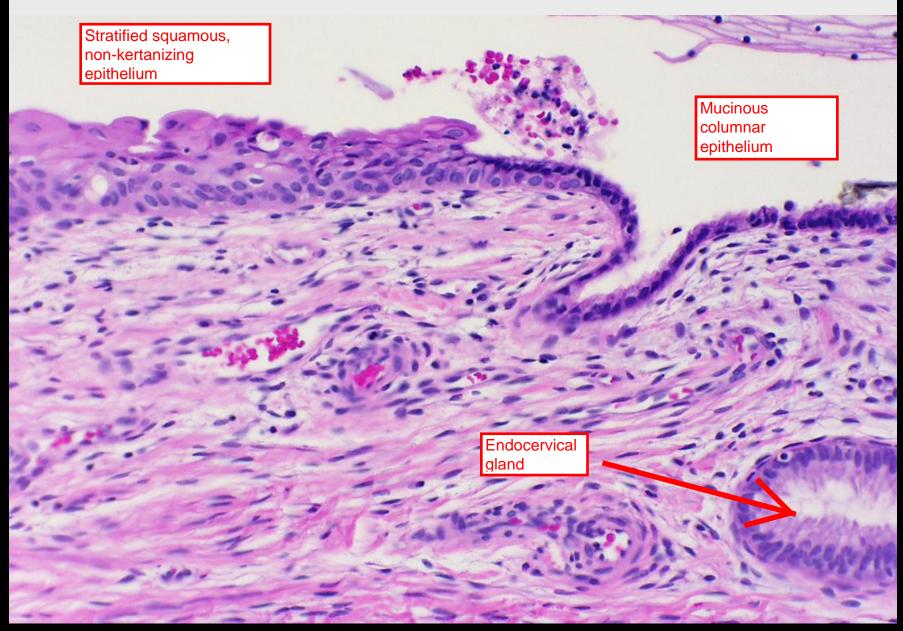
Postmenopausal



Squamous Metaplasia

- Process by which endocervical mucinous columnar epithelium changes to squamous epithelium
- Completely normal, no neoplastic potential by itself, but...
- "Transformation Zone" (entire region that has undergone squamous metaplasia) is site of cervical dysplasias and cancers.

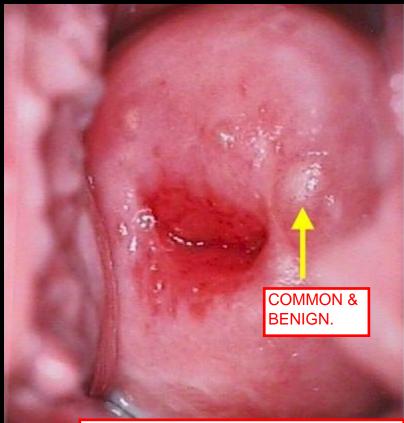
Early Squamous Metaplasia



Mature Squamous Metaplasia

Squamous epithelium has grown over endocervical glands

Nabothian cysts



Red appearing epithellium is columnar Pink appearing epithelium is squamous Border region is transformation zone Squamous metaplasia grows over endocervical glands

Mucin gets trapped in glands, leading to cystic dilation—
"Nabothian cyst" Can be very large

• Extremely common, of no clinical significance

Endometrial gland duct blocked off by metaplastic squamous epithelium. Secretions back up in the papillary dermis resulting in the formation of a large cyst.

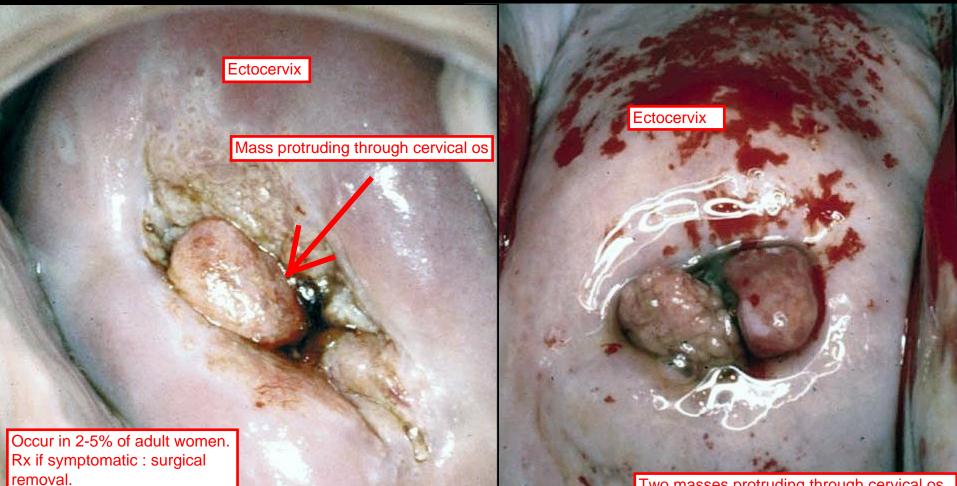
Nabothian cysts

Endocervical Polyp

 Present as mass lesions or with bleeding, completely benign



Endocervical Polyp



Two masses protruding through cervical os.



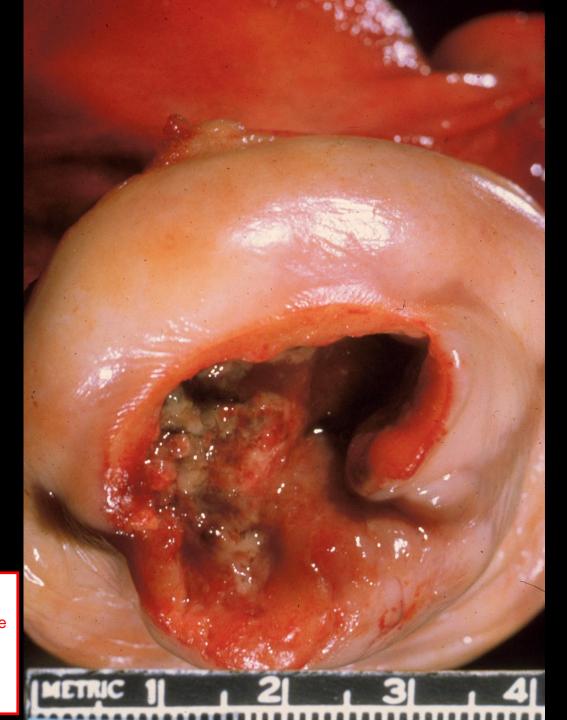
- Infectious
- Non-neoplastic lesions
- Neoplasms
 - Dysplasia
 - Cancer

Cervical Cancer

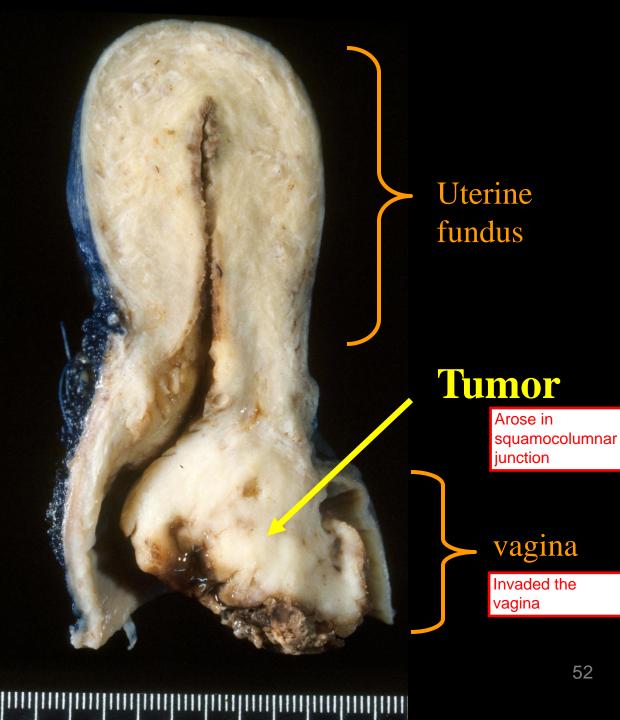
- 11,070 new U.S. cases in 2008 (estimated)
- 3,870 deaths
- Mean age 47
- Risk factors
 - Number of sexual partners
 - Male partners who have multiple previous partners
 - Early onset of sexual activity
 - History STD's
 - Genital HPV lesions
 - Smoking
 - Immunosuppression
 - No Pap smear screening

Cervical Cancer

Features demonstrated - Highly infitlrative (note erosion of the cervical os) - Hemorrhagic



Cervical Cancer



Cervical Cancer

Most patients with high stage cervical carcinoma die due to local extension into the urinary tract. Obstruction of the ureters can cause post-renal azotemia and predispose patients to pyelonephritis/ urosepsis. Pouch of douglas is filled with neoplasm.

Rectum

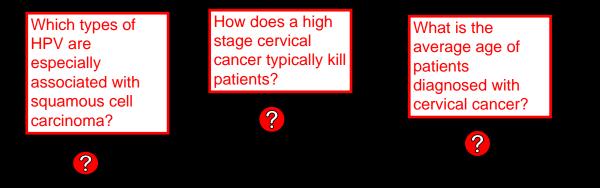
Bladder

Tumor 🦟

Tumor has invaded posteriorly into the rectum and anteriorly into the bladder. Vagina

Cervical Carcinoma

- 80-95% squamous cell carcinoma
- Remainder adenocarcinoma
- All contain HPV DNA



Squamous Cell Carcinoma

Cervical Cancer Staging

Stage 1: Limited to cervix •90% 5 yr survival Stage 2: Beyond cx but not

to pelvic wall or lower 1/3rd vagina

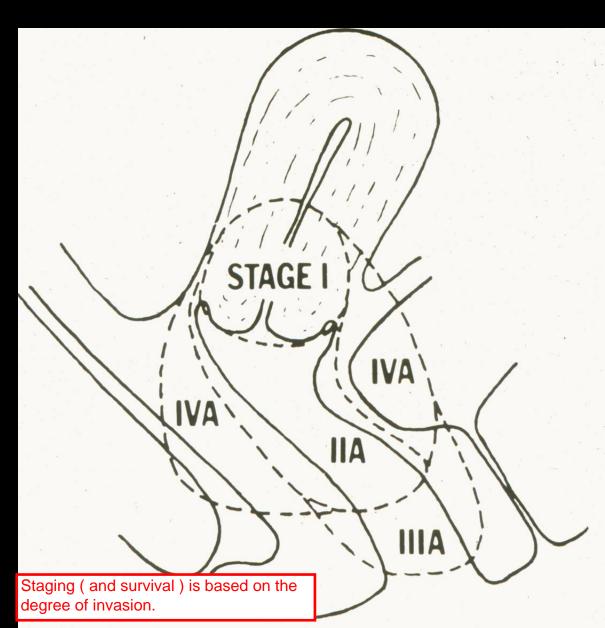
•82% 5 yr survival

Stage 3: To pelvic wall or lower 1/3rd vagina

•35% 5 yr survival

Stage 4: To mucosa of bladder or rectum, or beyond pelvis

•10% 5 yr survival



Cervical Cancer--Treatment

--Surgery for stage 1

--Chemoradiation for stage 2-4

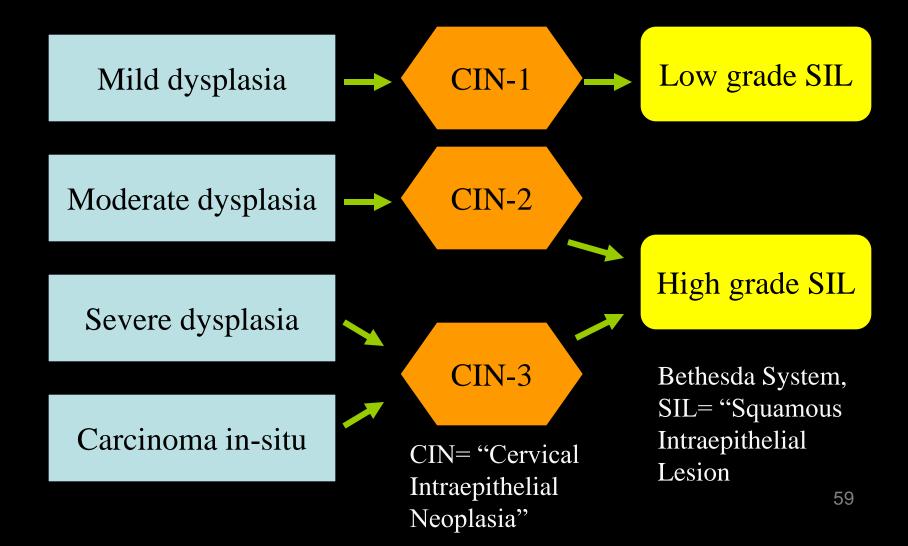
Cervical Dysplasia

Four Key Concepts!

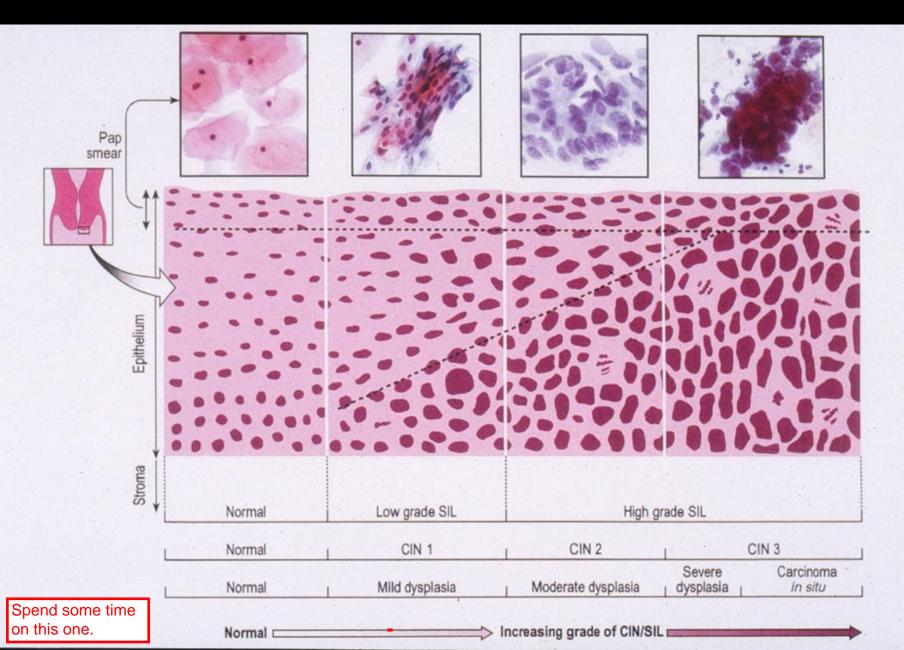
- **1. Caused by HPV infection**
- 2. Precursor to most if not all cervical cancers
- 3. Long interval to progression (up to 20 years or more)
- 4. Most will spontaneously regress

Cervical Dysplasia

Translating classification systems



Dysplasia

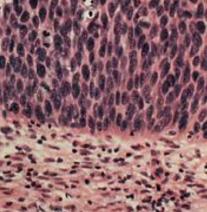


Features of dysplasia - Nuclear enlargemnt - Hyperchomasia - Variation in nuclear size and shape - Koilocytic atypia (if

HPV-induced)

Cervical Dysplasia

full thickness >1/2 dysplastic ~1/3 dysplastic dysplasia



Normal

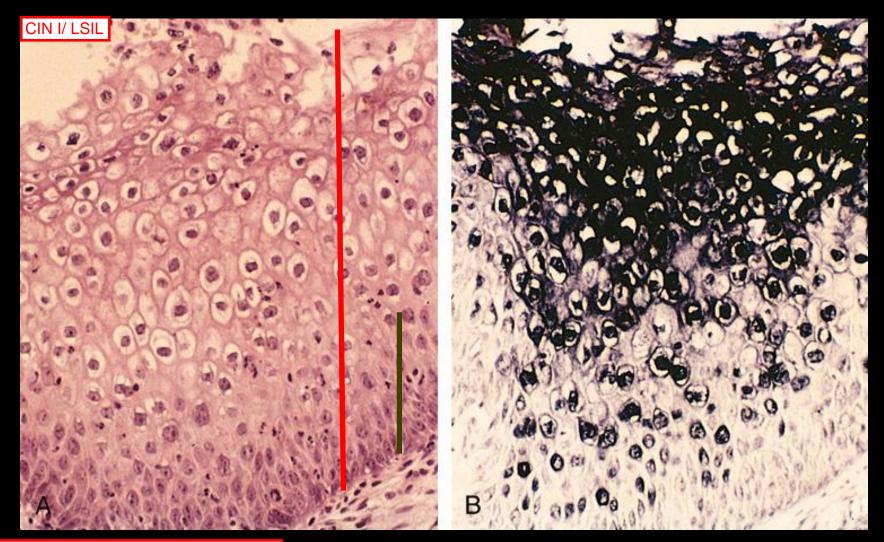
CINI



This progresion takes years (10-20+). This, in part, is the reason why the Pap smear has been so effective at reducing the tole of cervical cancer on American women.

Translating this to the Bethesda system: CIN 1/II = Low grade squamous intraepithelial lesion (LSIL) CIN III/CIS = High grade squamous intraepithelial lesion (HSIL)

HPV in-situ hybridization



The characteristic nuclear change with a perinuclear halo, indicative of HPV infection, is referred to as *koilocytic atypia*.



80% of LSIL and 100% of HSIL is associated with infection by high risk (16, 18, 31, 33, 45) strains of HPV.

>100 Known HPV types: Key concept: "High Risk Serotype"

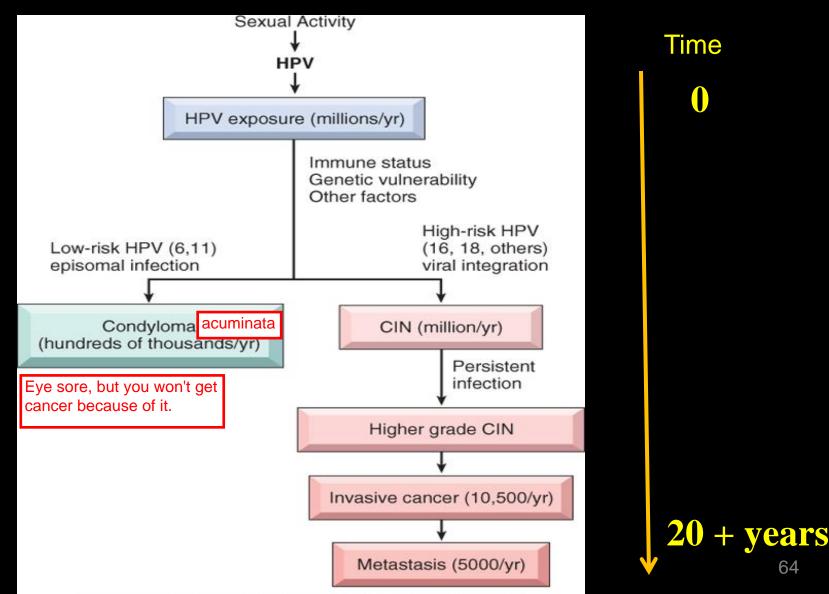
HPV & Neoplasia

Serotype Disease association

6, 11 ("low risk") Genital warts (condyloma acuminata) What causes condyloma lata?
16, 18 ("high risk") Dysplasias, 65% cancers

31, 33, 45, others Dysplasias, 35% cancers ("high risk")

Pathway to Cervical Cancer

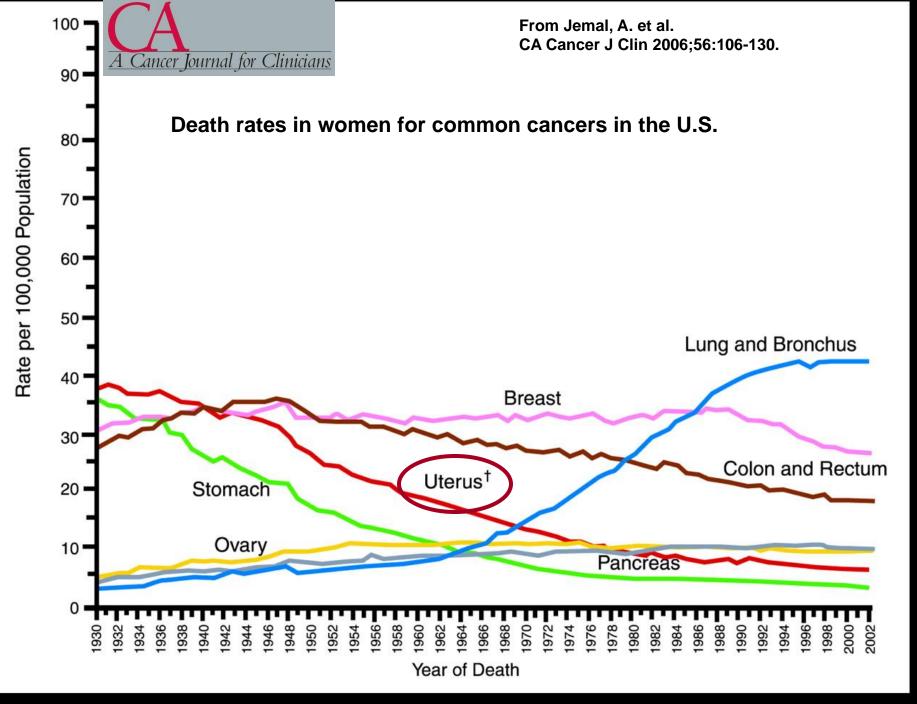


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Cervical Cancer Screening: Success of the Pap Smear

- 1940: Cervical cancer most common cancer in women in U.S.
- Use of Papanicolaou (cytologic) screening lowered cancer rate by 75% Incredible!
- 60% of patients with cervical cancer have not been screened in past 5 years or have never been screened

Pap smear is by far the most effective cancer screening and prevention technique in use



Pap Smear

Surface of cervix lightly scraped or

brushed The goal is to sample the squamocolumnar junction.

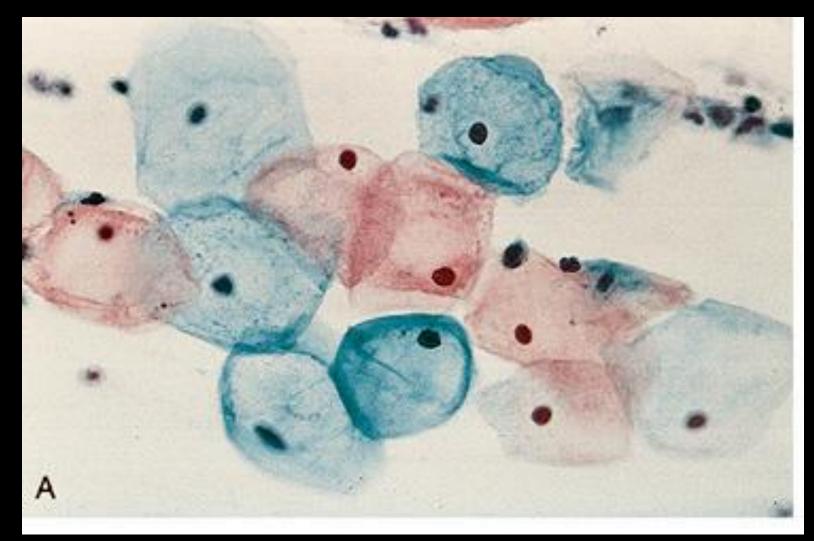
Smeared directly on slide and fixed with alcohol, or

- Transferred to liquid fixative and slide prepared in lab
- Stained with Papanicolaou stain.
- Can also be tested for high risk HPV

Robbins says:

- First smear should be at 21 years of age or within 3 years of onset of sexual activity followed by annual smears
- Women with three consecutive normal results may be screened every 2-3 years
- Women with high risk HPV serovars should have cervical cytology repeated every 6 -12 months
- HPV testing is not indicated in women under 30 due to low specificity of results

Pap Smear





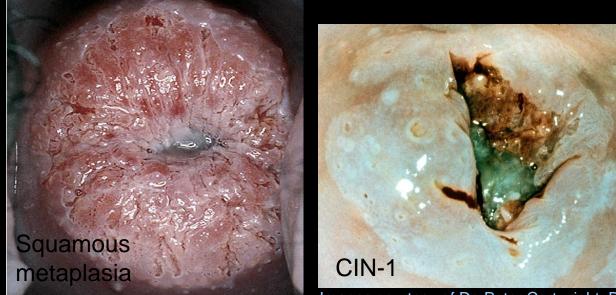
Pap Smear



High grade SIL (severe dysplasia)

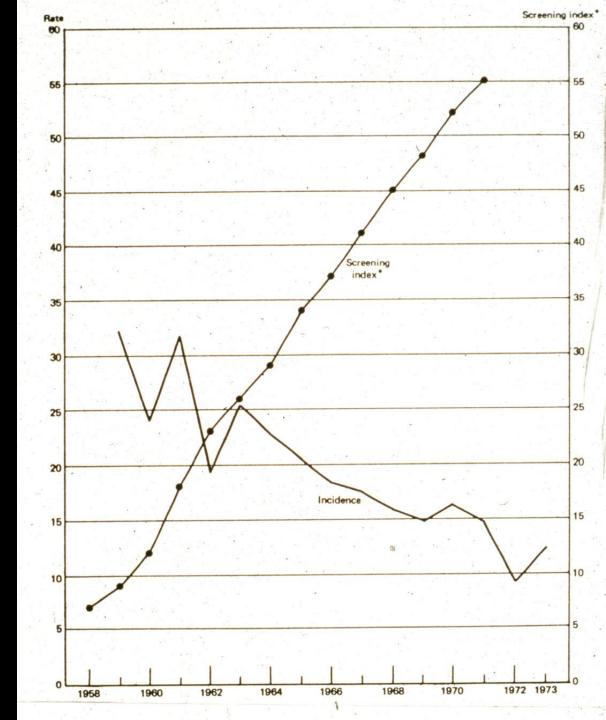
Cervical Dysplasia

 Screening →Pap Smear
 Confirmation →Colposcopy, Biopsy
 Treatment →Destroy Lesion: freeze, burn, or excise



Images courtesy of Dr. Peter Cartwright, DUMC

Colposcopy: Special examination of cervix with magnification and acetic acid or iodine to highlight abnormal areas for biopsy. Implementation of Pap screening markedly reduces rate of cervical cancer



Cervical Cancer

HPV vaccines

- Effective in preventing high grade CIN
- Approved by FDA for women age 9-26
- Less effective in older women already exposed to HPV
- Do not cover all oncogenic HPV types.
- Current recommendations are for vaccinated women to continue standard screening

Review

After today's lecture, you should be able to:

- 1. Identify common non-neoplastic diseases of the vulva and vagina based on clinical presentation and pathology
- 2. Recognize and describe the commonly occurring cancers of the vulva, vagina and cervix
- 3. Explain the role of human papilloma virus in cancers of the cervix
- 4. Explain the relationship of cervical dysplasia to cervical cancer
- 5. Describe the role of screening prevention of cervical cancer

Take home message:

Please make sure female patients age 21 and older get cervical cancer screening!

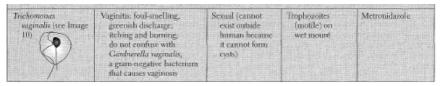
End Gyn Part 1

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Gard nerella vaginalis

A pleomorphic, gram-variable rod that causes vaginosis presenting as a gray vaginal discharge with a fishy smell: nonpainful, Mobiluncus, an anaerobe, is also involved. Associated with sexual activity, but not an STD. Bacterial vaginosis is characterized by overgrowth of certain bacteria in vagina, Treatment: metronidazole, Clue cells, or vaginal epithelial cells covered with bacteria, are visible under the microscope (see Image 13).

I don't have a clue why I smell fish in the vagina garden!



Vaginal carcinoma

1. Squamous cell carcinoma (SCC)-2° to cervical SCC.

Clear cell adenocarcinoma —affects women who had exposure to DES in utero.
 Sarcoma botryoides (rhabdomyosarcoma variant)—affects girls < 4 years of age; spindle-shaped tumor cells that are desmin positive.
 Bartholin's gland cyst—rare; pain in labia majora; can result from previous infection.

Renign breast himory

Cervical pathology Dysplasia and carcinoma in situ

Invasive carcinoma

Disordered epithelial growth; begins at basal laver of squamo-columnar junction and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (carcinoma in situ), depending on extent of dysplasia, Associated with HPV 16, 18, Vaccine available, May progress slowly to invasive carcinoma if left untreated. Risk factors multiple sexual partners, smoking, early sexual intercourse, HIV infection. Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Lateral invasion can block ureters, causing renal failure.

Kolocytic change typical of HPV infection



HPV cel

(Reproduced, with permission, from Kantar jian HM et al. MD Anderson Manual of Medical Oncology. New York: McGraw-Hill, 2006, Fig. 24-48.)

Gynecologic tumor Incidence – endometrial > ovarian > cervical (data pertain to the United States, cervical cancer is most common worldwide). epidemiology Worst prognosis – ovarian > cervical > endometrial.