



Pathology of Male and Female Genital System

CRISTIANE MIRANDA FRANCA, DDS, PHD

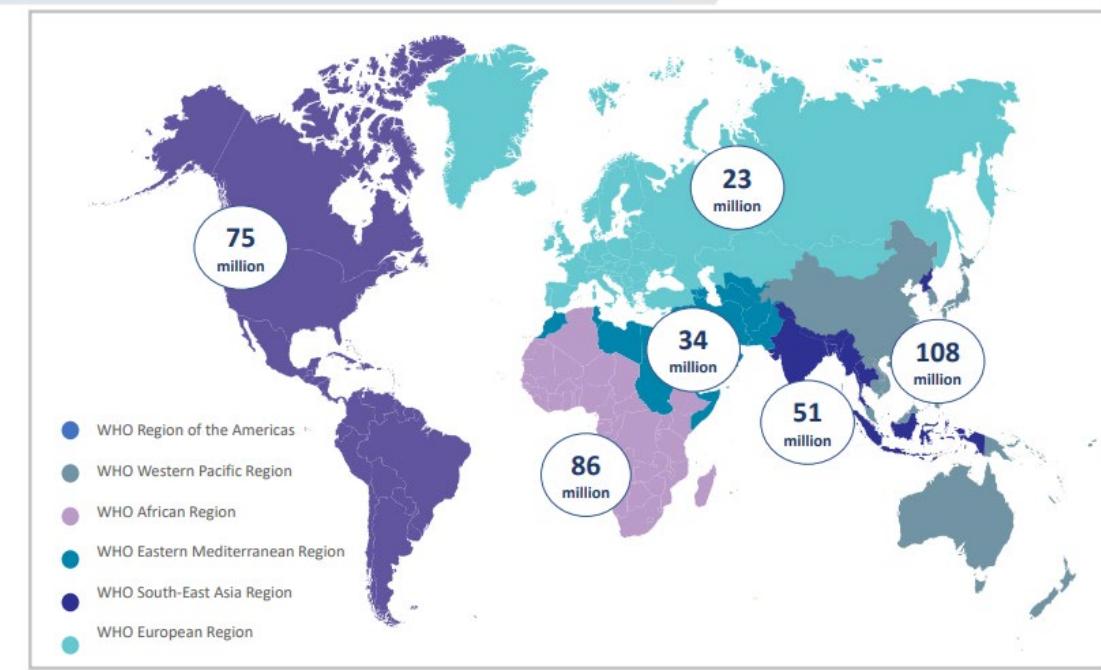
RESEARCH ASSISTANT PROFESSOR

DEPARTMENT OF RESTORATIVE DENTISTRY, OHSU

Sexually Transmitted Diseases

- ▶ More than 1 million STIs are acquired every day.
- ▶ 2020 (WHO) - 374 million new infections with STD
- ▶ Women are far more likely to be infected and to be asymptomatic
- ▶ U.S. - From the leading 10 infectious diseases that require notification to CDC, 5 are STD:
 - Chlamydial infection
 - Gonorrhea
 - Acquired immunodeficiency syndrome (AIDS)
 - Syphilis
 - Hepatitis B
- ▶ Common STDs with no required notification
 - Genital herpes
 - Genital HPV infection

WHO Incident case estimates of four curable STIs , 2016
(chlamydia, gonorrhoea, trichomoniasis, syphilis)
376 million new cases

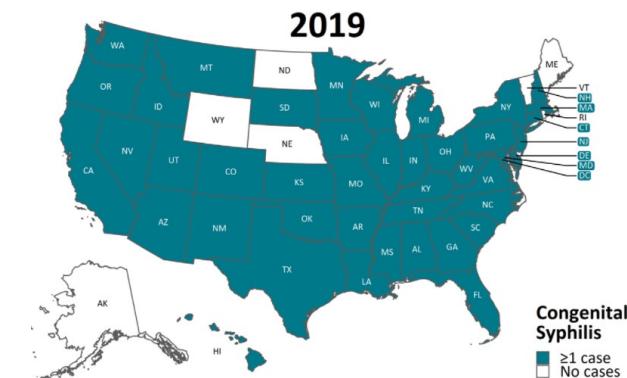
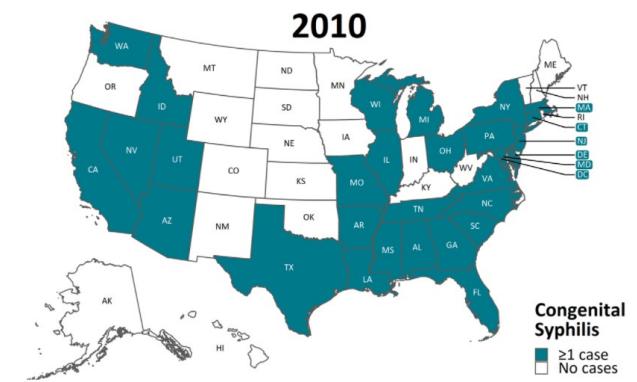


*Adults ages 15 to 49 years

Source: Rowley J, et al. WHO Bulletin, 2019

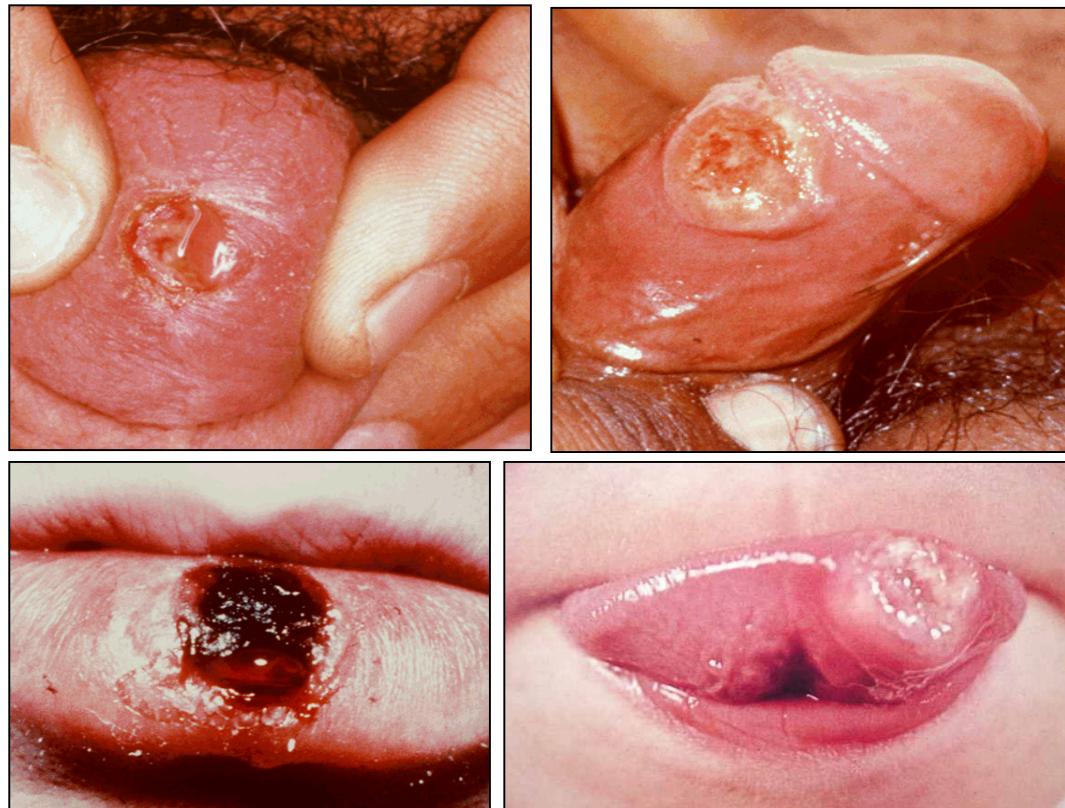
Syphilis

- ▶ Etiologic agent – spirochete *Treponema pallidum*
- ▶ 30,644 new cases in the U.S in 2017
 - Men who engage in sexual activity with men made up half of those cases
 - More common in HIV patients
 - African Americans are affected 6 times more often than whites
- ▶ Source of infection
 - **Acquired syphilis** - contact of cutaneous or mucosal lesion in a sexual partner in the early (primary or secondary) stages of syphilis
 - **Congenital syphilis** – placental transmission of *T. pallidum* from mother to fetus



Syphilis - stages

- ▶ Once inoculated in the body the bacteria rapidly disseminate through lymphatics and blood
- ▶ Primary syphilis
 - PRIMARY LESION – 3 weeks after infection
 - **Chancre** appears at the point of spirochete entry (30-50%)
 - Small, painless, firm papule which enlarges to produce an ulcer with well-defined, indurated margins. Highly infectious and non-specific appearance!
 - Systemic dissemination of *T. pallidum* while the host mounts the immune response – patient may be asymptomatic
 - Diagnosis – direct identification of spirochetes
 - Spontaneous resolution over a period of 4 to 6 weeks



Martins et al., personal archives

Syphilis - stages

► Secondary syphilis

- Generalized lymphadenopathy, mucocutaneous lesions, maculopapular skin rashes, scaly or pustular – palms of the hands and soles of the feet
- Headaches, arthralgia, muscle aches, malaise, fever
- Lesions teeming with spirochetes and highly infectious - positive serology tests
- Lesions resolve spontaneously



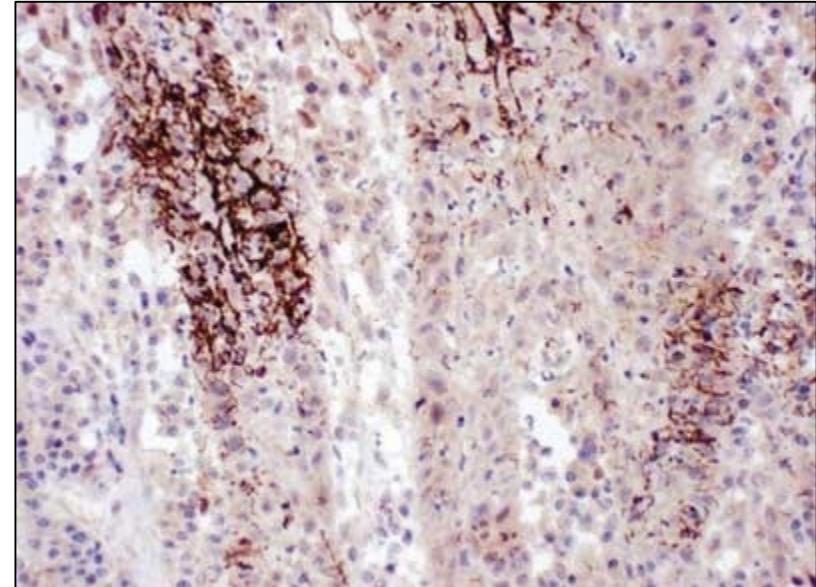
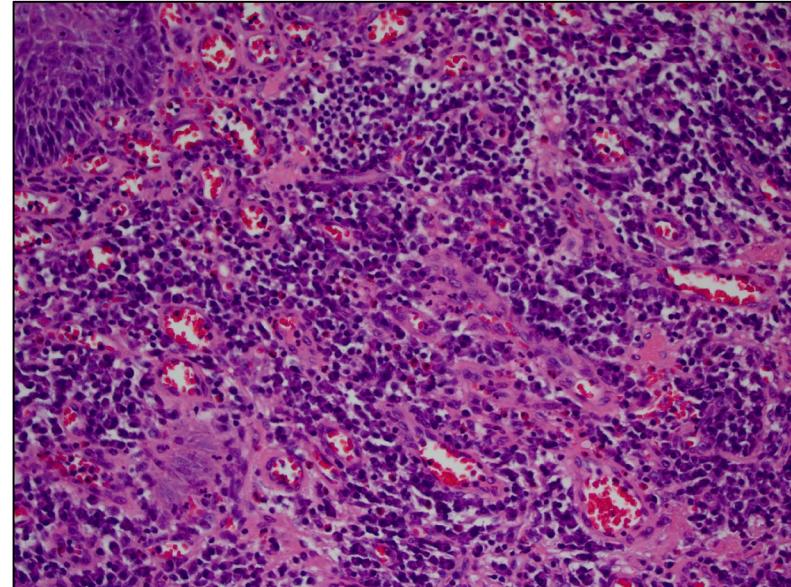
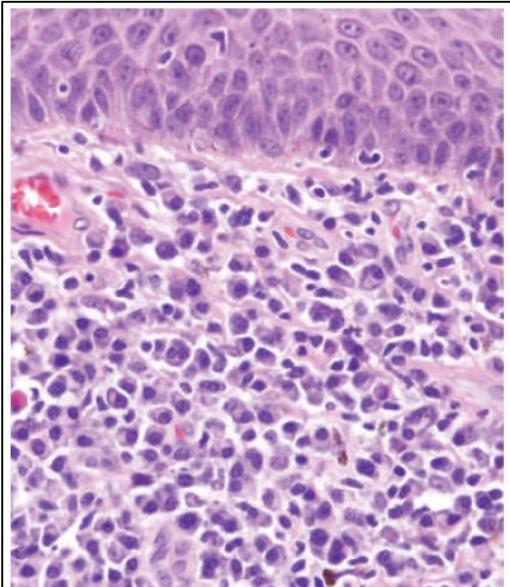
Martins et al., personal archives

Mucous patches – shallow ulcers with a greyish surface



Martins et al., personal archives

Proliferative **endarteritis**, inflammatory infiltrate rich in lymphocytes and **plasma cells**

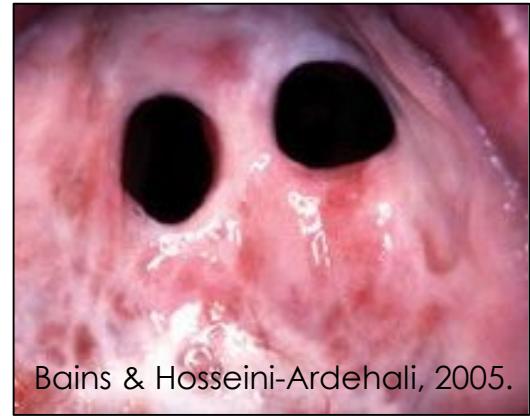


IHC to *T. pallidum*

Barret et al., J Oral Path Med (2004)

Syphilis - stages

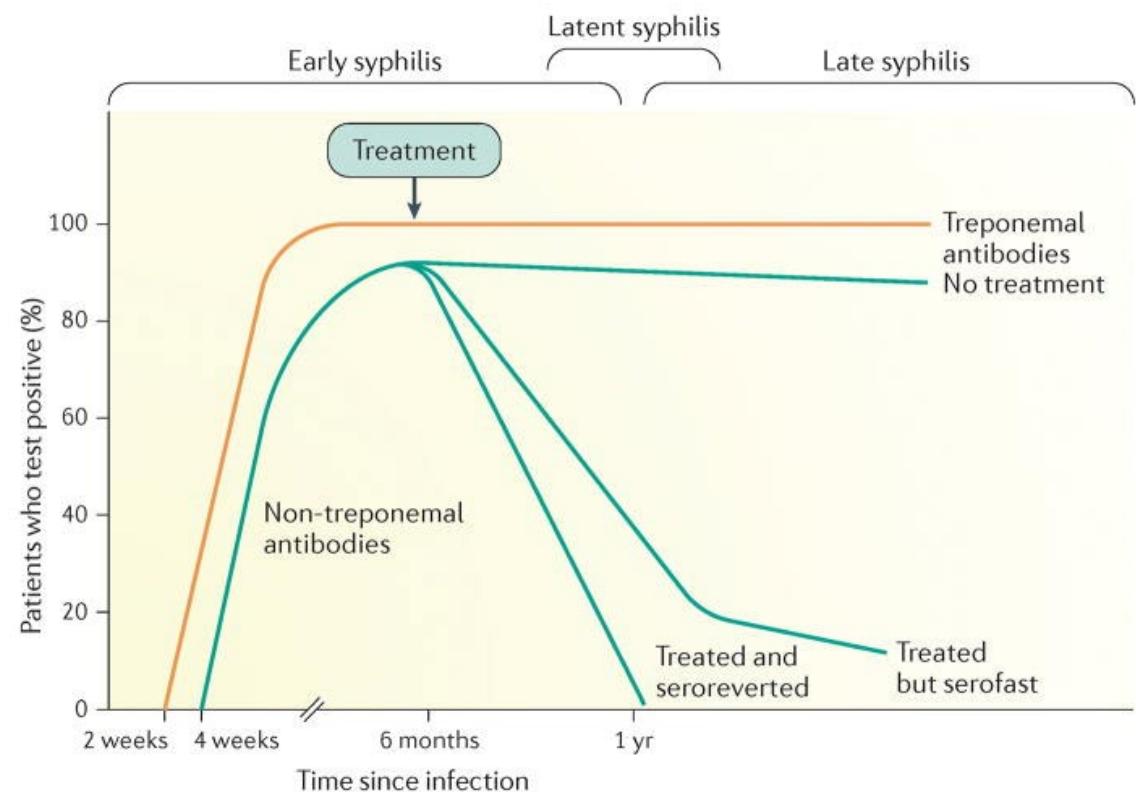
- ▶ If not treated, syphilis becomes asymptomatic and enters into a late latent phase – 1 year after the initial infection
- ▶ Tertiary syphilis
 - 1/3 of the cases – new symptoms over the next 5-20 years
 - Granulomatous, destructive lesions in mucosa, bone, liver,
 - Cardiovascular syphilis (**syphilitic aortitis**) - aneurysms
 - Neurosyphilis (increased with concomitant HIV infection), and syphilis myelopathy (tabes dorsalis)
 - **Gumma** – large areas of parenchymal damage, central zone of coagulative necrosis surrounded by dense fibrous tissue and mixed inflammatory infiltrate, activated macrophages – delayed hypersensitivity reaction



Bains & Hosseini-Ardehali, 2005.

Antibody Avoidance and Serological Response to *T. pallidum*

- ▶ Spirochetes fail to be cleared rapidly and are able to replicate and circulate in the midst of a prolific antibody response.
- ▶ IgM antibodies appear first, followed a few weeks later by IgG.
- ▶ **Diagnosis – a suggestive clinical history and supportive laboratory tests - serodiagnostic**



Diagnosis using serology

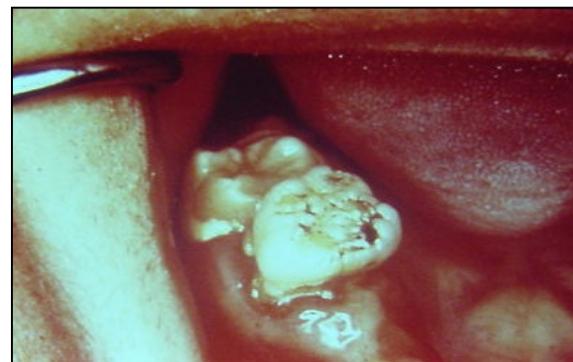
- ▶ Serodiagnostic tests
 - only means for screening asymptomatic individuals
 - most common methods to diagnose patients presenting with signs and symptoms suggestive of syphilis
- ▶ Broadly categorized into non-treponemal tests (NTTs) and treponemal tests (TTs)
- ▶ **NTTs** - Rapid Plasma Reagins (RPR) test and the Venereal Disease Research Laboratory (VDRL) test — flocculation (precipitation) tests
- ▶ Useful in detecting active syphilis
- ▶ Drawbacks
 - Tests do not become positive until 10–15 days after onset of the primary lesion, 25–30% of primary syphilis cases may be missed
 - Non-specific and may give false positive results in 2-5% of the population – chickenpox, measles, mononucleosis

Diagnosis using serology

- ▶ Treponemal tests (**TTs**)
 - Fluorescent treponemal antibody absorbed (FTA-ABS) test, the microhaemagglutination assay for antibodies to *T. pallidum* (MHA-TP), the *T. pallidum* passive particle agglutination (TPPA) and *T. pallidum* haemagglutination (TPHA) assays
- ▶ Detect antibodies directed against *T. pallidum* proteins - highly specific
- ▶ Confirmatory assays following a positive NTT result.
- ▶ TTs become positive 6–14 days after the primary chancre appears (~5 weeks after infection) - may be useful to detect early syphilis missed by NTT testing

Congenital Syphilis

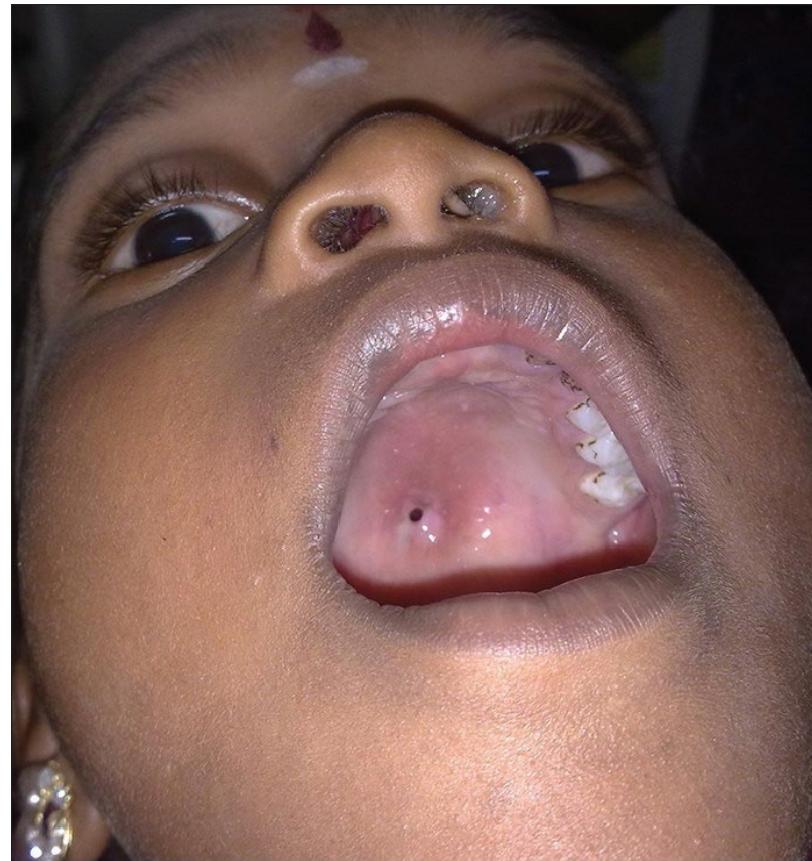
- Transmission of *T. pallidum* across the placenta from an infected mother to the fetus at any time during pregnancy
- Greatest likelihood of transmission during primary and secondary stages
- Stigmata of congenital syphilis typically do not develop until after the 4th month of pregnancy
- 40% of abortion
- Surviving children may present maculopapular rash, bone and cartilage destruction, saddle nose,
- Hutchinson's triad – interstitial keratosis, mulberry molars, Hutchinson's incisors, 8th nerve deafness



Saddle nose deformity



Perforated palate



CT showing the perforation
of right side of hard palate



Review questions

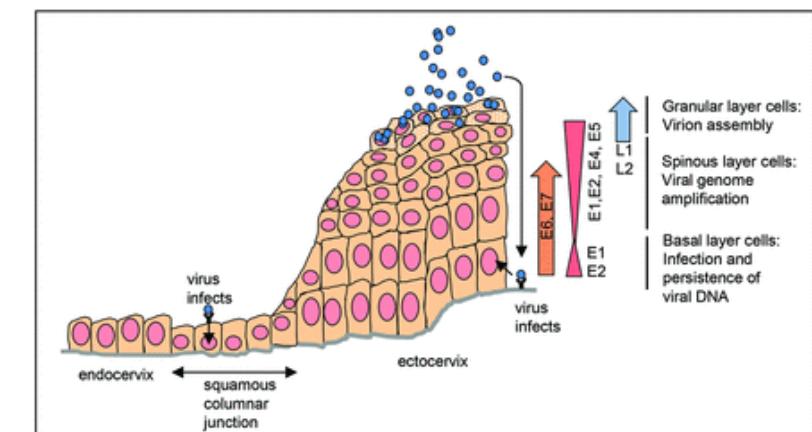
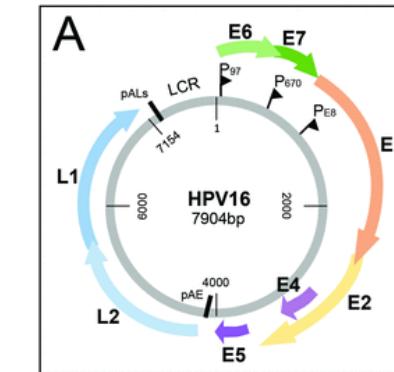
1. Identify and compare the 3 stages of syphilis, relating the systemic and oral lesions associated with each one of these stages.
2. Describe the clinical manifestations of congenital syphilis.
3. List the serologic tests available to perform syphilis diagnosis, indications and limitations according to each stage.



*Take home message

Human Papillomavirus (HPV) infection

- ▶ HPV – Papillomaviridae – more than 200 genotypes
- ▶ Viral genome codes for six early proteins (E1-7) and two late proteins (L1,L2)
 - E1 and E2 – viral replication
 - E4 – codes for a protein that disrupts the cytoplasmic keratin network, regulation of host cell cycle control
 - E5 – viral replication
 - **E6 - forms a complex with p53 accelerating ubiquitination and downregulation of p53 – cell malignant transformation**
 - **E7 – binds to the phosphorylated retinoblastoma protein (Rb) - mediates degradation of the Rb protein through the ubiquitin-proteosome pathway, also binds to p21 – loss of cell cycle control.**



Human Papillomavirus (HPV) infection

- ▶ Most HPV infections are transient and are eliminated within months
- ▶ HPV may cause benign proliferations, precancerous lesions and invasive cancers
- ▶ Low risk HPV 11 and 6 - *condylomata acuminata* – venereal warts
- ▶ High-risk HPV – HPV 16 and 18 – 70% of cases of cervical carcinoma
- ▶ Males - 30 to 60% of penile carcinomas are reported to harbor human papillomavirus (HPV) DNA
- ▶ Females – HPV is detected in nearly all cervical carcinomas and in a smaller fraction of vaginal and vulval carcinomas



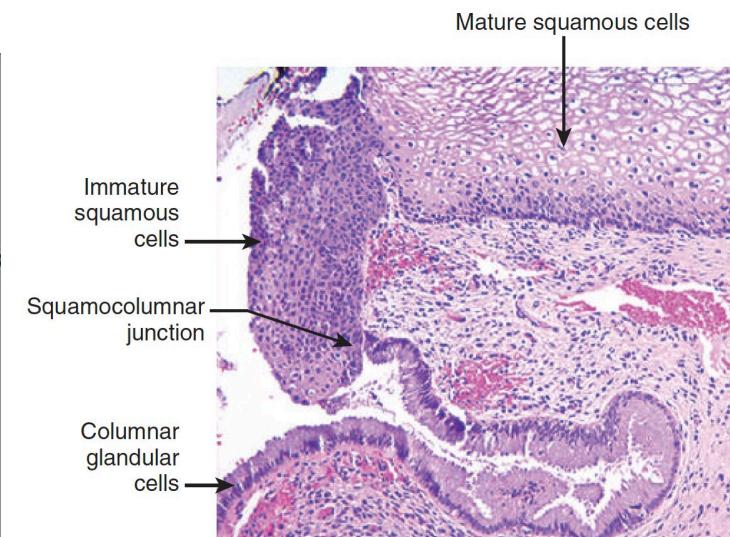
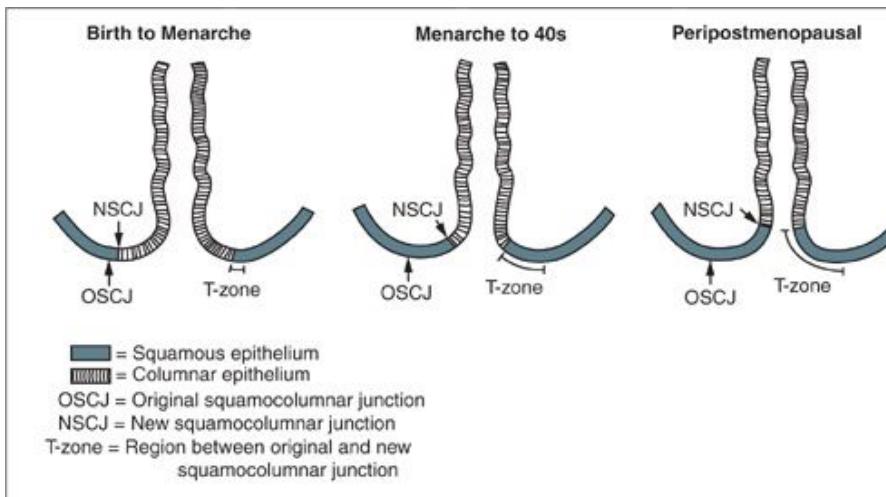
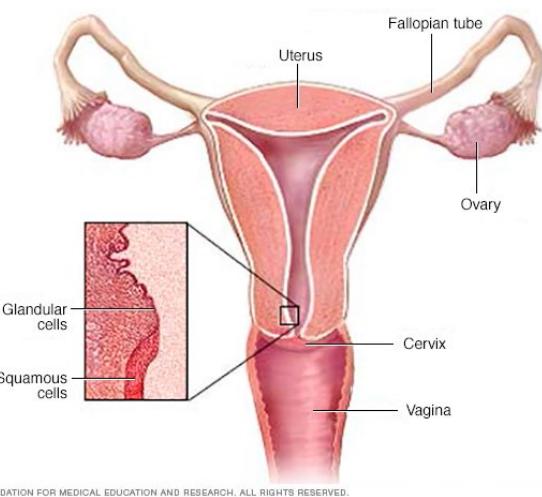
HPV and genital carcinomas

► Causal association

- HPV DNA is present in all precursor lesions and malignancies
- HPVs express the oncogenes E6 and E7 in all cells of these lesions
- These E6 and E7 proteins have pleiotropic molecular properties, which explain the properties of the transformed cell
- Repression of the E6 and E7 genes inhibits transformation and viability of the HPV containing cell lines
- HPVs may initiate neoplasia of the penis in a similar manner as genital carcinomas of females, but this is supported by relatively few data

Transformation zone:

Area where squamous cells of the vagina and the columnar or glandular cells of the uterus meet



Squamous Intraepithelial Lesion (SIL)

- ▶ HPV-related carcinogenesis begins with the precancerous epithelial change termed SIL, which usually precedes the development of an overt cancer by many years or decades.
- ▶ SIL – 30 year-old women
- ▶ Invasive cancer – 45 year-old women
- ▶ SIL classification
 - Low-grade squamous intraepithelial neoplasia I – **LSIL** or cervical intraepithelial neoplasia CIN I
 - High-grade squamous intraepithelial lesion (**HSIL**), encompassing cervical intraepithelial neoplasia II and III (CIN II and III)

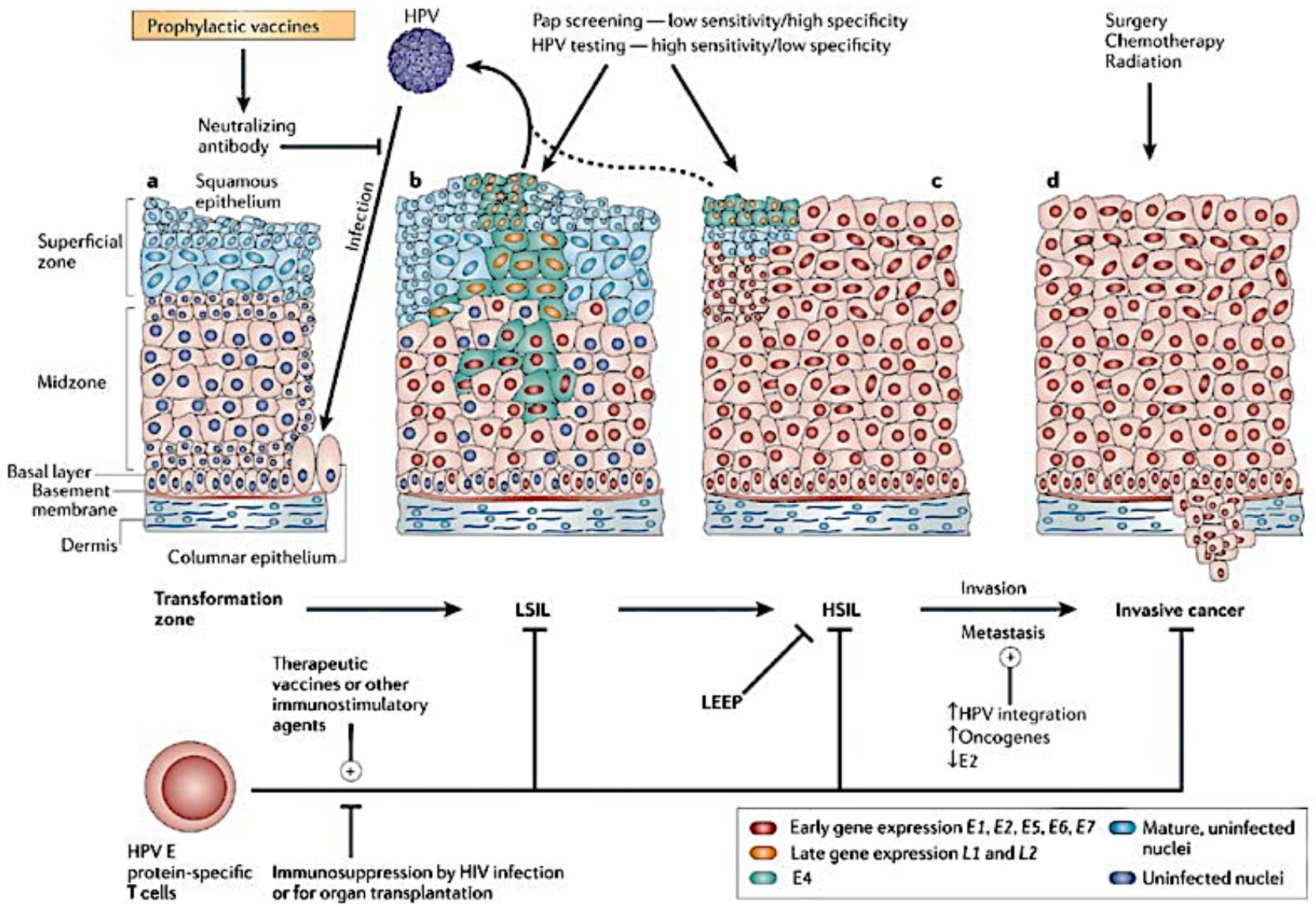
Squamous Intraepithelial Lesion (SIL)

- ▶ LSIL – association with productive HPV infection and does NOT progress directly to invasive carcinoma. May regress, and it is not treated as a pre-malignant lesion
- ▶ HSIL – increased proliferation, arrested epithelial maturation and lower levels of viral replication. High risk to cancer progression

Table 19.1 Natural History of Squamous Intraepithelial Lesions (SILs)

Lesion	Regress	Persist	Progress
LSIL (CIN I)	60%	30%	10% (to HSIL)
HSIL (CIN II, III)	30%	60%	10% (to carcinoma) ^a

^aProgression within 10 years.
LSIL, Low-grade SIL; HSIL, high-grade SIL.



Spectrum of squamous intraepithelial lesions

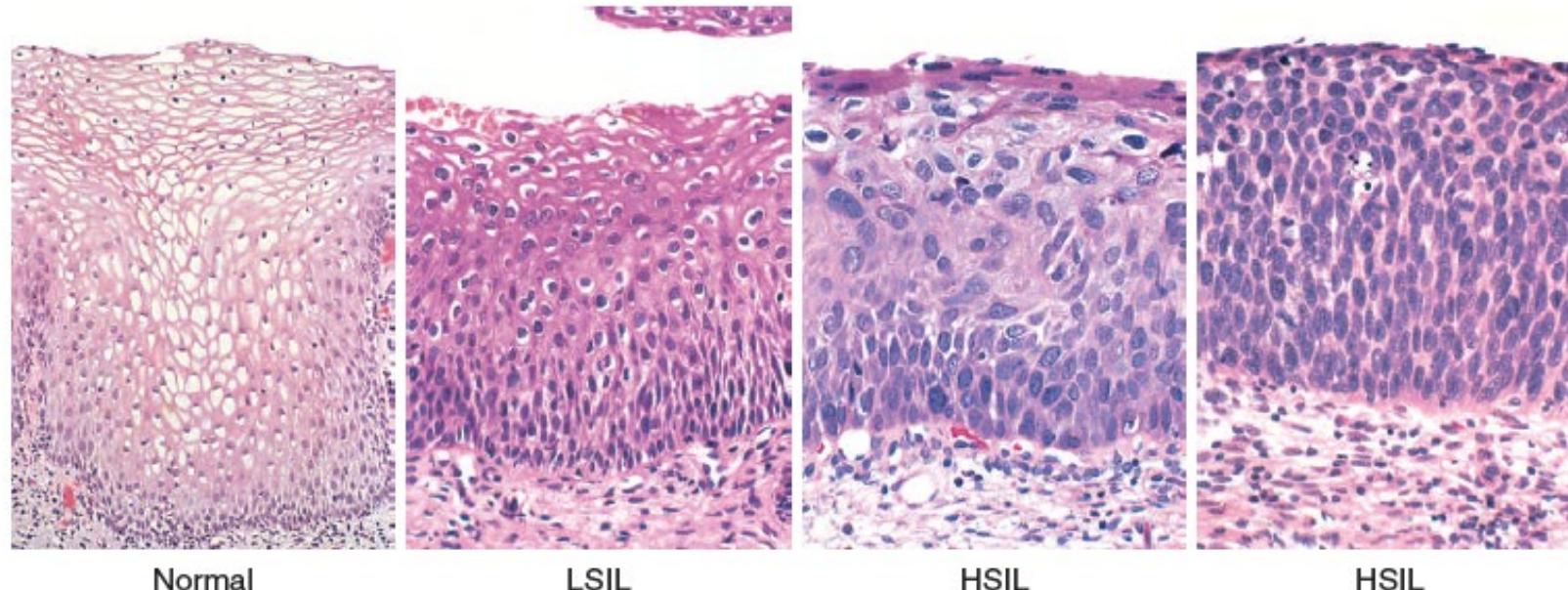


Fig. 19.6 Spectrum of squamous intraepithelial lesions (SIL) with normal squamous epithelium for comparison: LSIL with koilocytotic atypia; HSIL with progressive atypia in all layers of the epithelium; and HSIL with diffuse atypia and loss of maturation (carcinoma in situ, far right image).

Early detection of SIL is the rationale for the Papanicolaou (Pap) test

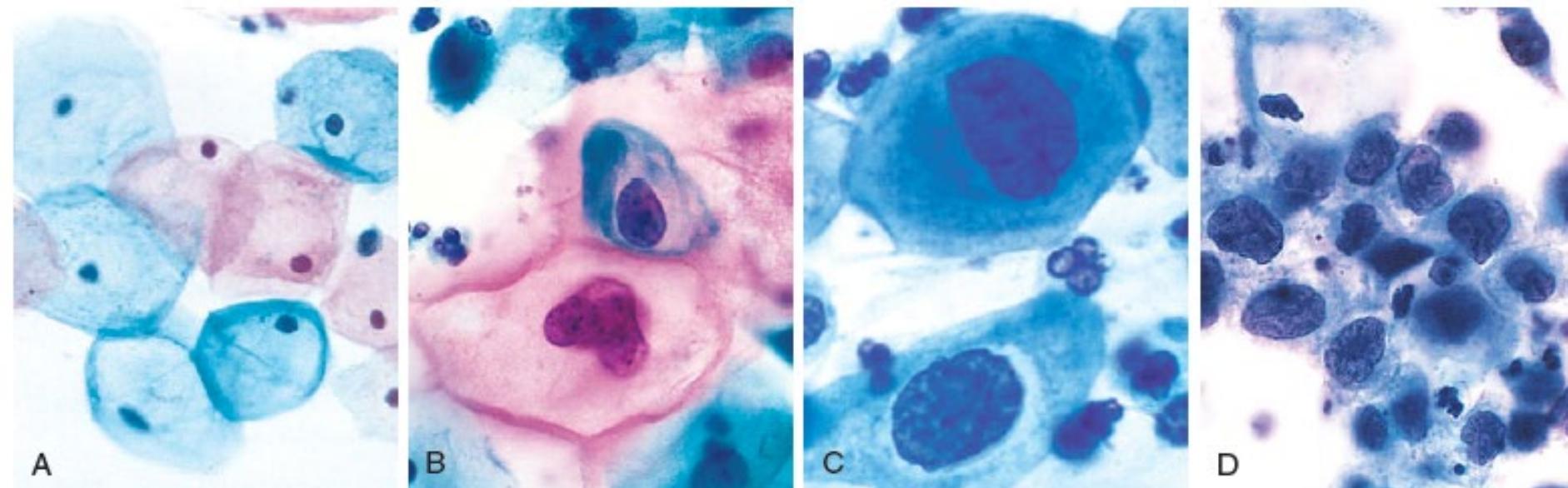
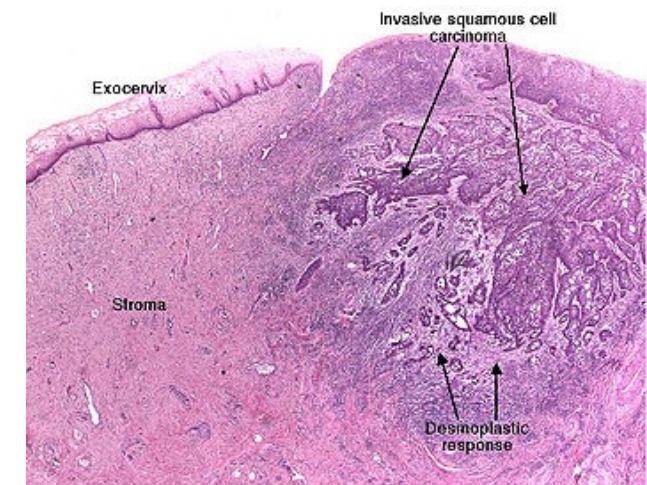


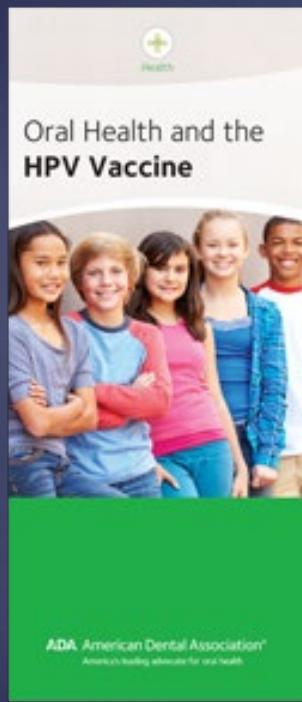
Fig. 19.7 Cytologic features of squamous intraepithelial lesion (SIL) in a Papanicolaou smear. Superficial squamous cells may stain either red or blue. (A) Normal exfoliated superficial squamous epithelial cells. (B) Low-grade squamous intraepithelial lesion (LSIL). (C and D) Both high-grade squamous intraepithelial lesions (HSILs). Note the reduction in cytoplasm and the increase in the nucleus-to-cytoplasm ratio as the grade of the lesion increases. This observation reflects the progressive loss of cellular differentiation on the surface of the cervical lesions from which these cells are exfoliated (see Fig. 19.6). (Courtesy of Dr. Edmund S. Cibas, Brigham and Women's Hospital, Boston, Massachusetts.)

Invasive carcinoma of the cervix

- ▶ 75% of cervical carcinomas are squamous cell carcinomas, 20% adenocarcinomas and others.
- ▶ All are related to HPV
- ▶ Peak of incidence about 45 years
- ▶ In association to HPV other risk factors are:
 - Cigarette smoking
 - HIV infection
 - Multiple sexual partners, early age at first intercourse
- ▶ **Pap smears, frequent physical examinations and biopsy of suspicious lesions are the only way to monitor the SIL course**



HPV vaccine for
types 6, 11, 16, 18,
31, 33, 45, 52 and 58



ADA Adopts Policy on HPV Vaccination for the Prevention of Oral HPV Infection

October 25, 2018

Contact Information:

mediarelations@ada.org

CHICAGO — With the number of cases of HPV-associated cancers on the rise, the American Dental Association (ADA) has adopted a policy that urges dentists to support the use and administration of the human papillomavirus (HPV) vaccine.

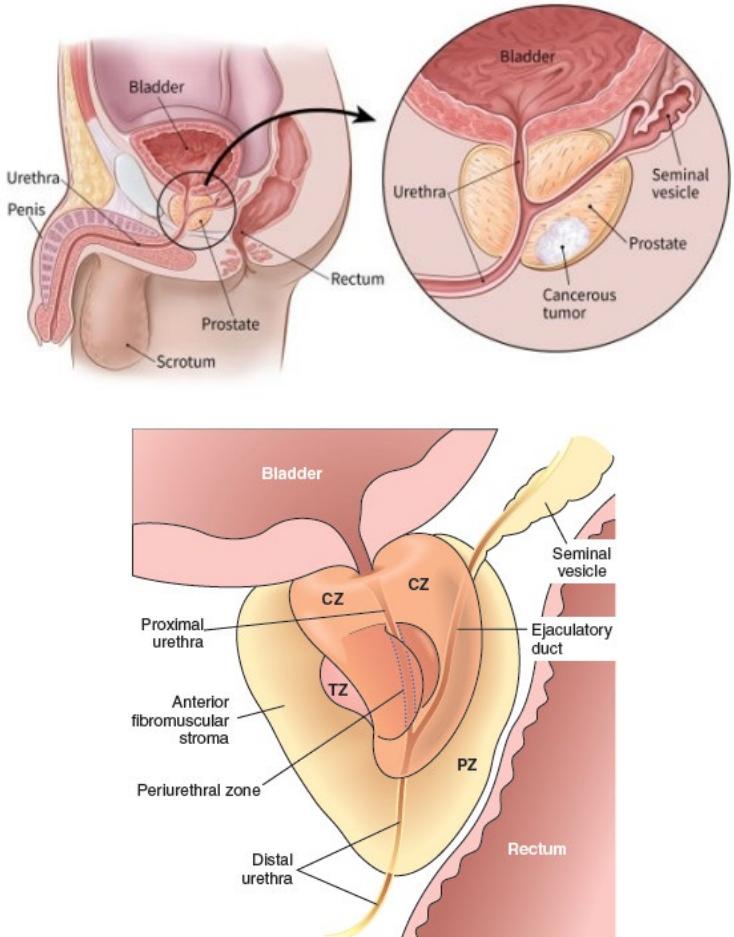
The combined estimate by the American Cancer Society is that there will be more than 50,000 new cases of oral and oropharyngeal cancers in 2018, of which 70 to 80 percent will be attributable to HPV. The HPV vaccine could help prevent the vast majority of the oropharyngeal cases, but compared to other vaccines in the U.S., it is underutilized. According to the ADA Council on Scientific Affairs, the single best predictor of whether a young person or adolescent receives the vaccine is a recommendation from a trusted health care professional.

Review questions

1. Explain the association between some types of HPV and cancer.
2. Define the cervical transformation zone. What is the importance of this area to the development of cervical cancer?
3. Define and classify squamous intraepithelial lesions (SIL).
4. Describe the cytologic features of SIL in a Pap smear.
5. What is the rationale behind the American Dental Association policy on HPV vaccination?

Prostate

- ▶ Male reproductive gland whose main function is to secrete prostate fluid, one of the components of semen. Prostate muscles also help propel this seminal fluid into the urethra during ejaculation
- ▶ Normal prostate zones – central, peripheral and periurethral
- ▶ Most carcinomas (70-80%) arise from the peripheral glands
- ▶ Nodular hyperplasia arises from glands in the inner transition zone
- ▶ Clinically – carcinomas are often detected by rectal examination, whereas hyperplasias are more likely to cause urinary obstruction

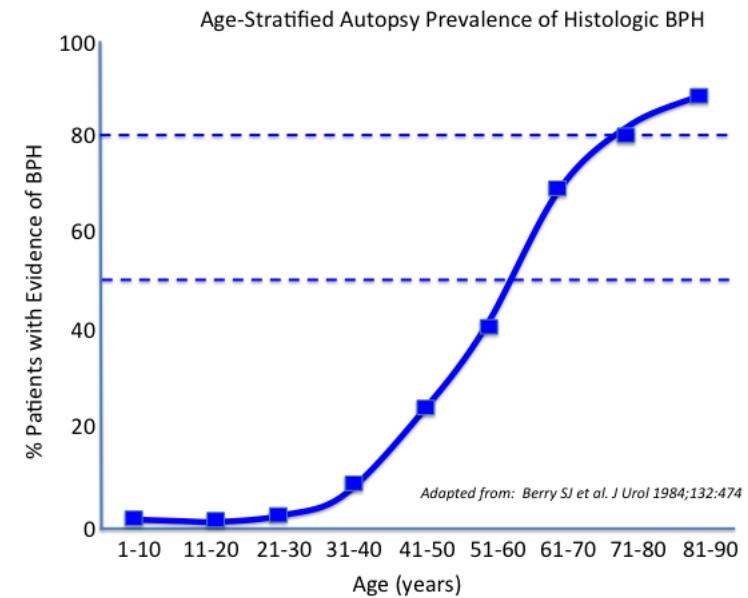


Benign Prostate Hyperplasia incidence

Percent diagnosis seen by urologists

Urinary tract infection	32%
Benign prostatic hyperplasia	23%
Painful bladder	12%
Prostate cancer	10%
Kidney/bladder stones	8%
Erectile dysfunction	8%
Urinary incontinence	7%

adapted from Amerson D²⁶



Benign Prostate Hyperplasia

- ▶ In the prostate circulating testosterone is modified by the 5 α -reductase into dihydrotestosterone (DHT)
- ▶ DHT binds to nuclear androgen receptors and stimulates growth and survival of prostatic epithelium and stromal cells
- ▶ Inflammation is linked to the development of BPH and lower urinary tract symptoms (LUTS)
- ▶ Probably metabolic syndrome, which promotes systemic inflammation and oxidative stress, contributes to the development of BPH and LUTS
- ▶ Fruits and vegetables intake and physical activity decreases the risk of BPH

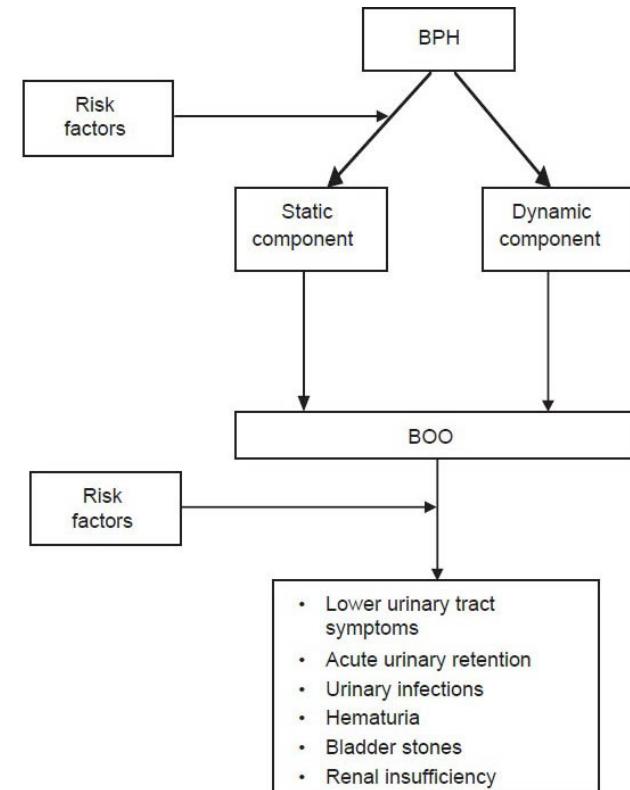
Etiology

Non-modifiable	Modifiable
Age	Hormones
Genetics	Testosterone
Geography	Dihydrotestosterone
	Estrogen
	Metabolic syndrome
	Obesity
	Diabetes
	Diet
	Physical activity
	Inflammation

LUTS=Lower urinary tract symptoms, BPH=Benign prostatic hyperplasia,
DHT=Dihydrotestosterone

Benign Prostate Hyperplasia

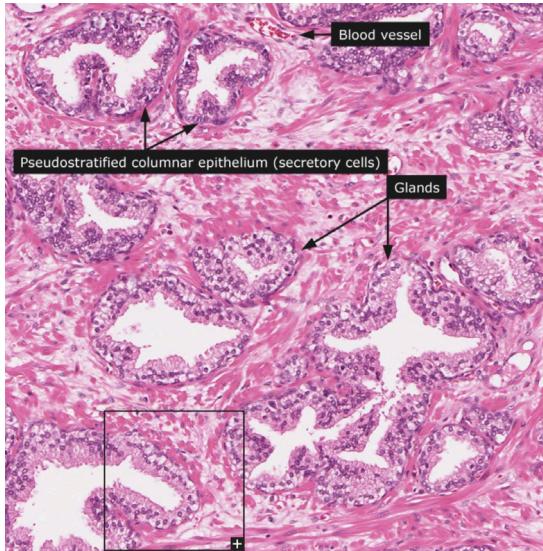
- ▶ BPH may cause physical compression of the urethra and result in anatomic bladder outlet obstruction (BOO) through two distinct mechanisms
 1. increase in prostate volume, termed the static component
 2. increase in stromal smooth muscle tone, termed the dynamic component
- ▶ BOO, in turn, may present clinically as lower urinary tract symptoms (LUTS), urinary tract infections, acute urinary retention (AUR), renal failure hematuria, and bladder calculi
 - Stream of urine (hesitancy) and intermittent interruption of the urinary stream while voiding
 - Urinary urgency, frequency, nocturia – bladder irritation



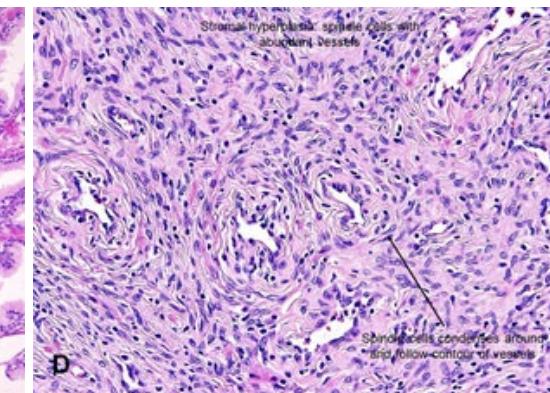
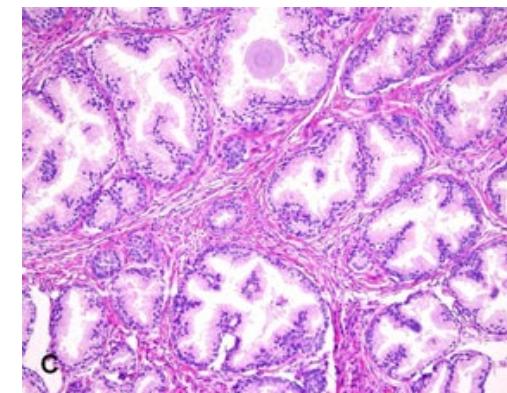
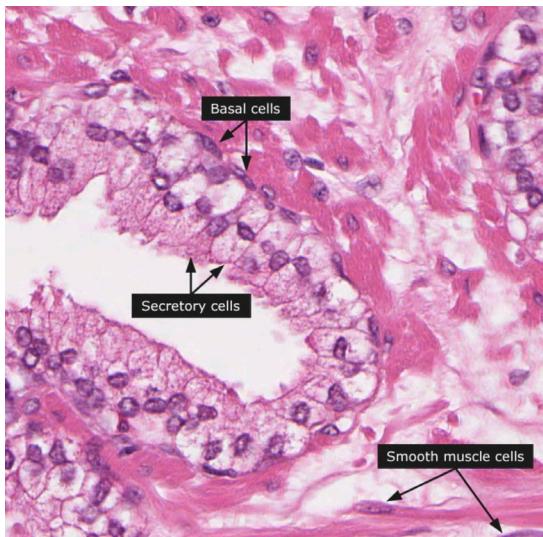
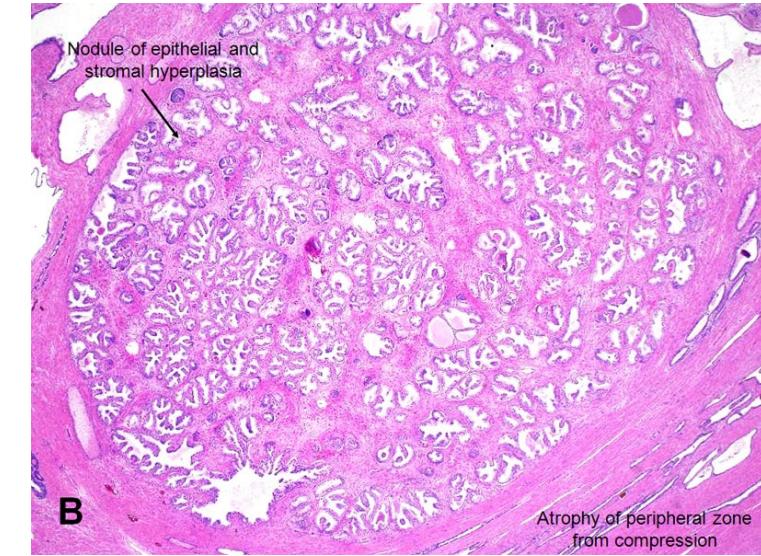
BPH



Normal Prostate



BPH



Benign Prostate Hyperplasia

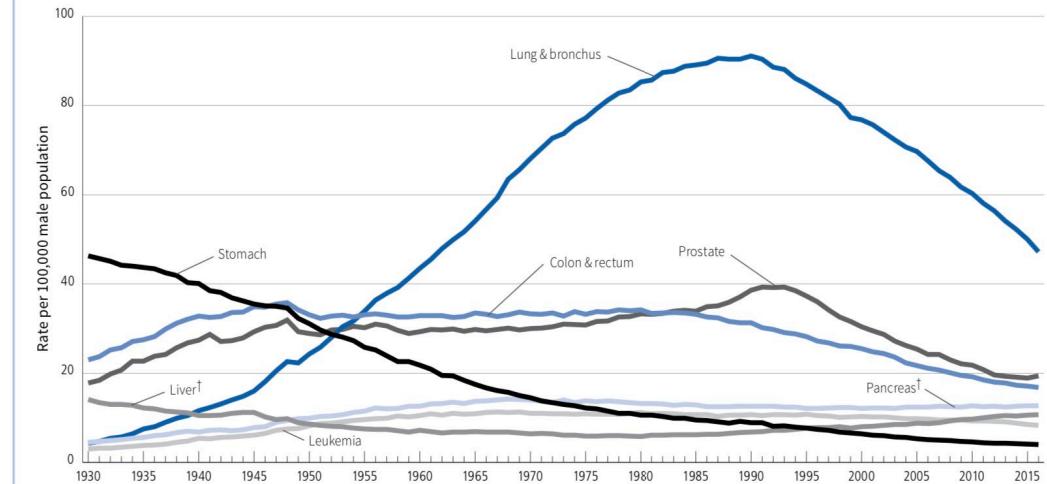
- ▶ The goal of treatment - relieve LUTS and slow the clinical progression of BPH while improving patient quality of life
- ▶ Lifestyle modifications and behavior recommendations
 - nightly fluid restriction, timed bladder voiding, double-voiding techniques, regular physical activity, and avoiding caffeine, alcohol, and highly seasoned or irritative foods
- ▶ Pharmacological treatment
 - Inhibitors of 5-alpha-reductase – avoid the formation of DHT from testosterone
 - Alpha1-adrenergic receptors blockers to relax prostatic smooth muscle
 - Adverse effects - libido impairment, abnormal ejaculations, erectile dysfunction, mastalgia, gynecomastia, xerostomia
- ▶ Surgical treatment

Carcinoma of the Prostate



- ▶ Adenocarcinoma is the most common form cancer in men – 27% of all cancer cases in the U.S.
- ▶ 60% of cases are diagnosed in men over 65
- ▶ Irregular, palpable, asymptomatic nodules associated with elevated serum prostate-specific antigen (PSA) levels.
- ▶ 70-80% arise in the outer (peripheral) glands

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2016



*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

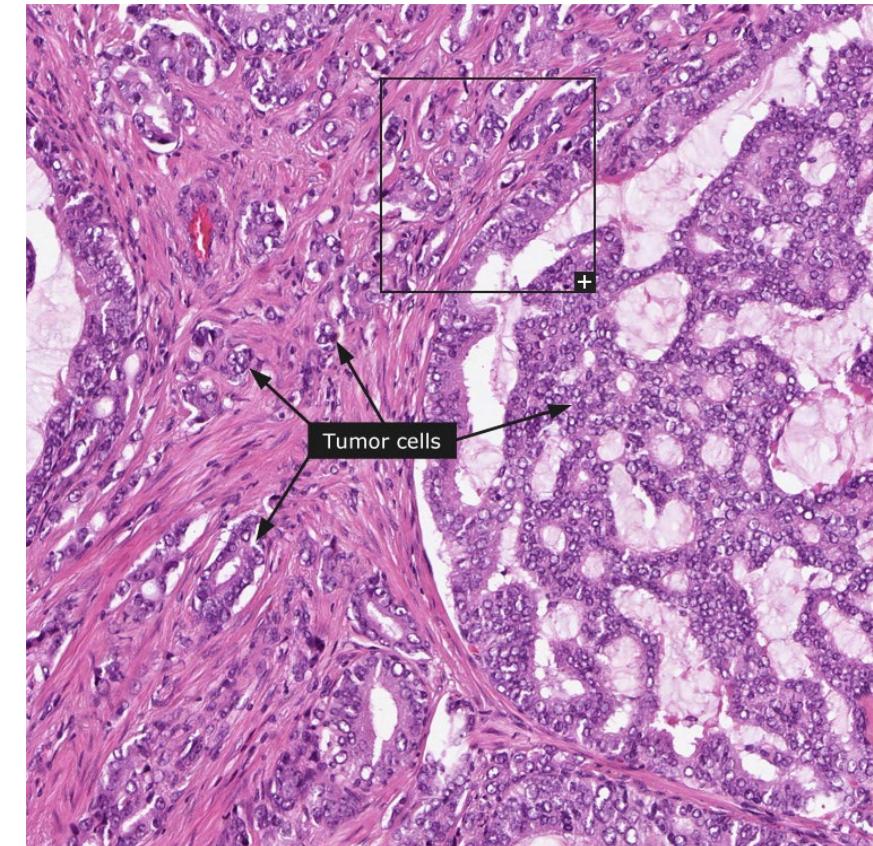
Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention.

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Carcinoma of the Prostate



- ▶ Pathogenesis
- ▶ Androgens – central importance
 - Tumor depends on androgens for its survival
- ▶ Heredity
 - Genetic variants of multiple risk alleles
 - African-Americans have more aggressive, clinically significant diseases
- ▶ Environment – studies in migratory populations
- ▶ Acquired genetic aberrations
 - Gene rearrangements create fusion genes consisting of the androgen-regulated promoter of the TMPRSS2 gene and the coding sequence of ETS family transcription factors



Carcinoma of the Prostate

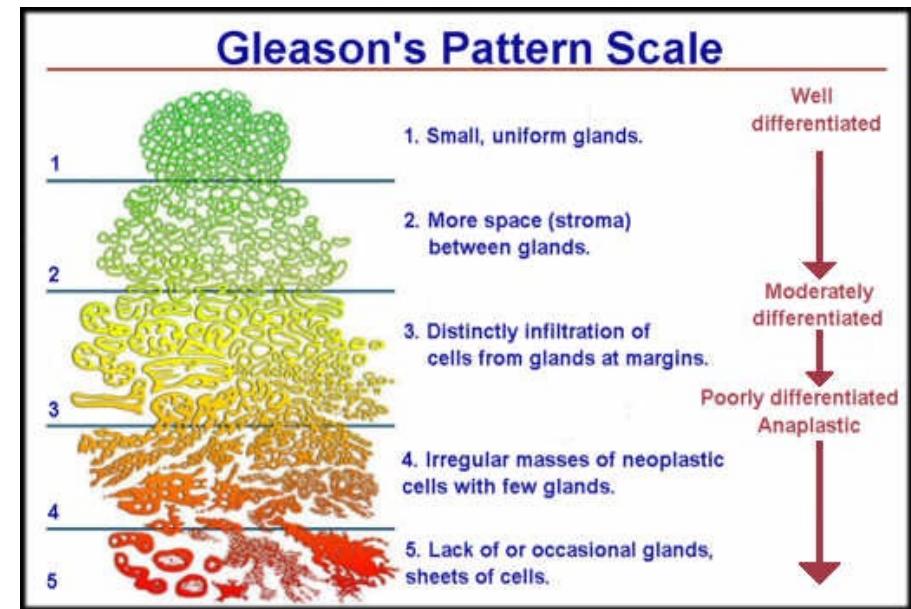


- ▶ PSA is a glycoprotein enzyme produced exclusively by epithelial prostate cells
- ▶ PSA assay is the most widely used test in prostate cancer diagnosis and evaluation of therapy response
- ▶ Limitations
 - Can detect early cancers that in 'watch and wait' studies have proved to be clinically insignificant
 - PSA may be present in BPH, prostatitis, and other conditions whereas 20-24% of patients with organ confined prostate cancer have low PSA

Carcinoma of the Prostate



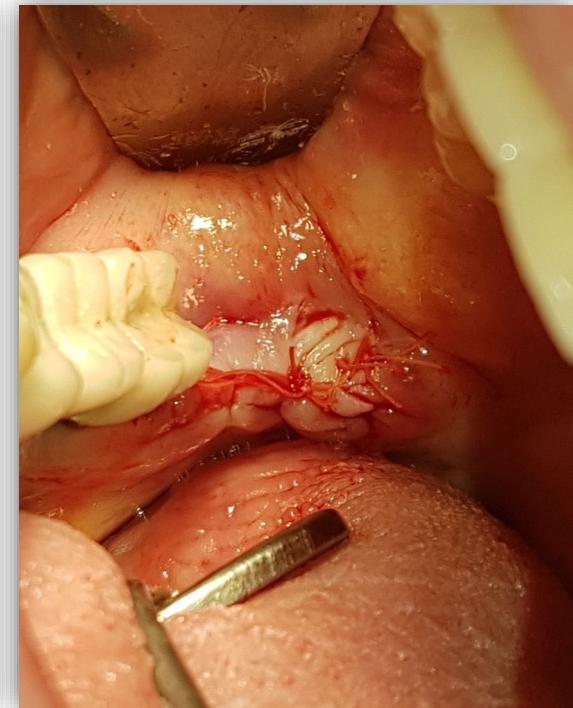
- ▶ Treatment – prostatectomy and radiotherapy
- ▶ Based on the clinical stage, serum PSA values, Gleason grade (histology) and if the margins of resected lesion are free of tumor or not.
- ▶ Gleason system – 5 grades on the basis of glandular patterns of differentiation
 - Primary grade is assigned to the dominant pattern and a secondary grade to the next most frequent pattern, i.e., well differentiated tumor scores 2 (1+1) whereas poor differentiated scores 10 (5+5)



Carcinoma of the Prostate



- ▶ Bone tropism – only 1/3 of patients with bone metastasis have a 5-year survival
- ▶ Oral manifestations due to the treatment of metastatic disease
 - ▶ Oral mucositis – chemotherapy drugs
 - ▶ Osteonecrosis of the jaws - zolendronic acid or other bisphosphonates



Oral mucositis



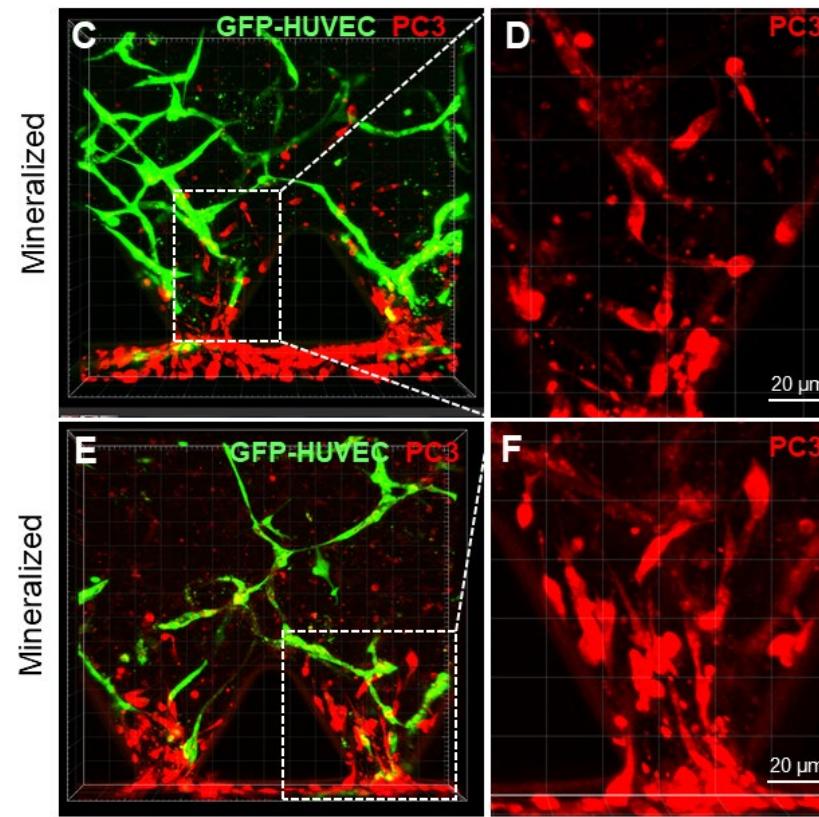
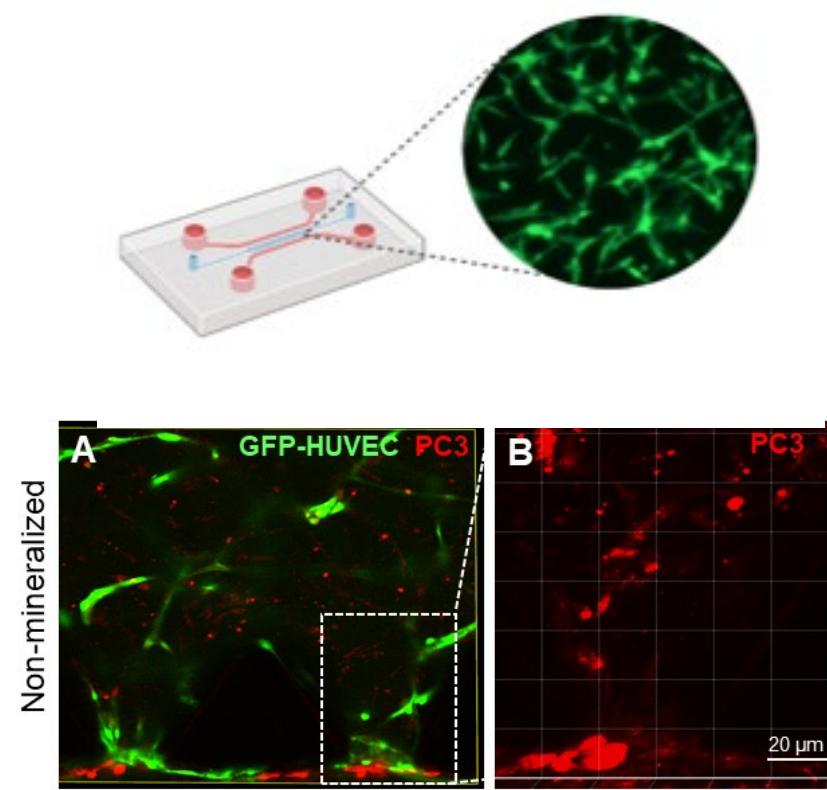
SOTTILI. M et al; Head Neck. 2017 Nov 20.

Prostate
cancer

the disease is more common in the Caucasian population. It is believed that risk factors involved include a diet high in processed meat products or low in certain vegetables. Prostate cancer can be diagnosed by biopsy. Medical imaging may then be used to determine if the cancer has spread to other parts of the body.

Prostate Cancer research

► Bone tropism



Review questions

1. Provide a comprehensive review of the etiology of BPH and association with lower urinary tract symptoms.
2. What is the goal of BPH treatment? List the current approaches for the management of BPH.
3. List the factors involved in the pathogenesis of prostate cancer.
4. Explain the rationale behind the use of PSA as a cancer marker for diagnosis and evaluation of prostate cancer treatment.
5. Define the Gleason system.
6. List the possible oral manifestations of the metastatic prostate cancer treatment.

Breast cancer



Estimated age-standardized incidence rates (World) in 2018, breast, females, all ages

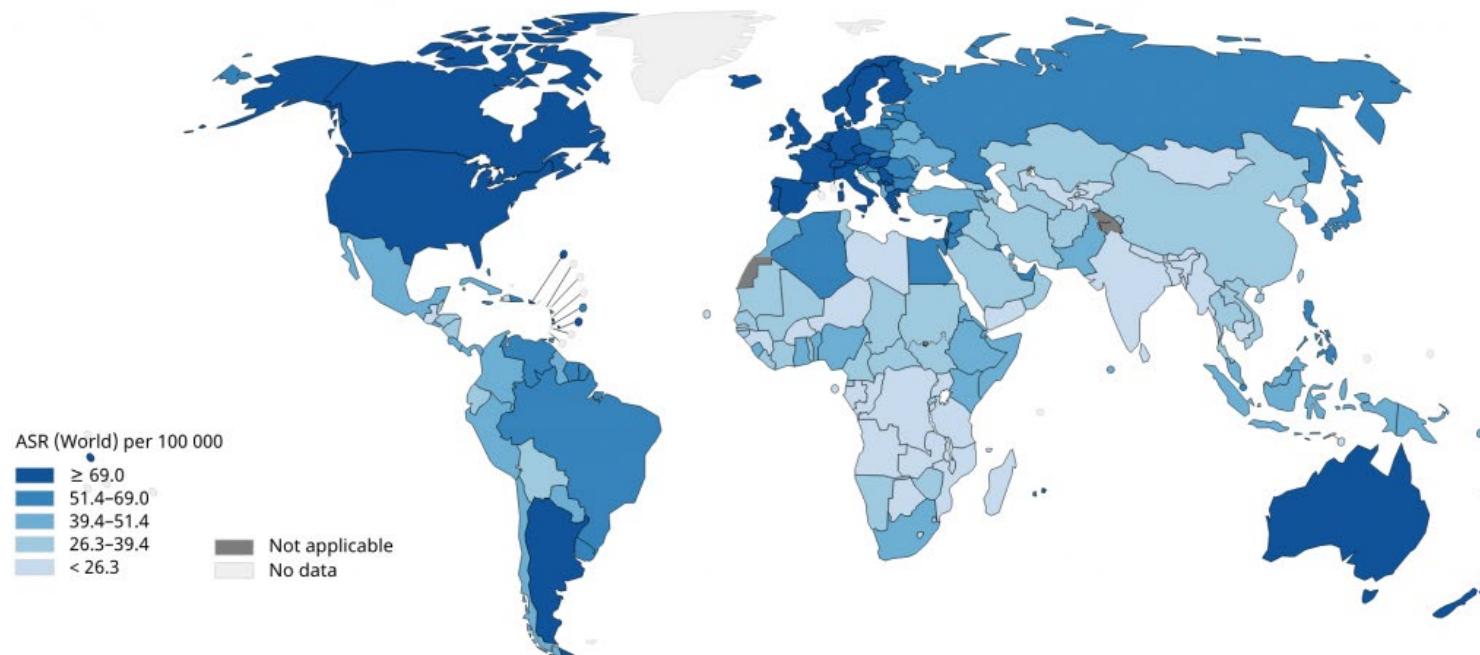
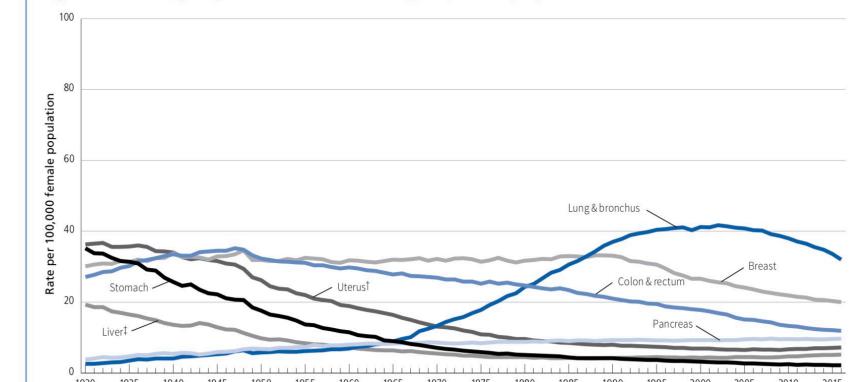


Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930–2016



*Per 100,000, age adjusted to the 2000 US standard population. Rates exclude deaths in Puerto Rico and other US territories. †Uterus refers to uterine cervix and uterine corpus combined.

‡The mortality rate for liver cancer is increasing.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, colon and rectum, and uterus are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention.

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Benign Epithelial Lesions

- ▶ Three groups:
 - **Nonproliferative disease** (cysts, fibrosis, adenosis) not associated with an increased risk of breast cancer
 - **Proliferative disease without atypia** (epithelial hyperplasia, sclerosing adenosis, papilloma) - encompasses polyclonal hyperplasias that are associate with a slightly increased risk of breast cancer
 - **Proliferative disease with atypia** (atypical lobular hyperplasia, atypical ductal hyperplasia) includes monoclonal 'precancers' with an increase in the risk of breast cancer
- ▶ Atypical lobular hyperplasia (ALH) resembles lobular carcinoma in situ (LCIS) and atypical ductal hyperplasia (ADH) resembles ductal carcinoma in situ (DCIS)

Benign Epithelial Lesions

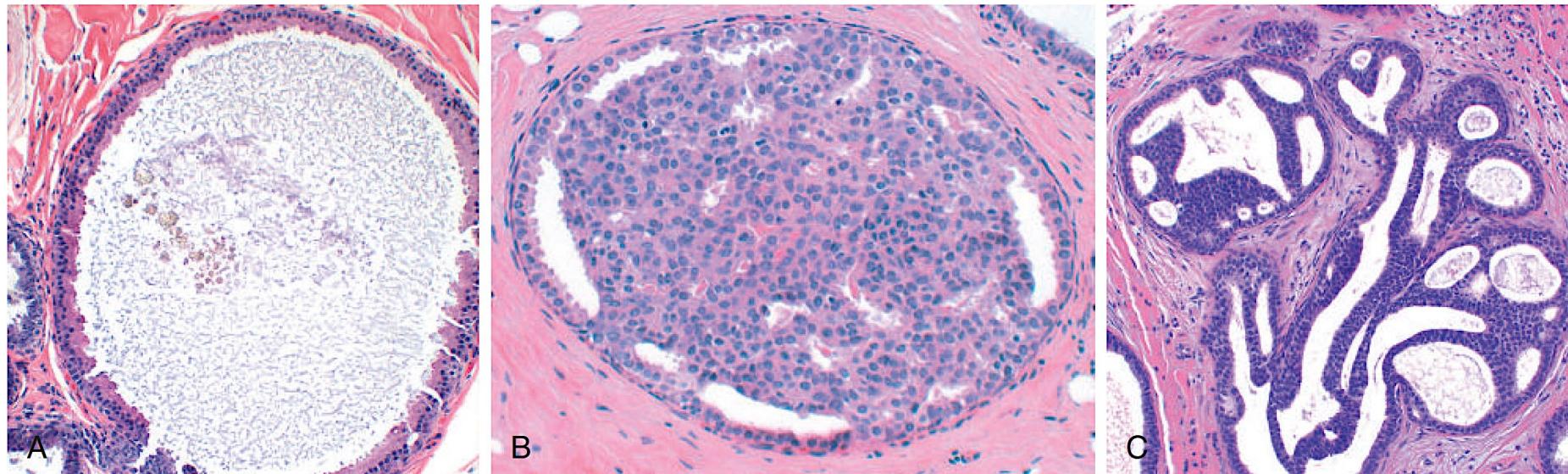


Fig. 19.25 Benign epithelial breast disease. (A) Nonproliferative disease. An apocrine cyst is shown that is a common feature of nonproliferative breast disease. (B) Proliferative breast disease is characterized by increased numbers of epithelial cells, as in this example of epithelial hyperplasia. (C) Proliferative breast disease with atypia. The proliferating epithelial cells are monomorphic in appearance and pile up to form abnormal architectural structures.



Breast Cancer - morphology

- ▶ Adenocarcinomas (95%)
- ▶ Common location – upper outer quadrant (50%) and central portion of the breast (20%)
- ▶ Morphological classification – **according whether they have invaded the basement membrane**

A. NONINVASIVE

1. Ductal carcinoma in situ
2. Lobular carcinoma in situ - ER positive and HER2 negative (low-grade cancers, respond to hormonotherapy)

B. INVASIVE

1. Invasive ductal carcinoma (includes all carcinomas that are not of a special type) – 70 to 80%
2. Invasive lobular carcinoma – 10-15%
3. Carcinoma with medullary features – 5%
4. Mucinous carcinoma – 5%
5. Tubular carcinoma – 5%
6. Other types

Breast Cancer - noninvasive (in Situ) carcinoma



- Ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS)

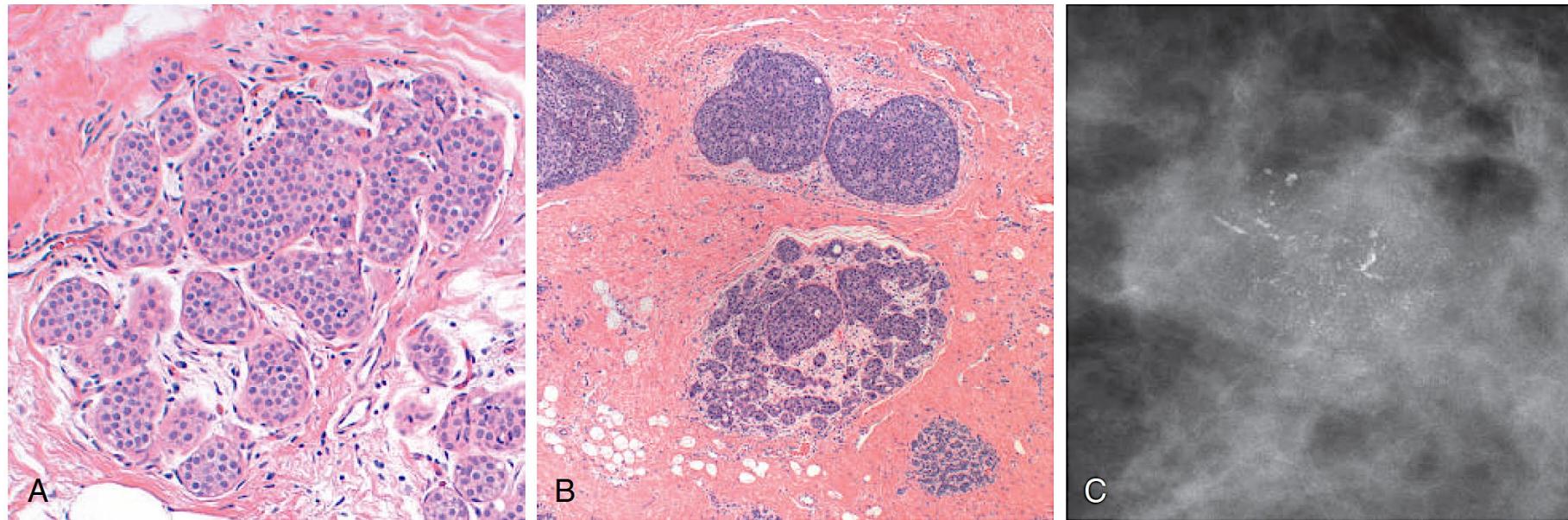


Fig. 19.28 Carcinoma in situ. (A) Lobular carcinoma in situ (LCIS). (B) Ductal carcinoma in situ (DCIS). DCIS partially involves the lobule in the lower half of this photo and has completely effaced the upper lobules, producing a ductlike appearance. (C) Mammographic detection of calcifications associated with DCIS.

Breast Cancer - invasive carcinoma

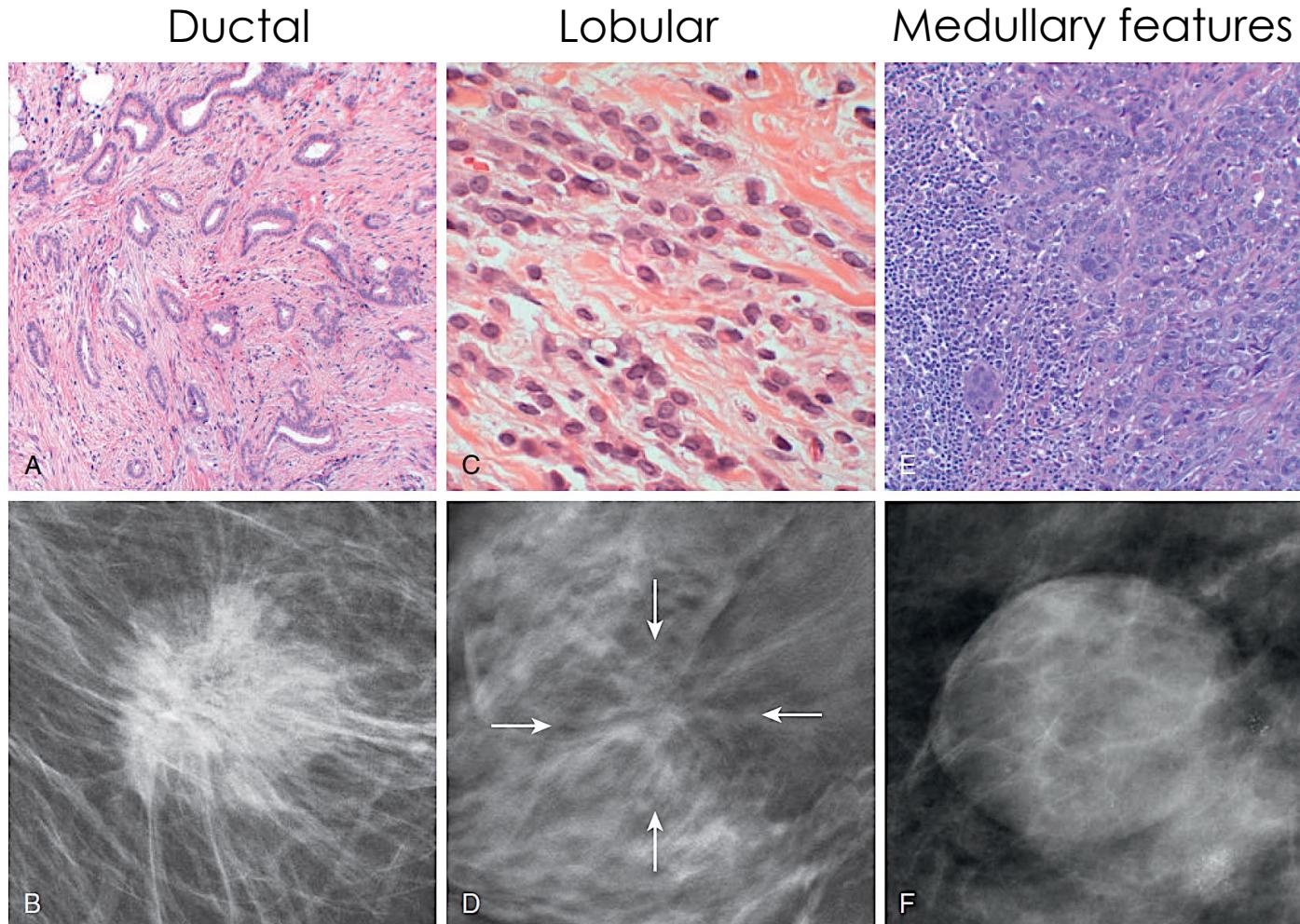


Fig. 19.29 Growth patterns of invasive breast carcinomas. (A) Most grow as tubules ("ductal" carcinoma) and stimulate a reactive desmoplastic stromal proliferation. In mammograms (B), these carcinomas appear as dense masses with spicular margins resulting from invasion of adjacent radiolucent breast tissue. (C) Lobular carcinomas are composed of noncohesive tumor cells that invade as linear cords of cells and induce little stromal response. Accordingly, in mammograms (D) lobular carcinomas often appear as relatively subtle, irregular masses (arrows). (E) Uncommonly, carcinomas consist of tightly adhesive clusters of cells, as in this carcinoma with medullary features, or when there is abundant extracellular mucin production. (F) Such tumors may appear as well-circumscribed masses in mammograms, mimicking the appearance of a benign lesion.

Breast Cancer



- ▶ Most clinically useful classification system – immunohistochemistry
- ▶ Expression of hormone receptors (estrogen receptor – ER, progesterone receptor – PR and the expression of the human epidermal growth factor receptor 2 – HER2
 - **ER positive** (HER2 negative) – 50-65% of cancers
 - **HER2 positive** (ER positive or negative) – 10-20% of cancers
 - **Triple negative** (ER, PR, and HER2 negative) – 10-20% of cancers

Breast Cancer



- ▶ Alternative classification system – gene expression profiling
- ▶ Used in the context of clinical research
 - **LUMINAL A** - ER positive and HER2 negative (low-grade cancers, respond to hormonotherapy)
 - **LUMINAL B** - ER positive and HER2 positive (higher grade cancers)
 - **HER2-ENRICHED** – HER2 positive and ER negative
 - **BASAL-LIKE** – by gene expression profiling the majority of these tumors resembles basally located myoepithelial cells and are ER-negative and HER2-negative



Table 19.7 Summary of the Major Biologic Types of Breast Cancer

Feature	ER Positive/HER2 Negative	HER2 Positive (ER Positive or Negative)	Triple Negative (ER, PR, and HER2 Negative)
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline <i>BRCA2</i> mutation carriers	Young women; germline <i>TP53</i> mutation carriers	Young women; germline <i>BRCA1</i> mutation carriers
Ethnicity			
European/American	70%	18%	12%
African/American	52%	22%	26%
Hispanic	60%	24%	16%
Asian/Pacific Islander	63%	26%	11%
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	Low grade (<10%), higher grade (10%)	ER positive (15%), ER negative (>30%)	30%
Timing of relapse	May be late (>10 years after diagnosis)	Usually short (<10 years after diagnosis)	Usually short (<8 years after diagnosis)
Metastatic sites	Bone (70%), viscera (25%), brain (<10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Similar group defined by mRNA profiling	Luminal A (low grade), luminal B (high grade)	Luminal B (ER positive), HER2-enriched (ER negative)	Basal-like
Common special histologic types	Lobular, tubular, mucinous, papillary	Apocrine, micropapillary	Carcinoma with medullary features
Common somatic mutations	<i>PIK3CA</i> (40%), <i>TP53</i> (26%)	<i>TP53</i> (75%), <i>PIK3CA</i> (40%)	<i>TP53</i> (85%)

PIK3CA encodes phosphoinositide 3-kinase (PI3K).



Breast Cancer – clinical outcome

- ▶ Prediction based on the molecular and morphologic features of the cancer and stage at the time of diagnosis
 - A. Biologic type
 - B. RNA expression profiling
 - C. Tumor stage (TNM)

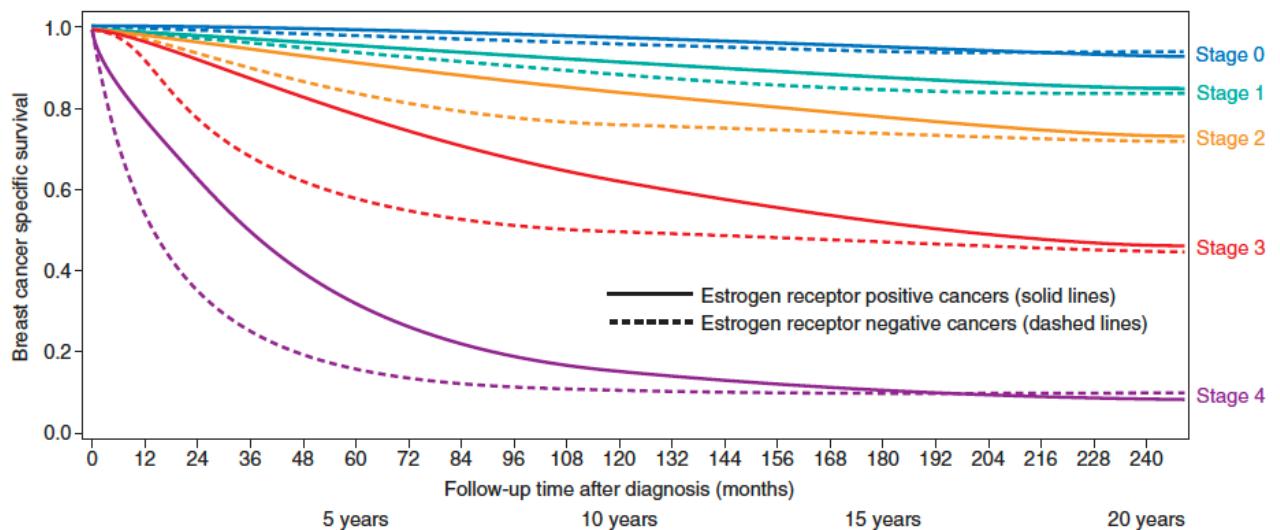


Fig. 19.30 Ten-year breast cancer specific survival according to AJCC stage for ER-positive and ER-negative cancers. Both stage and biologic type of cancer are important determinants of survival. ER-positive invasive cancers have improved survival over ER-negative cancers at all stages, but this advantage diminishes after 5 years because of late recurrences of ER-positive tumors. (Graph courtesy of Dr. Stephanie Wong; data from SEER-18, 1992–2012. <http://seer.cancer.gov>.)

Ulcerative lesions caused by mTOR inhibitors



Mucositis induced by chemotherapy



BROJ



Pilotte AP, et al. *Clin J Oncol Nurs.* 2011;15(5):E83-E89
Sonis S, et al. *Cancer.* 2010;116(1):210-215
Franca CM, personal archives

Review questions

1. List the breast benign epithelial lesions and how each type is associated with breast cancer risk.
2. Provide a review of the breast cancer classification system tumors based on the expression of hormone receptors and gene profiling. Try to understand the overlap between both classifications.
3. Describe the morphological classification of breast cancer.
4. Provide the parameters used for the prediction of breast cancer outcomes.
5. List the possible oral manifestations of metastatic breast cancer treatment.



Thank You

mirandaf@ohsu.edu