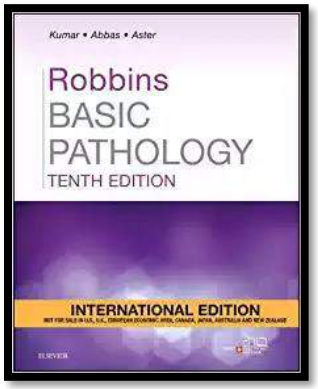
FEMALE GENITAL SYSTEM & BREAST PATHOLOGY

Mousa Al-Abbadi, MD, FCAP,CPE, CPHQ,FIAC, ABMQ
Professor of Pathology & Cytopathology
University of Jordan
College of Medicine

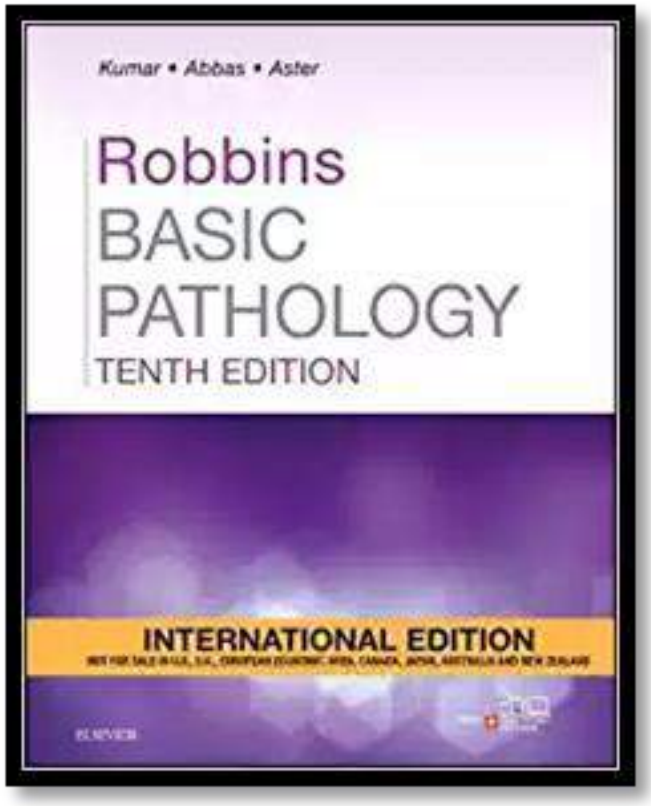
MY DUTIES

- 8 lectures
- Simplify
- Understand the concepts
- Help U all Understand…understand… understand X 10…only then memorize and recall
- Answer questions & inquiries
- Respect



YOUR DUTIES

This Book is your main source of knowledge & EXAM QUESTIONS



YOUR DUTIES

- **ON TIME ATTENDANCE**
- **Plz…plz…plz…NO CHATTING during lecture**
- **Understand first then memorize and recall**
- **Respect to the process**
- **NO MOBILE**
- **No inquiries about the nature of the exam…I tell you**

PLEASE DON'T ASK THESE QUESTIONS AT ALL

- How many questions on my material?
- What should we concentrate on?
- Are the slides enough?
- Should we memorize this or that?
- Is this or that required?

[YOU SHOULD NOT ONLY STUDY FOR THE EXAM]

[YOU ARE NOT STUDYING FOR ME EITHER]

[YOU ARE LEARNING SO THAT YOU WILL BE A GOOD CARING & THOROUGH PHYSICIAN WHO WILL APPLY THE STNADRAD OF CARE]

REMEMBER

“Success in life is 90% hard work and 10% talent, luck and high IQ”

INTENDED LEARNING OBJECTIVES

- **Recognize the common infections of the vulva & vagina**
- **Understand the pathogenesis of common vulvar and vaginal tumors**
- **Comprehend common infections of the cervix**
- **Grasp the details of HPV associated cervical carcinogenesis and the successful screening program**

ILOs….continue

- **Recognize and understand common uterine diseases and its clinicopathological features (endometritis, adenomyosis, endometriosis, abnormal uterine bleeding)**
- **Absorb the common benign proliferative & neoplastic uterine diseases (leiomyoma, polyps, endometrial hyperplasia).**
- **Recognize common endometrial malignancies and its pathogenesis (endometrial carcinoma, leiomyosarcoma & MMT)**

ILOs….continue

- **Recognize the pathology of ovarian and fallopian tube cysts and its diagnostic features**
- **Understand the clinicopathological characteristics of polycystic ovarian syndrome**
- **Identify common ovarian tumors and recognize their clinicopathological features**
- **Grasp common benign diseases of placenta (infections, ectopic pregnancy)**

ILOs….continue

- **Understand the concept of gestational trophoblastic diseases (molar pregnancy, invasive mole, choriocarcinoma and placental site trophoblastic tumor)**
- **Recognize and understand the pathogenesis of preeclampsia and eclampsia (Toxemia of pregnancy)**

ILOs….continue

- Recognize the variable clinical presentations of breast diseases
- Brief grasp of common inflammatory breast processes
- Understand the concept of stromal breast neoplasms
- Recognize the pathology of benign breast epithelial tumors
- Understand the details of mammary carcinoma pathogenesis (epidemiology, risk factors, and clinicopathological features)

BREAST PATHOLOGY

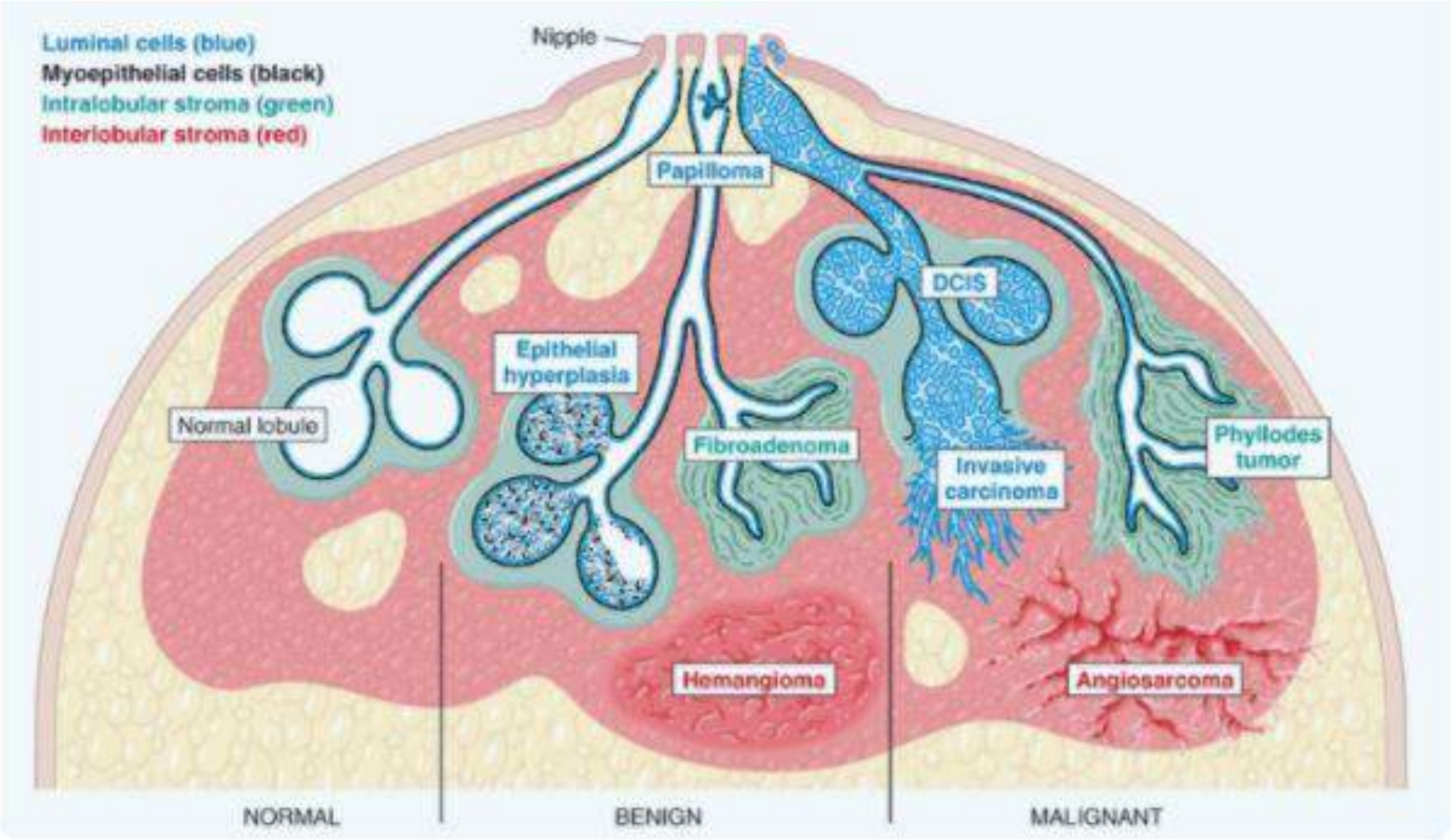


FIG. 19.22 Origins of breast disorders. Benign epithelial lesions include intraductal pa…

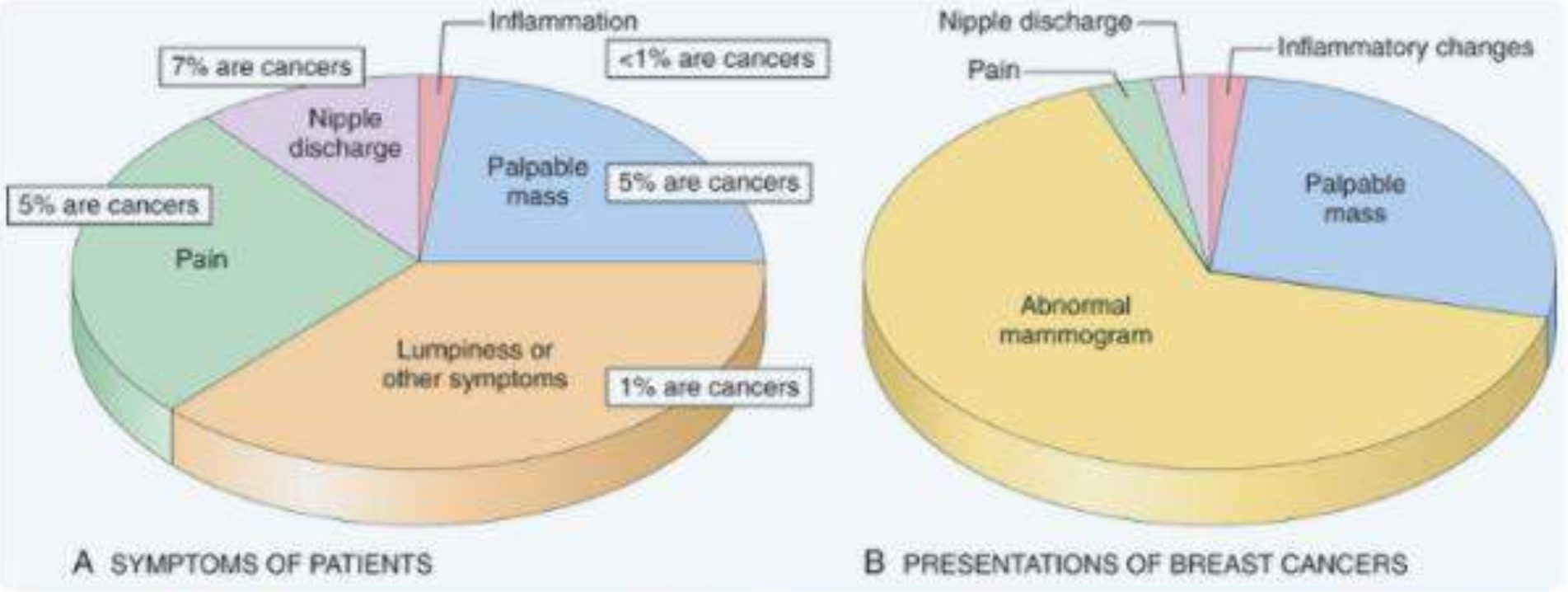


FIG. 19.23 Presenting symptoms of breast disease. (A) Common breast-related sympto…

CLINICAL PRESENTATIONS OF BREAST DISEASES:

- **Pain**
- **Inflammation (edema and erythema)**
- **Nipple discharge (bloody is serious)**
- **“Lumpiness”**
- **Palpable masses**
- **Gynecomastia (males)**

FACTS

- **Likelihood of malignancy increase with age**
- **Mammography was introduced in the 1980s to detect asymptomatic breast cancer cases (It did), now smaller (1 cm) cancers are found**
- **Palpable Ca breast (2-3 cm)**
- **Abnormal mammogram: increase likelihood of cancer with increase in age**

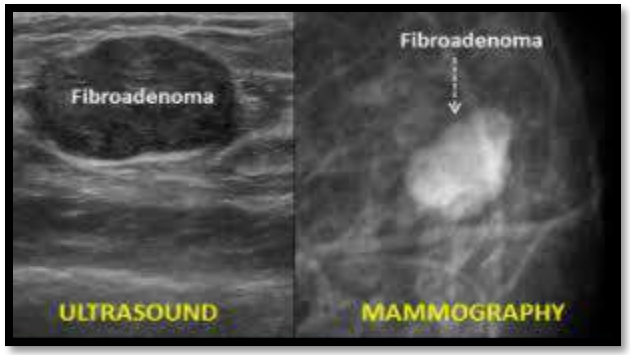
INFLAMMATORY PROCESSES:

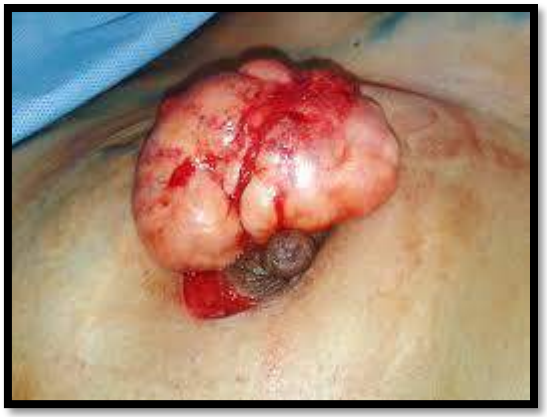
- **Infections, autoimmune diseases, and F. Body type reactions.**
- **Lactational infections (mastitis, staph) may be complicated by abscess formation which needs surgical drainage**

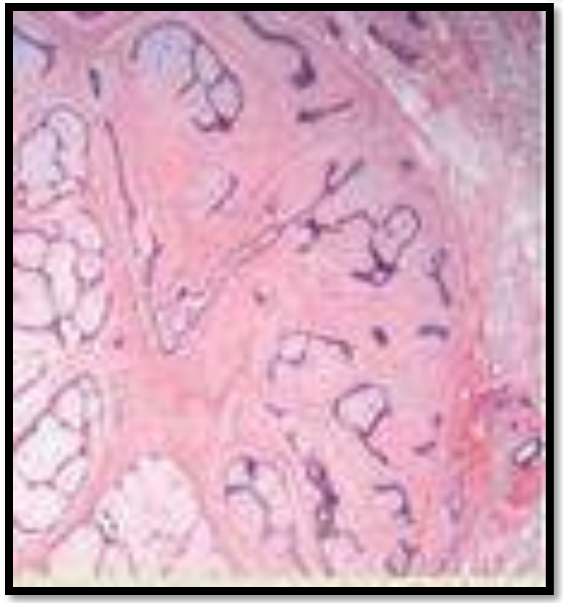
STROMAL NEOPLASMS:

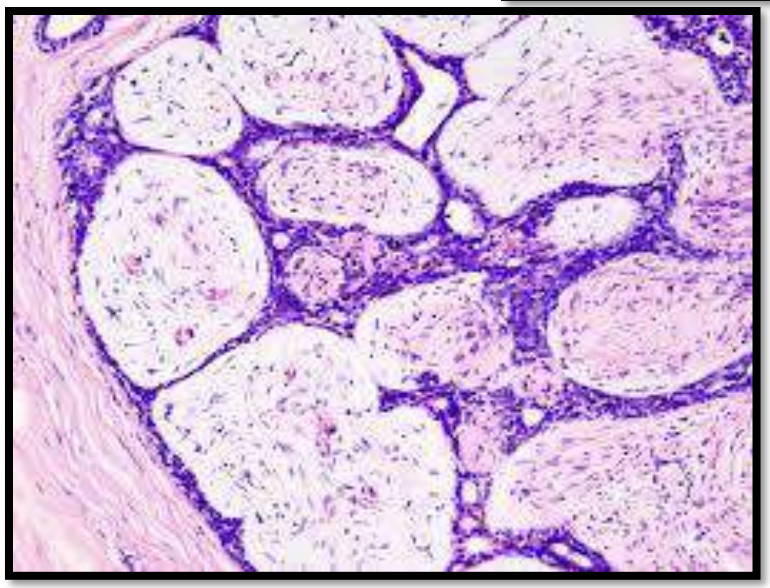
FIBROADENOMA	PHYLLODES TUMORS
• Biphasic tumor • Low cellularity • Slit-like glands • Well-circumscribed mass, mobile (breast mouse) • Young age, Always benign • Surgical removal (anxiety relief and rule out malignancy)	• Stroma >>> epithelia • Stromal hypercellularity • Leaf-like appearance (phyllodes = Greek for leaf) • Not well-circumscribed • Older age, can be high grade and malignant • Surgical removal with safe margin (avoid recurrence)

FIBROADENOMA FEATURES:

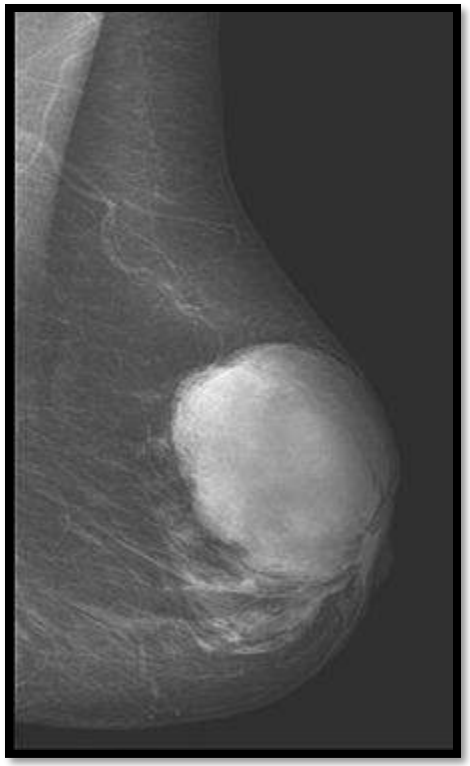


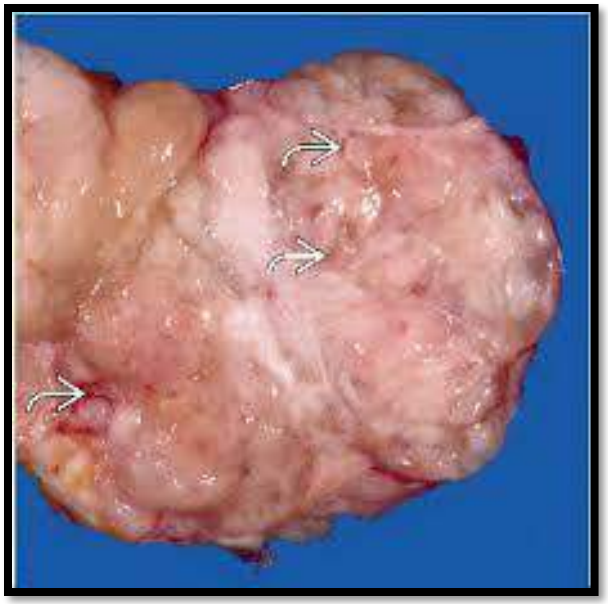


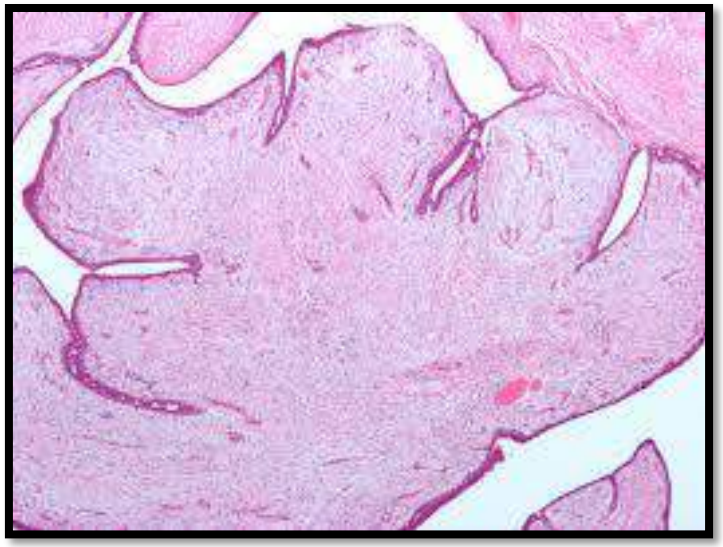


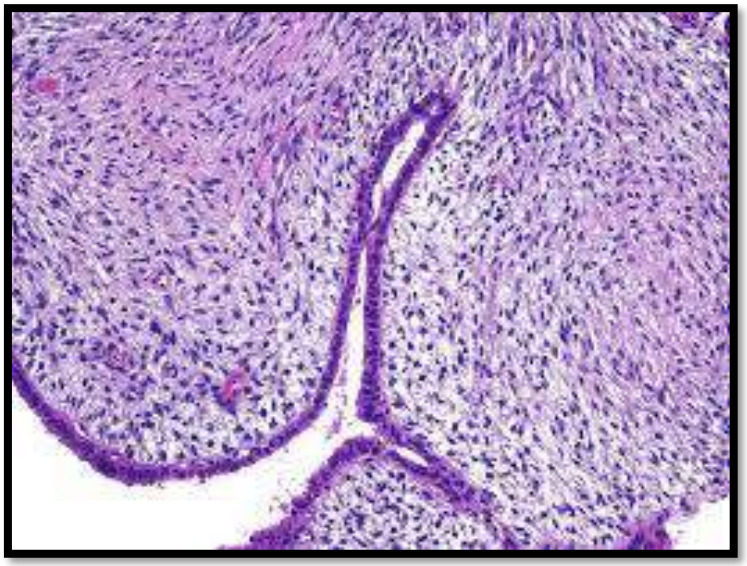


PHYLLODES TUMOR FEATURES





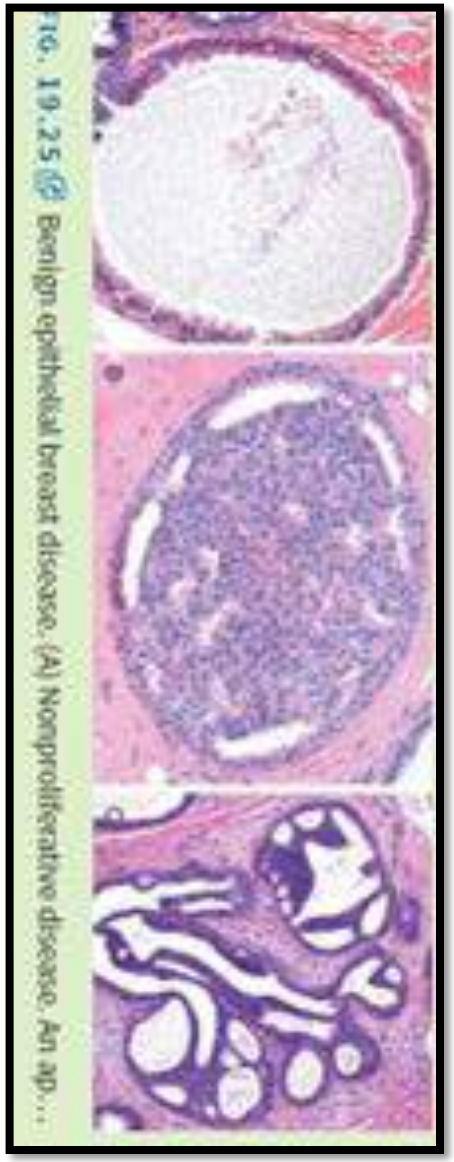




Subclassification of Phyllodes Tumors

	Benign	Borderline	Malignant
Mitoses/10 hpfs	0-3	4-9	10 or more
Stromal cellularity/atypia	mild	moderate	marked
Stromal overgrowth	-	+/-	+
Tumor interface	circumscribed	circumscribed or infiltrative	infiltrative

BENIGN EPITHELIAL LESIONS:



Non-proliferative disease: Cysts and fibrocystic changes; no increased risk of malignancy

Proliferative disease without atypia: usual-type epithelial hyperplasia, no atypia; slight increased risk of malignancy 5-6% life time risk

Proliferative disease with atypia: ADH and ALH, atypia present; modest increased risk of malignancy 13-17% life time risk

TABLE 19.6 Factors Associated With Development of Invasive Carcinoma

Factor	Relative Risk[a]	Absolute Lifetime Risk[a]
Women with no risk factors	1.0	3%
First-degree relative(s) with breast cancer[b]	1.2–9.0	4%–30%
Germline tumor suppressor gene mutation (e.g., *BRCA1* mutation)	2.0–45.0	6% to >90%
Menstrual History		
Age at menarche <12 years	1.3	4%
Age at menopause >55 years	1.5–2.0	5%–6%
Pregnancy		
First live birth <20 years (protective)	0.5	1.6%
First live birth 20–35 years	1.5–2.0	5%–6%
First live birth >35 years	2.0–3.0	6%–10%
Never pregnant (nulliparous)	3.0	10%
Breast-feeding (slightly protective)	0.8	2.6%
Benign Breast Disease		
Proliferative disease without atypia	1.5–2.0	5%–6%
Proliferative disease with atypia (ALH and ADH)	4.0–5.0	13%–17%
Carcinoma in situ (ductal or lobular)	8.0–10.0	25%–30%
Ionizing radiation	1.1–1.4	3.6%–4.6%
Mammographic density	3.0–7.0	10%–23%
Postmenopausal obesity and weight gain	1.1–3.0	3.6%–10%
Postmenopausal hormone replacement	1.1–3.0	3.6%–10%
Alcohol consumption	1.1–1.4	3.6%–4.6%
Alcohol consumption	1.1–1.4	3.6%–4.6%

MAMMARY CARCINOMA:

- **Most common women malignancy (excluding non-melanotic skin cancer)**
- **Incidence stable in USA; however, the incidence and mortality is increasing world-wide due to:**
  - **Delayed childbearing**
  - **Fewer pregnancies**
  - **Reduced breast feeding**
  - **No access to proper healthcare**

MAMMARY CARCINOMA:

- **Lifetime risk 1/8 (USA)**
- **Cancer death; 2nd after lung**
- **Mortality decreases from 30 to 20% due to:**
  - **Better screening**
  - **Diagnosing more early stage**
  - **Better treatment**

CLASSIFICATIONS OF MAMMARY CARCINOMA:

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 *BRCA2* mutation carriers	Young women; germline *TP53* mutation carriers	Young women; germline *BRCA1* 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	*PIK3CA* (40%), *TP53* (26%)	*TP53* (75%), *PIK3CA* (40%)	*TP53* (85%)

PIK3CA encodes phosphoinositide 3-kinase (PI3K).

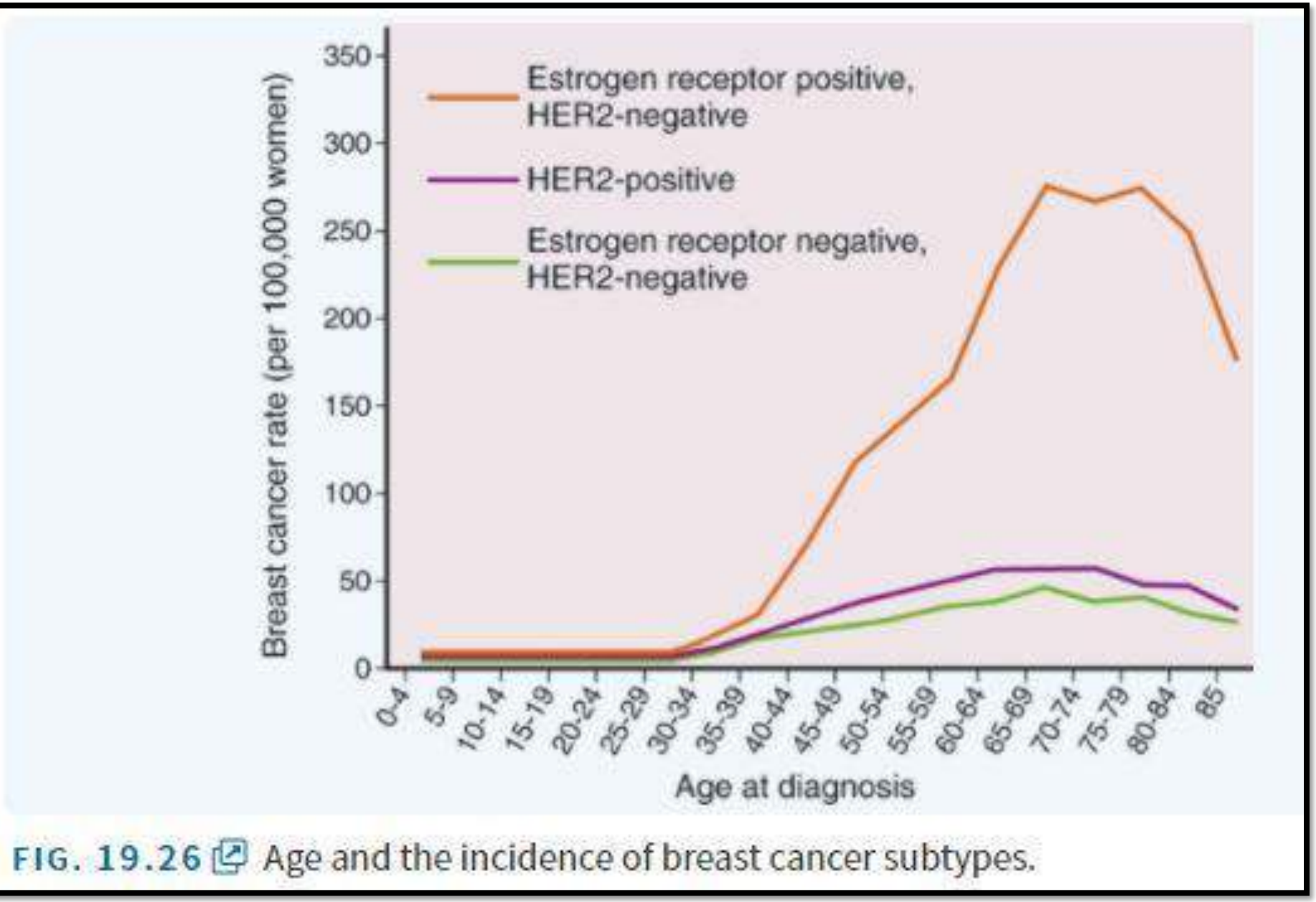
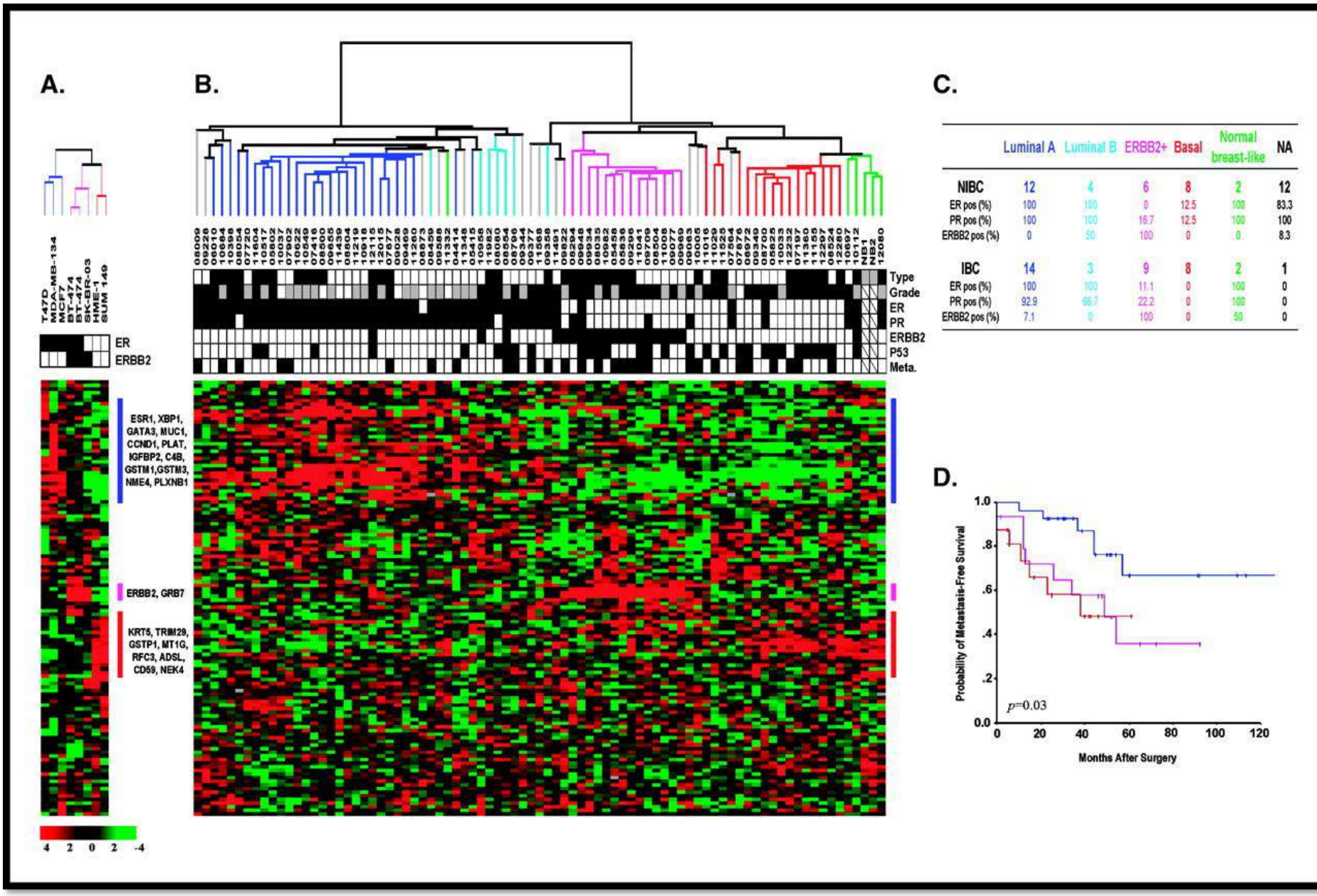


FIG. 19.26 Age and the incidence of breast cancer subtypes.

CLASSIFICATION BY GENE EXPRESSION PROFILING

LUMINAL A	LOWER GRADE, ER +VE, HER-2-NEU -VE
LUMINAL B	HIGHER GRADE, ER+VE, HER-2-NEU +VE
HER-2-ENRICHED	HER-2-NEU +VE, ER-VE
BASAL-LIKE	HER-2-NEU -VE, ER-VE

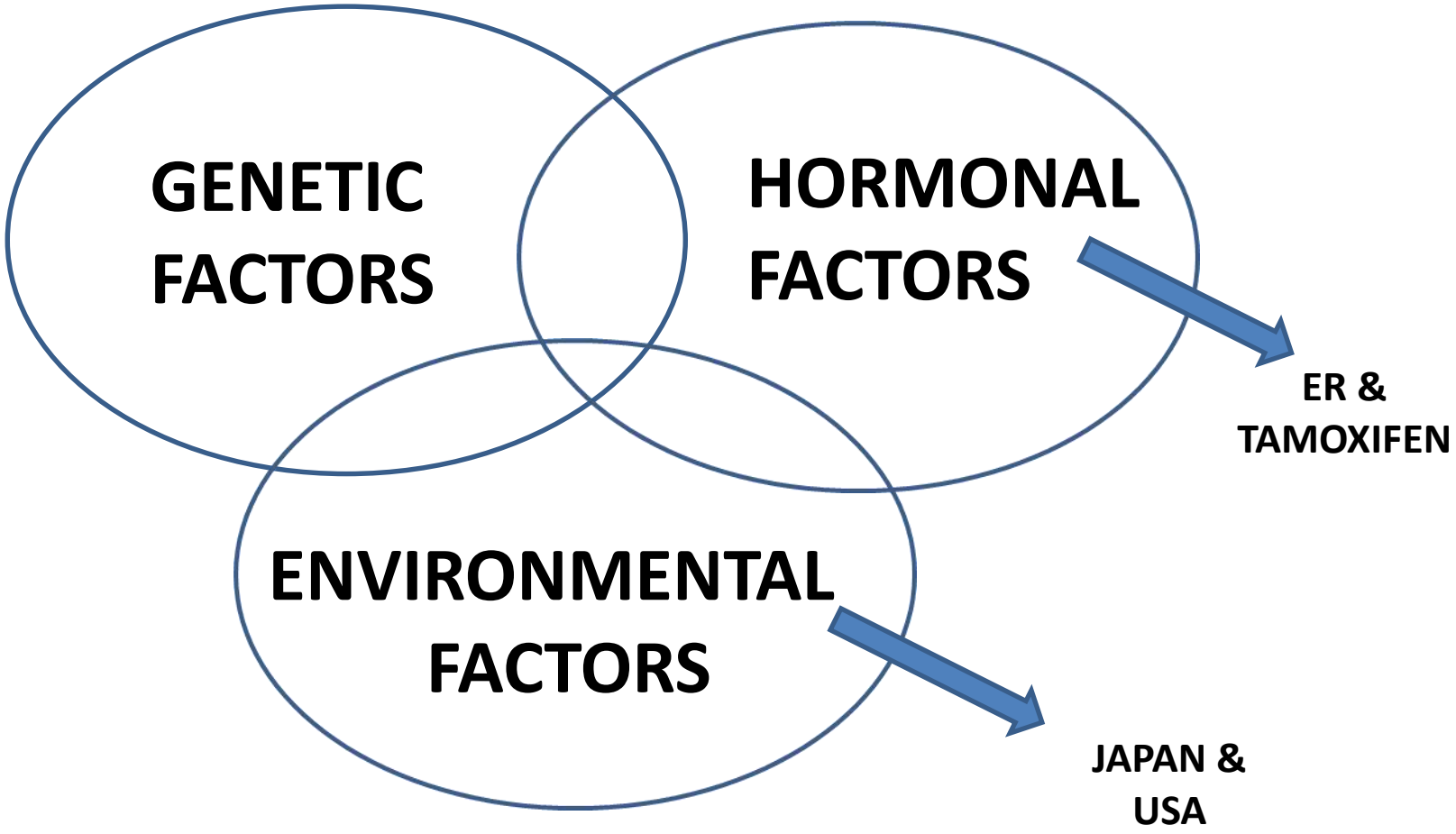


	Luminal A	Luminal B	ERBB2+	Basal	Normal breast-like	NA
NIBC	12	4	6	8	2	12
ER pos (%)	100	100	0	12.5	100	83.3
PR pos (%)	100	100	16.7	12.5	100	100
ERBB2 pos (%)	0	50	100	0	0	8.3
IBC	14	3	9	8	2	1
ER pos (%)	100	100	11.1	0	100	0
PR pos (%)	92.9	66.7	22.2	0	100	0
ERBB2 pos (%)	7.1	0	100	0	50	0

EPIDEMIOLOGY & RISK FACTORS

- 1. Age and gender
- 2. Family history
- 3. Geography (diet, late pregnancy, breast feeding)
- 4. Race and ethnicity (ER+ve European; worse cancers in hispanic and AA and at younger age)
- 5. Reproductive hx. (early menarche, nulliparity, no breast feeding, older age at pregnancy)…more Estrogenic effect
- 6. Ionizing radiation at younger age
- 7. Other factors: post M obesity, HRT, Mammographic density, alcohol consumption

PATHOGENESIS:



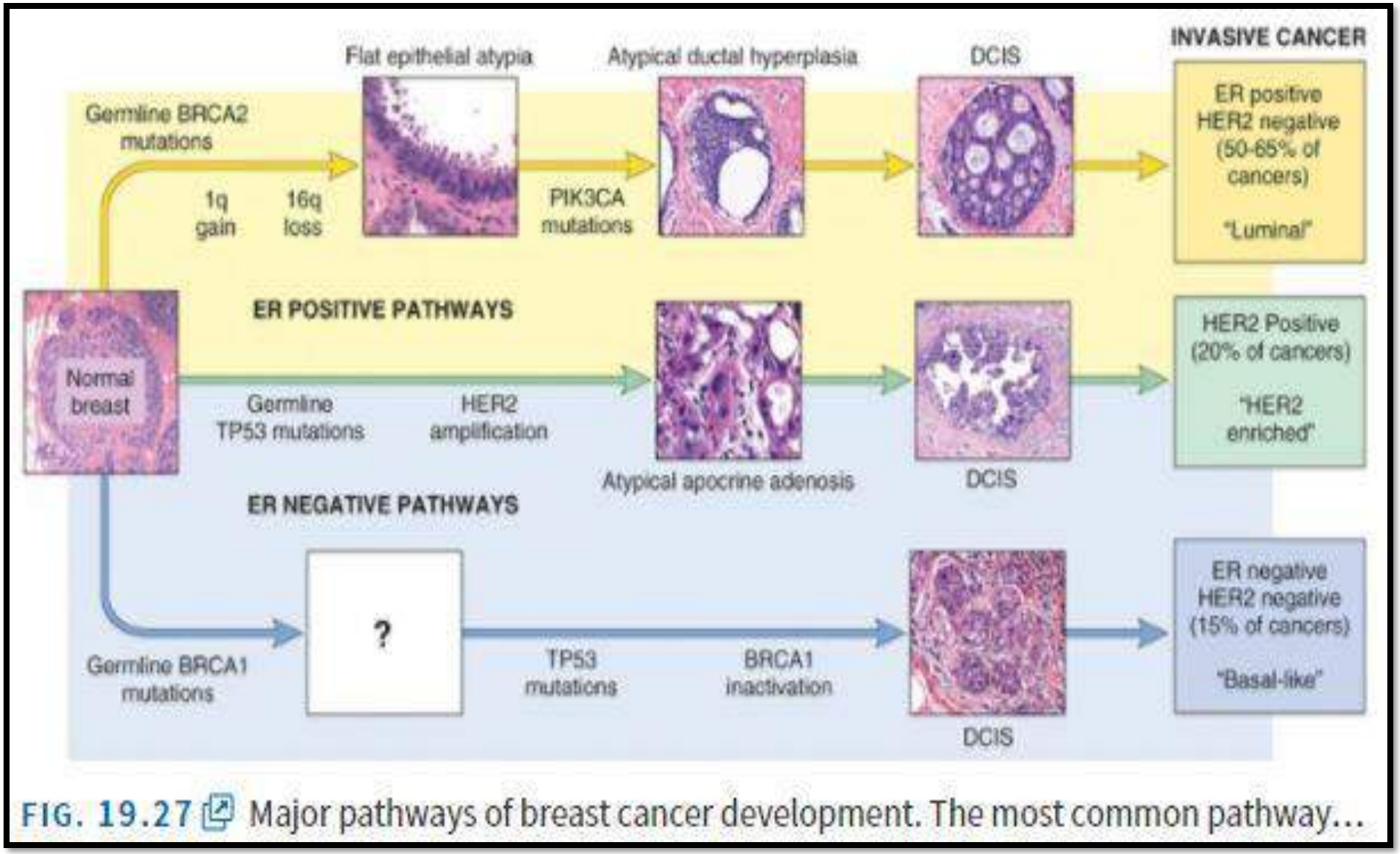


FIG. 19.27 Major pathways of breast cancer development. The most common pathway…

CLASSIFICATION UNDER THE MICROSCOPE (MORPHOLOGICAL CLASSIFICATION):

NON –INVASIVE CARCINOMA	INVASIVE CARCINOMA
Ductal carcinoma in situ (DCIS) Lobular carcinoma in situ (LCIS)	Invasive ductal carcinoma (IDC) 70-80% Invasive lobular carcinoma (ILC) 10-15% Medullary carcinoma 5% Colloid (mucinous carcinoma) 5% Tubular carcinoma 5% Other types

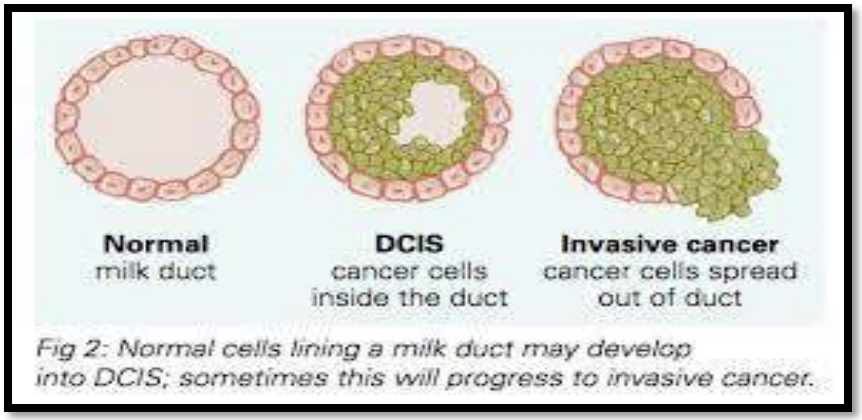
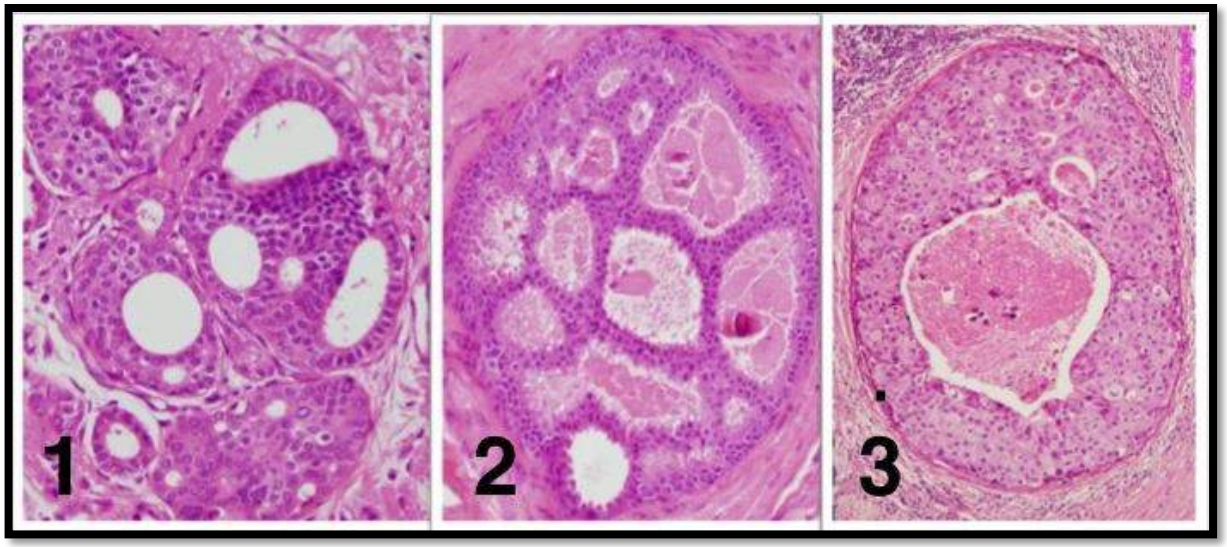
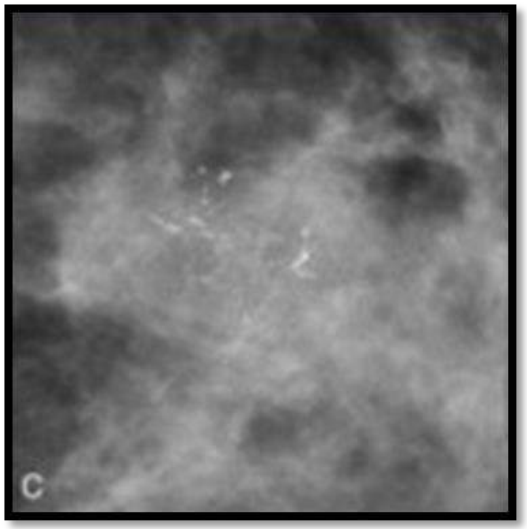


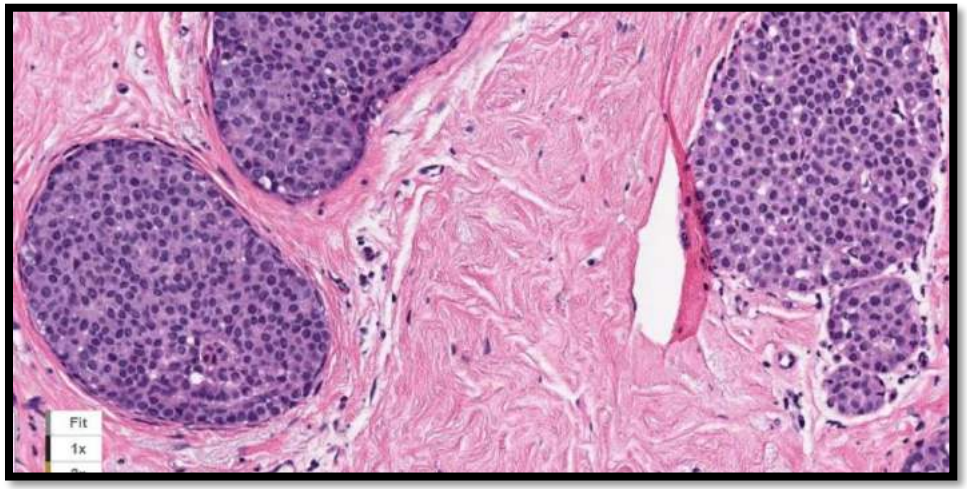
Fig 2: Normal cells lining a milk duct may develop into DCIS; sometimes this will progress to invasive cancer.

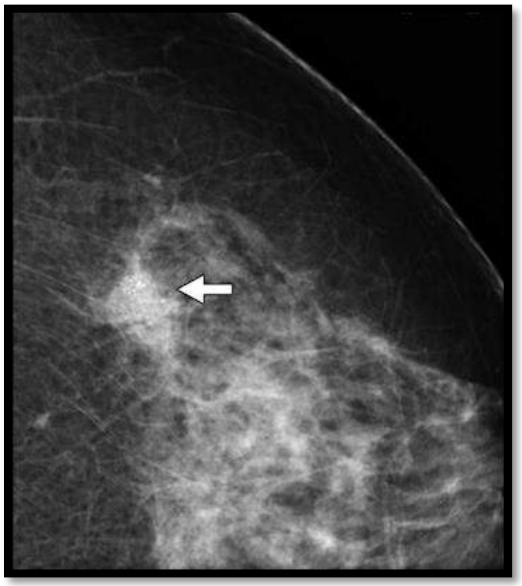
DCIS





LCIS





INVASIVE CARCINOMA

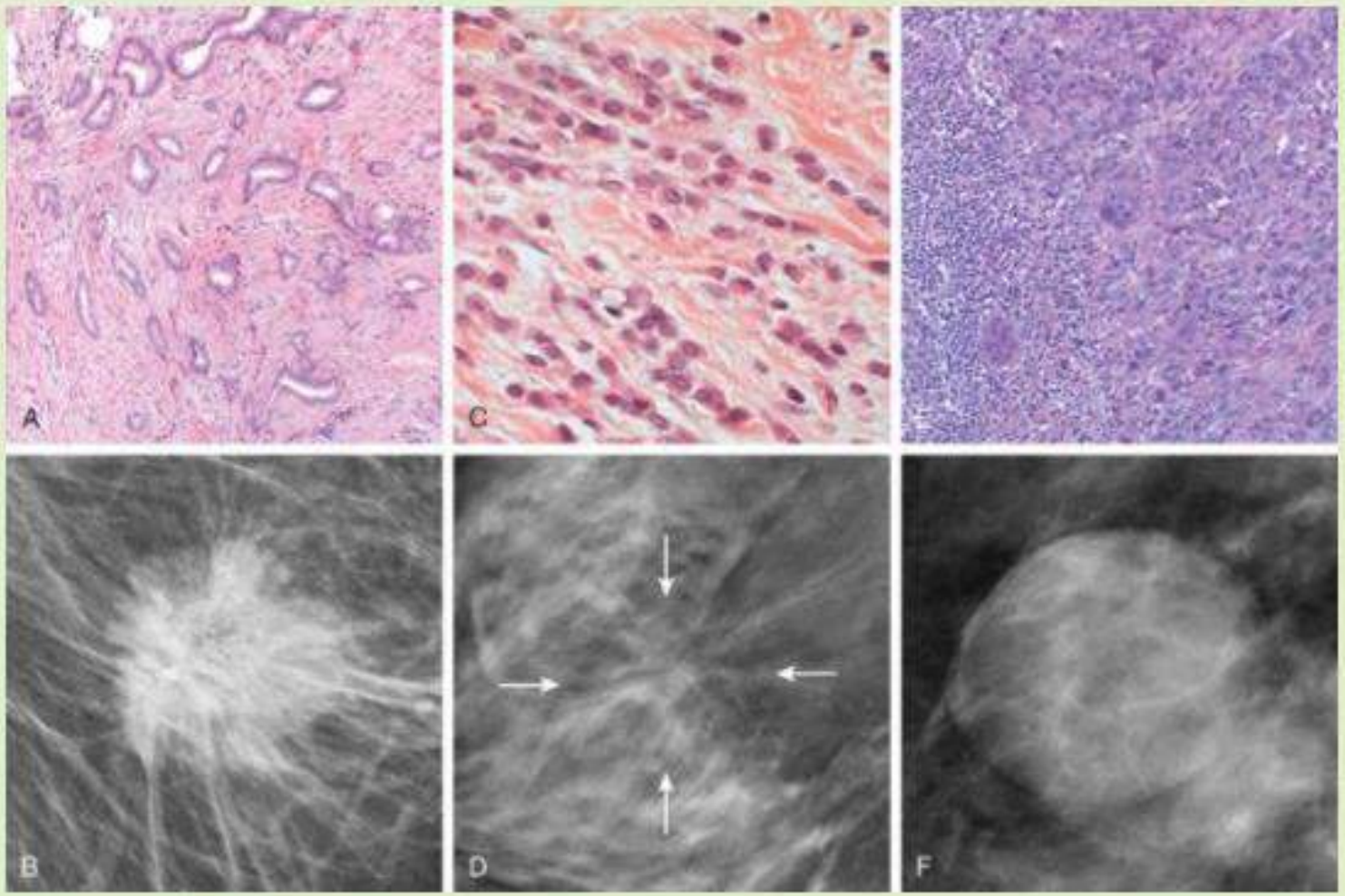
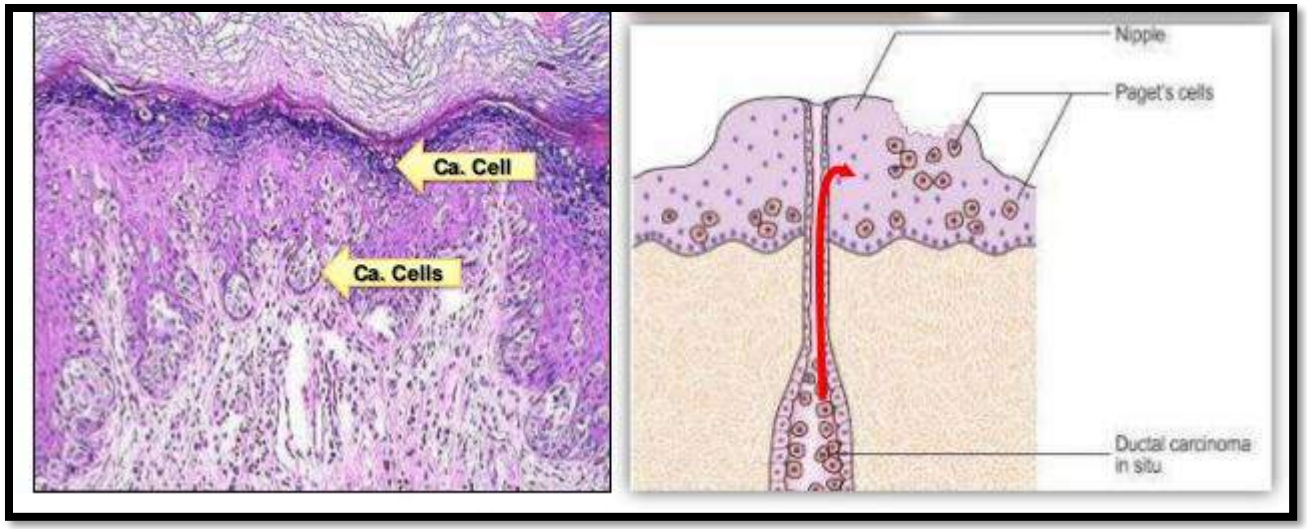
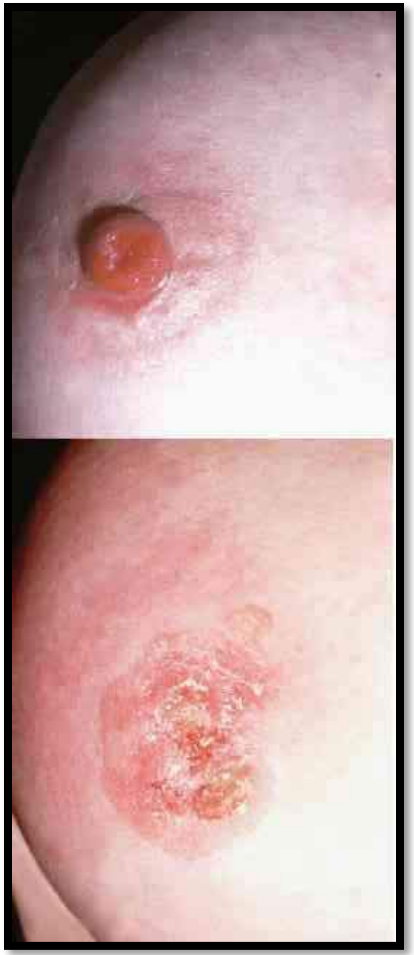


FIG. 19.29 Growth patterns of invasive breast carcinomas. (A) Most grow as tub…

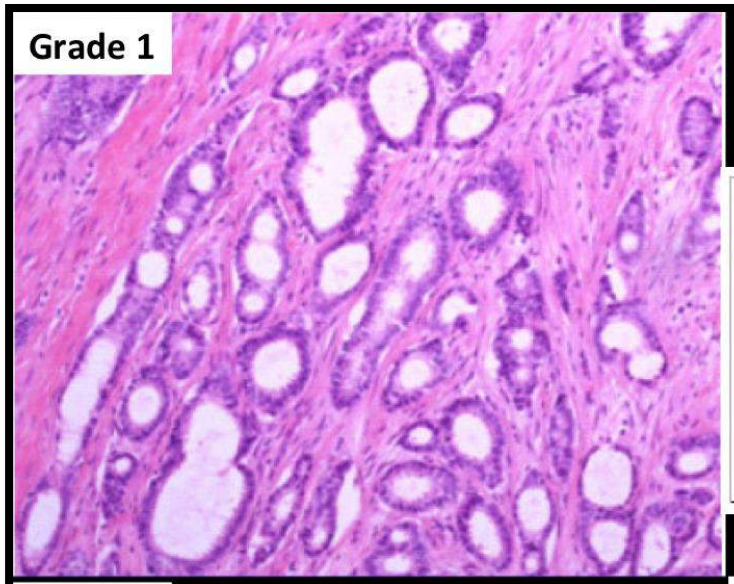
PAGET DISEASE OF THE NIPPLE:

- **Spread of carcinoma cells into nipple ducts and skin**

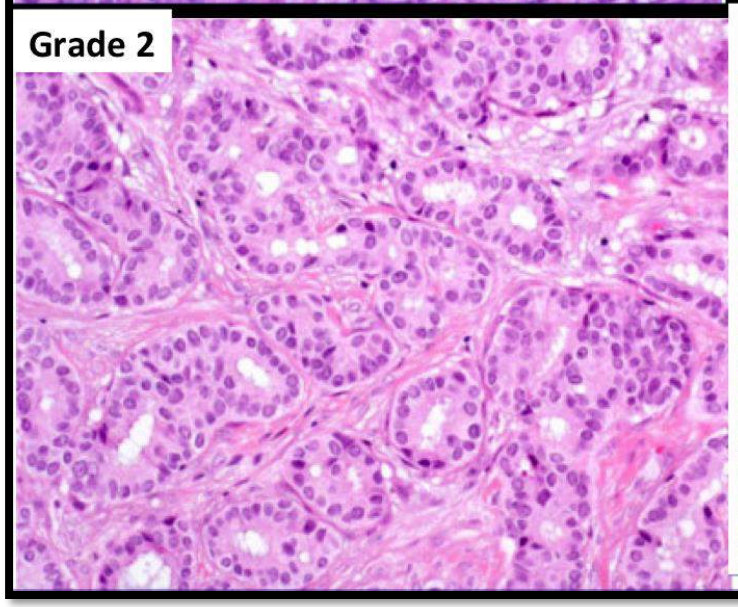


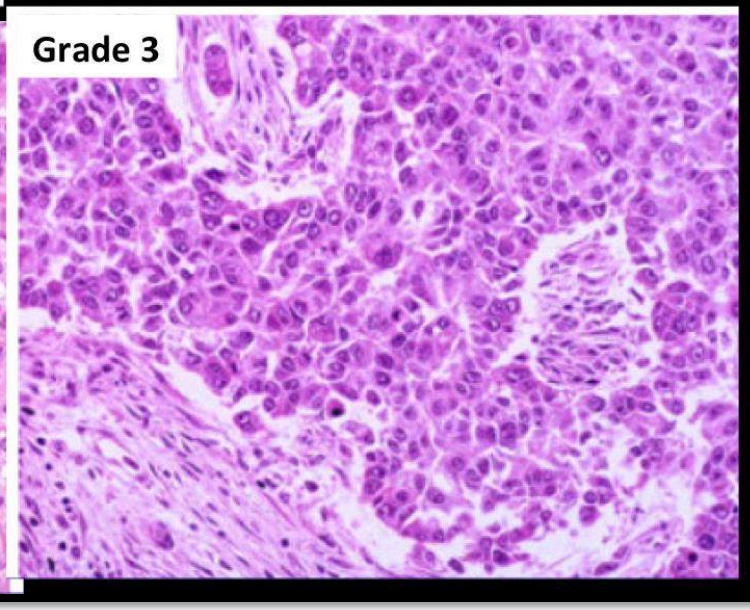


GRADING OF BREAST CANCER: 1-3 SCORE (GLANDS, NUCLEI & MITOSIS)



Total Feature Score	Tumor Grade	Appearance of Cells
3-5	Grade 1 Tumor	Well-differentiated (appear normal, growing slowly, not aggressive)
6-7	Grade 2 Tumor	Moderately-differentiated (semi-normal, growing moderately fast)
8-9	Grade 3 Tumor	Poorly-differentiated (abnormal, growing quickly, aggressive)





CLINICAL FEATURES:

- **Unscreened: palpable mass, 2-3 cm, 50% spread to regional lymph nodes**
- **Screened; 60% of cancer discovered before symptoms; 20% are in situ carcinomas.**
- **IC in screened are 1-2 cm, 15% spread to LN at time of dx.**
- **“Interval cancers”: palpable discovered between screening intervals (high grade)**
- **Behavior depends on: Molecular, morphological and stage of cancer at time of dx**

CLINICAL OUTCOME OF BREAST CANCER DEPENDS ON:

- **Biologic type:**
  - **Grade and hormonal studies (targeted therapy)**
- **RNA expression profiling (identify slow growing ER +ve cancers to avoid toxic CT)**
- **Tumor stage: measure of extent of tumor. TNM staging system at time of dx: T: tumor size. N: number of nodes involved. M: presence of distant metastasis**

TNM CATEGORIES:

Triple-negative & Her-2-Neu +ve breast cancers are more likely to metastasize to brain and viscera

ER +ve cancers: are more likely to metastasize to bone

Table 1: Breast Cancer T, N, and M Categories

Primary Tumor (T):

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ (DCIS, LCIS, or Paget's disease of the nipple with no tumor mass)
T1: Tumor is ≤2 cm
T2: Tumor is >2 cm but <5 cm
T3: Tumor is >5 cm
T4: Tumor of any size growing into the chest wall or skin

Lymph Node Status (N):

NX: Nearby lymph nodes cannot be assessed
N0: Cancer has not spread to nearby lymph nodes
N1: Cancer has spread to 1 to 3 axillary lymph nodes, and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy
N2: Cancer has spread to 4 to 9 axillary lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes
N3: One of the following applies:
- Cancer has spread to 10 or more axillary lymph nodes
- Cancer has spread to the lymph nodes under the clavicle
- Cancer has spread to the lymph nodes above the clavicle
- Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes
- Cancer involves 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy

Metastases (M):

MX: Presence of distant metastases cannot be assessed
M0: No distant spread
M1: Spread to distant organs is present

DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ.
Source: References 6, 12, 21.

Stage	Definition
Stage 0 is carcinoma *in situ*	Tumors that have not grown beyond their site of origin and invaded the neighboring tissue. They include: - ductal carcinoma *in situ* - lobular carcinoma *in situ*
Stage 1	Tumor size <2 cm, metastases to other organs and tissues not available
Stage 2a	Tumor <2 cm in cross-section with involvement of the lymph node or tumor from 2 to 5 cm without involvement of the axillary lymph nodes
Stage 2b	Tumor more than 5 cm in cross-section (the result of axillary lymph node research is negative for cancer cells) or tumor from 2 to 5 cm in diameter with the involvement of axillary lymph nodes
Stage 3a	Also called local spread of *breast cancer*: tumor more than 5 cm with spread to axillary lymph nodes or tumor of any size with metastases in axillary lymph nodes, which are knitted to each other or with the surrounding tissues
Stage 3b	Tumor of any size with metastases into the skin, chest wall or internal lymph nodes of the mammary gland (located below the breast inside of the chest)
Stage 3c	Tumor of any size with a more widespread metastases and involvement of more lymph nodes
Stage 4	Defined as the presence of tumors (regardless of the sizes), spread to parts of the body that are located far removed from the chest (bones, lungs, liver, brain or distant lymph nodes)

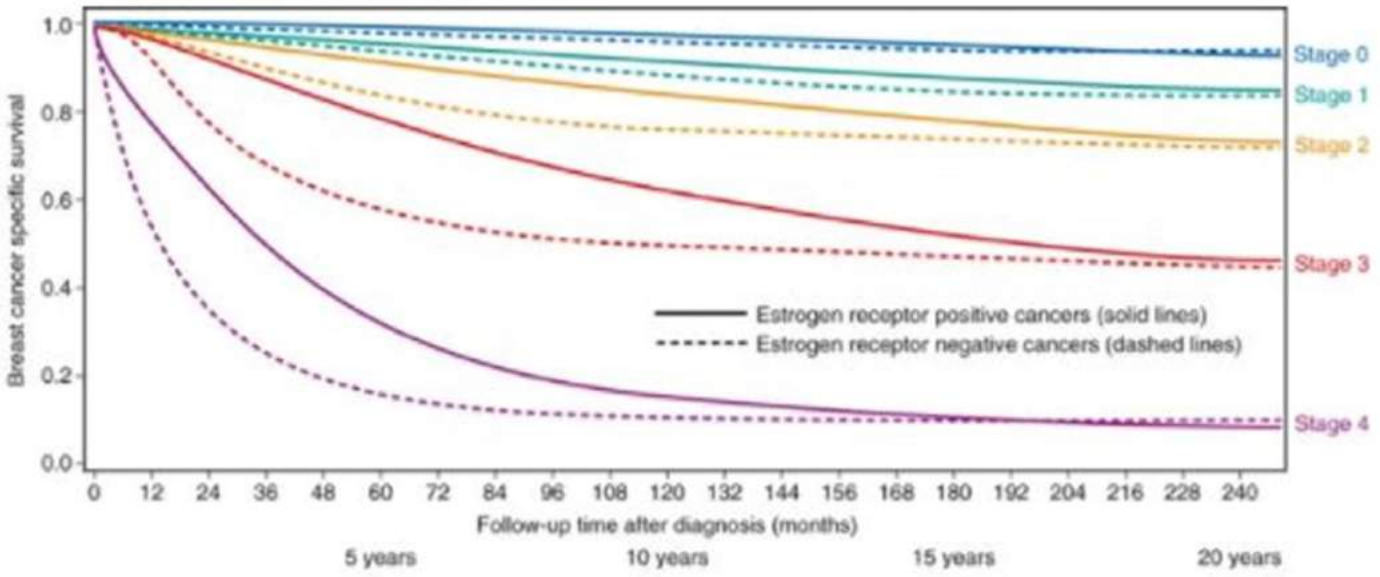


FIG. 19.30 Ten-year breast cancer specific survival according to AJCC stage for ER-p...

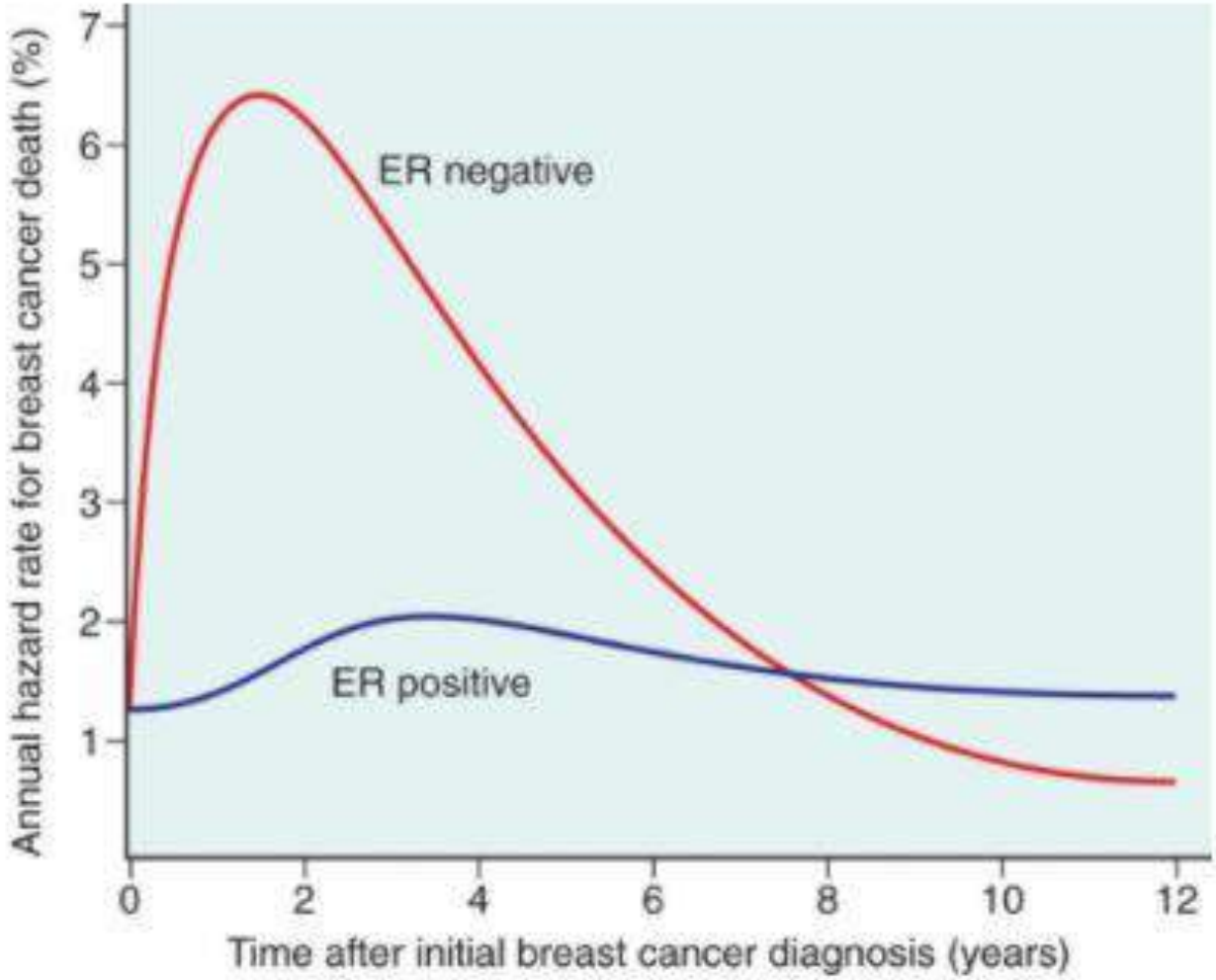


FIG. 19.31 Time to recurrence of breast cancers. The hazard ratio reflects the risk of re...

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 *BRCA2* mutation carriers	Young women; germline *TP53* mutation carriers	Young women; germline *BRCA1* 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	*PIK3CA* (40%), *TP53* (26%)	*TP53* (75%), *PIK3CA* (40%)	*TP53* (85%)

PIK3CA encodes phosphoinositide 3-kinase (PI3K).

TABLE 19.8 Targeted Treatment of Breast Cancer

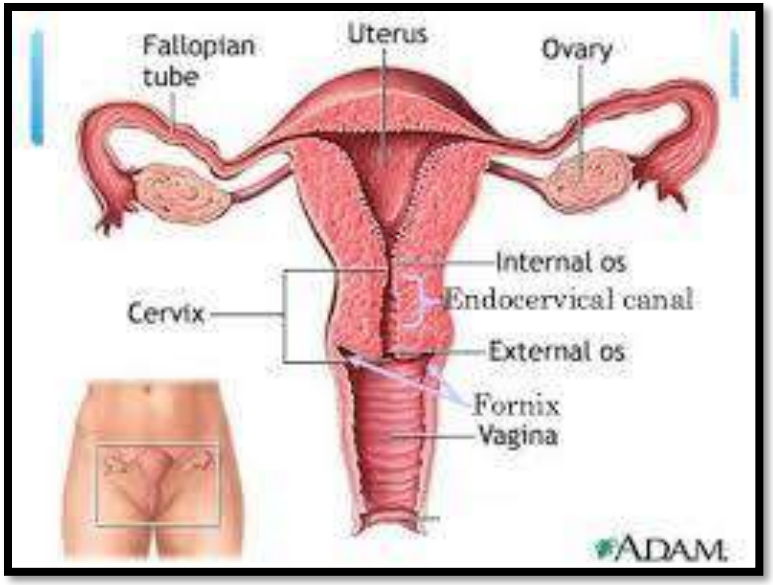
Target	Treatment	Assay	Comments
ER	Estrogen deprivation (oophorectomy, aromatase inhibitors) Blockage of ER (tamoxifen)	IHC for nuclear ER	Effective cytostatic (but not cytotoxic) therapy for ER-positive cancer
HER2	Antibodies to HER2 Cytotoxic therapy linked to HER2 antibody Tyrosine kinase inhibitors	IHC for membrane HER2 ISH for HER2 gene amplification	Effective for HER2-positive cancers
Susceptibility to DNA damage resulting from BRCA 1 and BRCA2 mutations that cause defects in HRR	Chemotherapy with agents causing DNA damage that requires HRR (e.g., platinum agents) Inhibition of alternative DNA repair pathway (poly-ADP ribose polymerase or PARP inhibitors)	Sequencing of *BRCA1* and *BRCA2*	May be effective for carcinomas arising in patients with germline *BRCA1* or *2* mutations or cancers with somatic loss of BRCA function
PI3K/AKT pathway	Inhibition of proteins in the pathway	Activating mutations or pathway activation—not yet validated	>80% of breast cancers have alterations in this pathway Effectiveness of treatment not yet demonstrated
Immune checkpoint proteins	Blocking antibodies to PD-L1, PD-1, and other immune checkpoint proteins	IHC for immune checkpoint proteins—not yet validated	Under investigation in patients with triple-negative breast cancer

ER, Estrogen receptor; *HRR,* homologous recombination repair; *IHC,* immunohistochemistry; *ISH,* in situ hybridization.

FINAL COMMENTS:

- **Combining stage and biologic factors are better predictors of outcome**
- **Women with untreated breast cancer die within 3-4 years**
- **80% of women who receive optimal treatment survive**
- **Early detection and easy access to optimal care are key factors**

FEMALE GENITAL TRACT PATHOLOGY



VULVA:

- **Most diseases are inflammatory; tumors are rare.**
- **Uncomfortable and annoying rather than serious**
- **Vulvitis:**
  - **Dermatitis, contact and allergic**
  - **Infections: STDs such as HPV (condyloma accuminatum & VIN); HSV, *N. Gonorrhoea, Treponema pallidum.* Candida (not STD)**
  - **Infection may obstruct glands and cause "Bartholin cyst"**

NON-NEOPLASTIC EPITHELIAL DISORDERS:

LICHEN CHRNICUS	LICHEN SIMPLEX CHRONICUS
• Leukoplakia “white plaque” • Postmenopausal & prepuberty • Etiology: ? T cell, ? Autoimmune • 1-5% of symptomatic LS may develop HPV –ve SQ.C Carcinoma • Atrophic epithelium	• Leukoplakia “white plaque” • Chronic irritation, pruritis due to other inflammatory dermatoses • No increased risk for cancer • Hyperplastic epithelium

LICHEN CHRNICUS

LICHEN SIMPLEX CHRONICUS

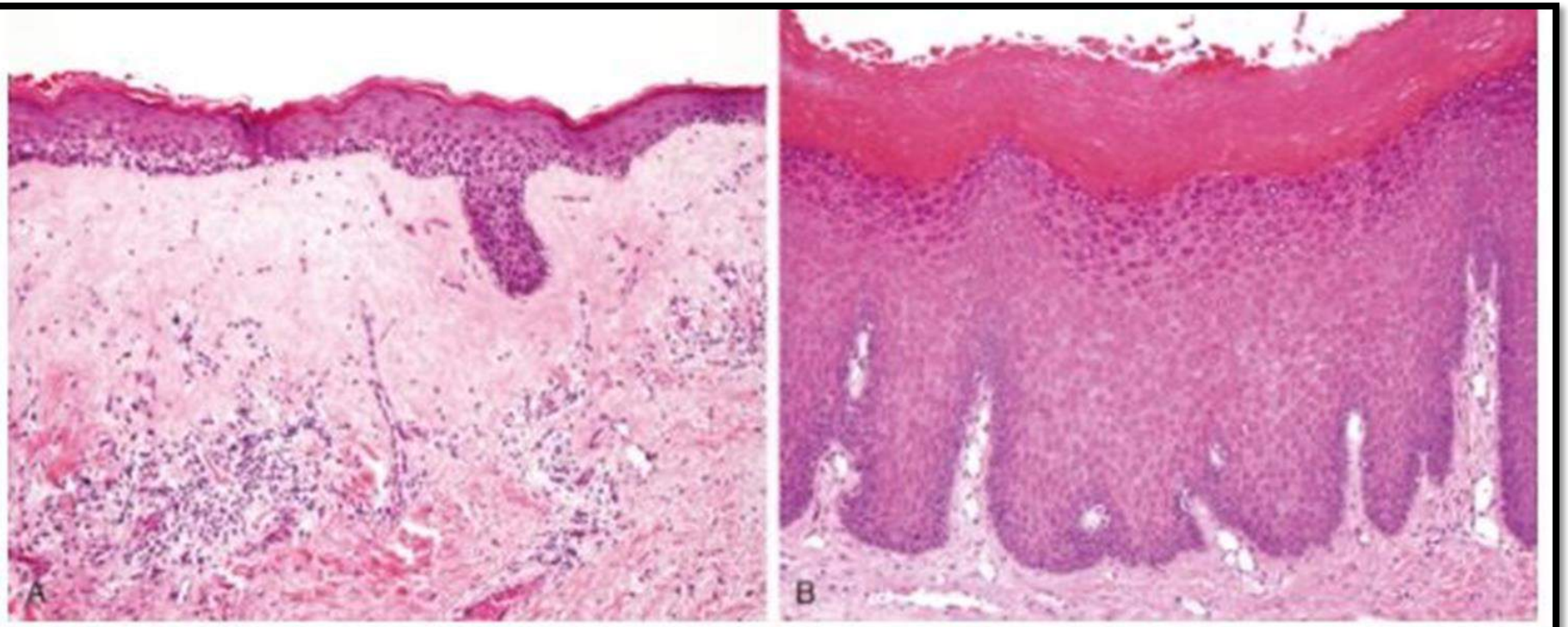
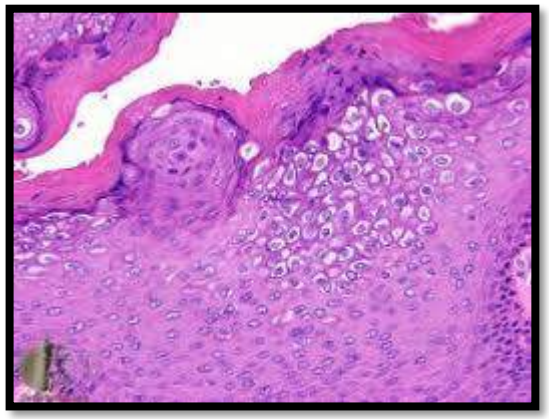
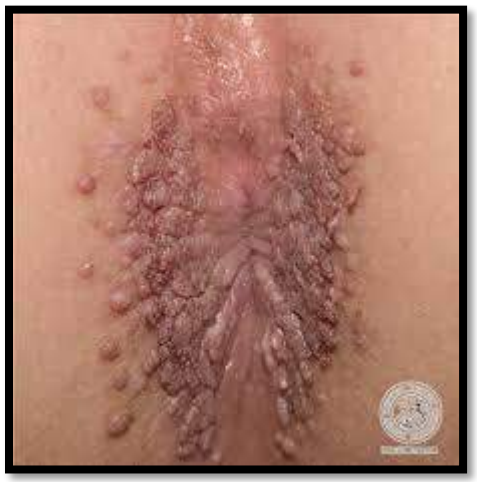


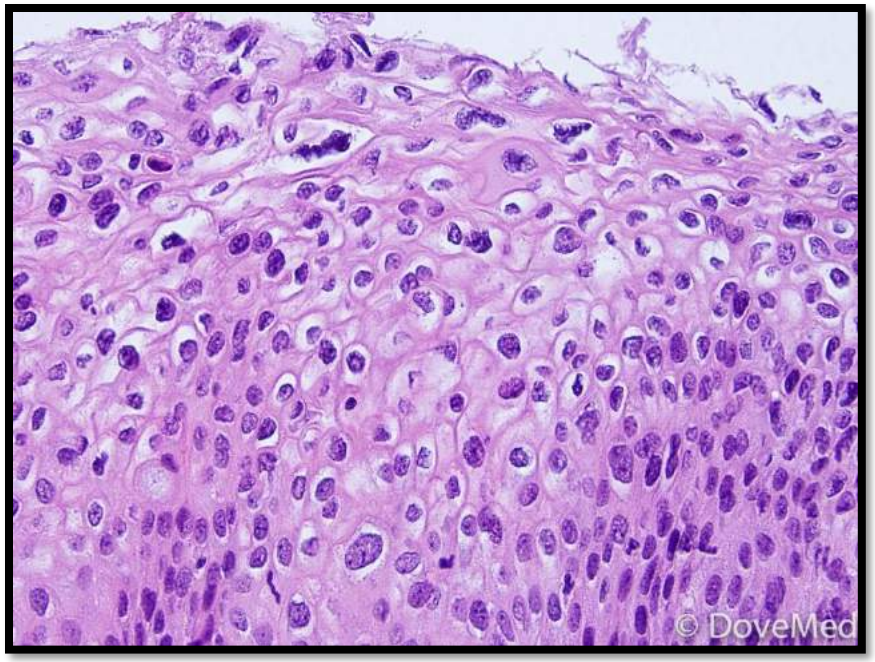
FIG. 19.1 Nonneoplastic vulvar epithelial disorders. (A) Lichen sclerosus. There is mark...

CONDYLOMA ACCUMINATUM:

- Wart "ثؤلول"
- HPV 6 & 11
- Elevated white plaques
- "Koilocytosis"
- No progression to cancer





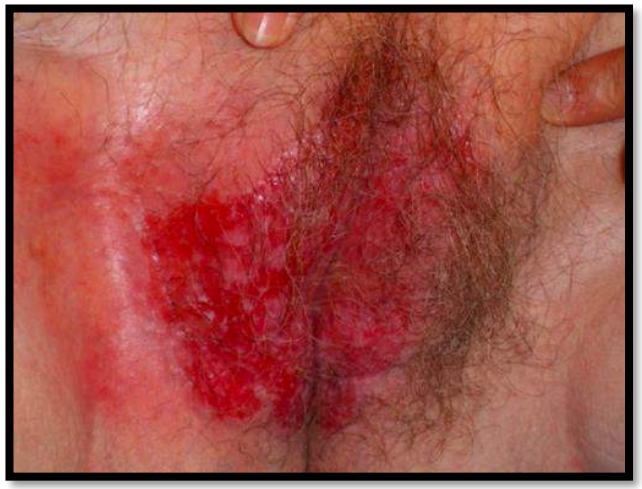


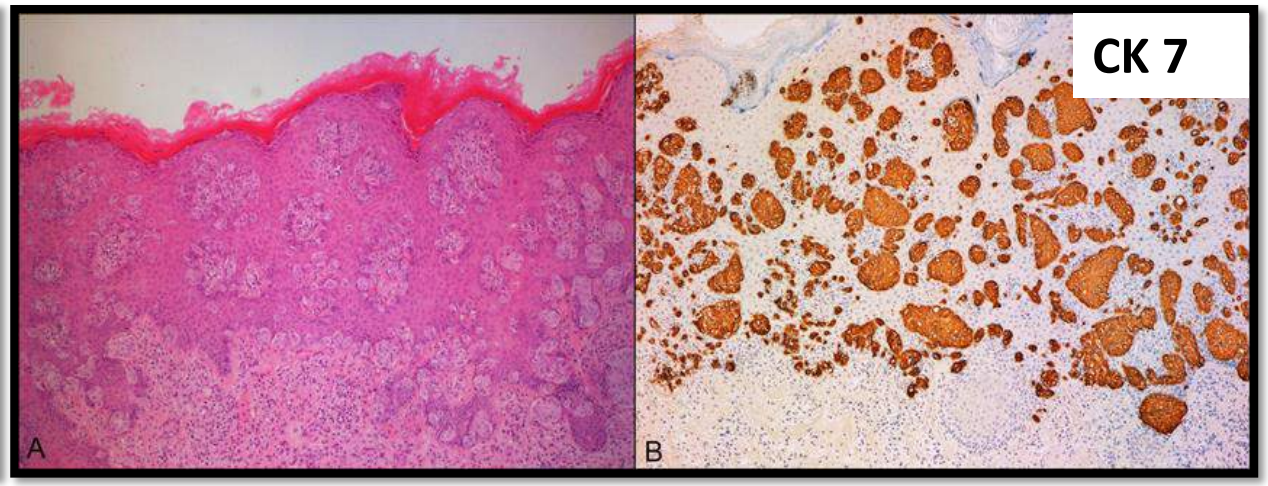
CARCINOMA OF VULVA:
90% SQUAMOUS CELL CARCINOMA

HPV related	HPV –ve
• Leukoplakia • HPV 16 & 18 • Middle aged women • Cigarette smoking and immunodeficiency (AIDs) • VIN (vulvar intraepithelial neoplasia) • Poorly differentiated, multifocal • Depth of invasion and lymph node mets are important px. Factors (stage)	• Leukoplakia • HPV –ve • Older women > 60 • Unifocal • Well-differentiated • Depth of invasion and lymph node mets are important px. Factors (stage)

PAGET DISEASE OF VULVA

- Carcinoma cells in the epidermis
- Red scaly crusted plaque
- Minority will have underlying carcinoma "adenocarcinoma", mucin +ve (in contrast to mammary Paget, almost all have underlying carcinoma)
- Poor px. when metastasis are present





VAGINAL PATHOLOGY:

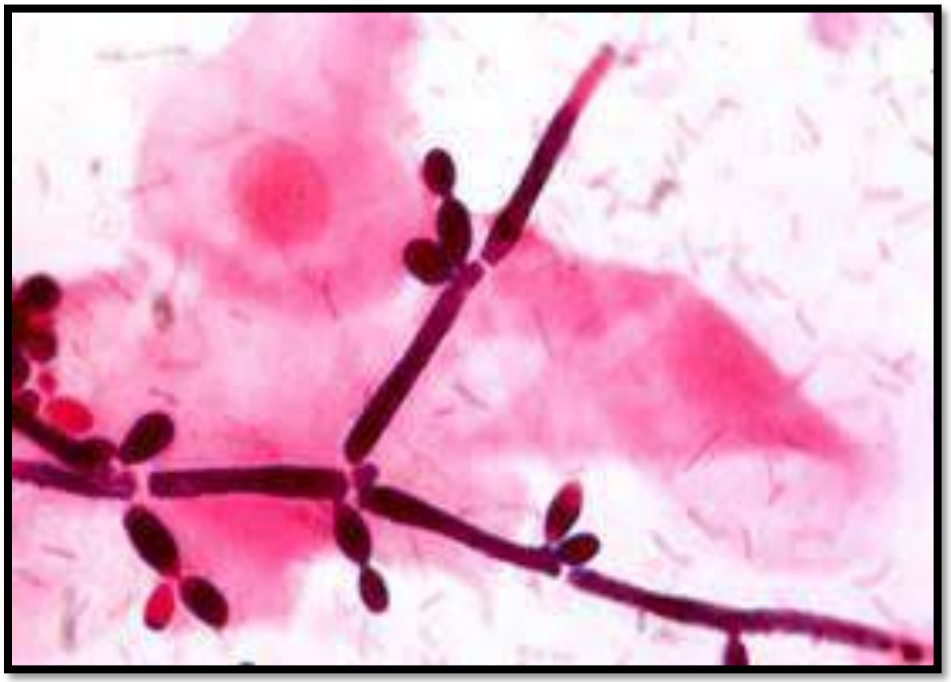
- **Rarely involved by primary disease; more secondary (infections and tumors)**
- **Congenital anomalies are rare: septate or double vagina part of septate uterus; congenital lateral Gartner duct cyst (persistent Wollfian duct rests)**

VAGINITIS:

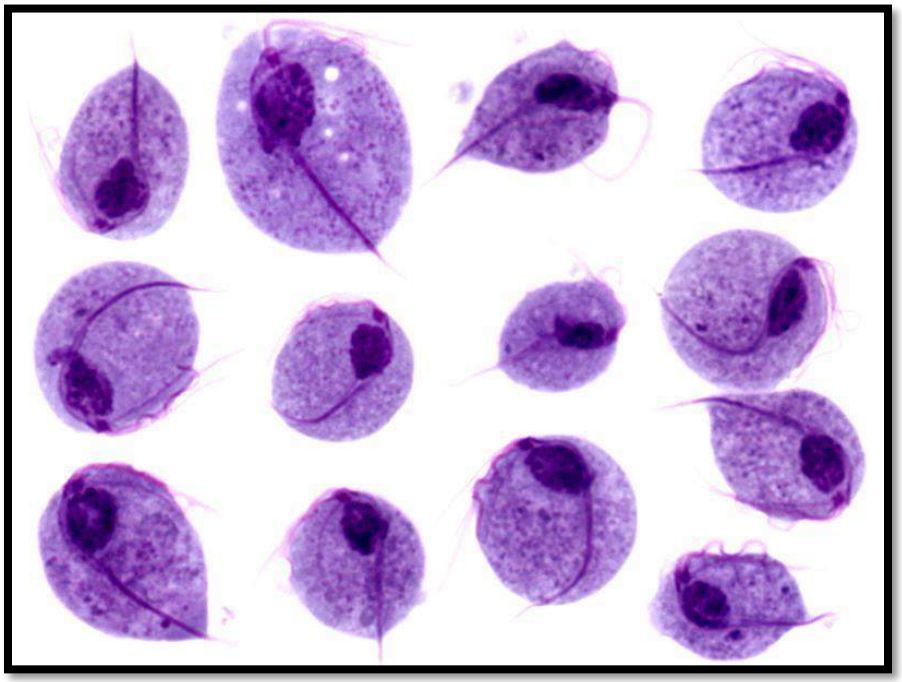
- **Common transient infections**
- **Candida infections (monilial) vaginitis: common in DM, pregnancy, with AB use and immunodeficiency. “White thrush”**
- ***Trichomonas vaginalis*: parasitic infection, STD, watery , copious gray-green discharge, can be seen on vaginal (& cervical Pap smears)**

PAPANICOLAOU SMEAR:

CANDIDA



T. VAGINALIS



MALIGNANT NEOPLASMS:

- **Very rare**
- **Squamous cell Ca: HPV & VAIN associated**
- **Clear cell adenocarcinoma: with vaginal adenosis triggered by the use od Diethylstilbestrol during pregnancy for threatened abortion (1970s)**
- **Sarcoma botryoides; embryonal rhabdomyosarcoma in children (< 5years)**

CERVIX PATHOLOGY:

- **Cervicitis, cervical polyps and cervical cancer**
- **Cervicitis: common, infectious and noninfectious**
- **Infectious: STDs; *Chlamydia Trachomatis* (most common), *Ureaplasma urealyticum*, *T. vaginalis, N. gonorrhoea*, HSV2 and HPV**
- **Pap smear detection after discharge**
- **HSV infection may affect babies if vaginal delivery**

CERVICAL NEOPLASIA:

- **Transformation zone (squamocolumnar junction); most common area**
- **Mostly are HPV associated squamous cell carcinoma**
- **HPV tropism for immature sq epithelium**
- **Cervical intraepithelial neoplasia or squamous intraepithelial neoplasia (old name: dysplasia)**

RISK FOR CERVICAL CANCER:

- Early age of first intercourse
- Multiple sexual partners
- Male partner with multiple partners
- Persistent infection with high risk HPV serotypes (HPV 16 & 18)
- HPV resides in the DNA of squamous epithelium and replicates

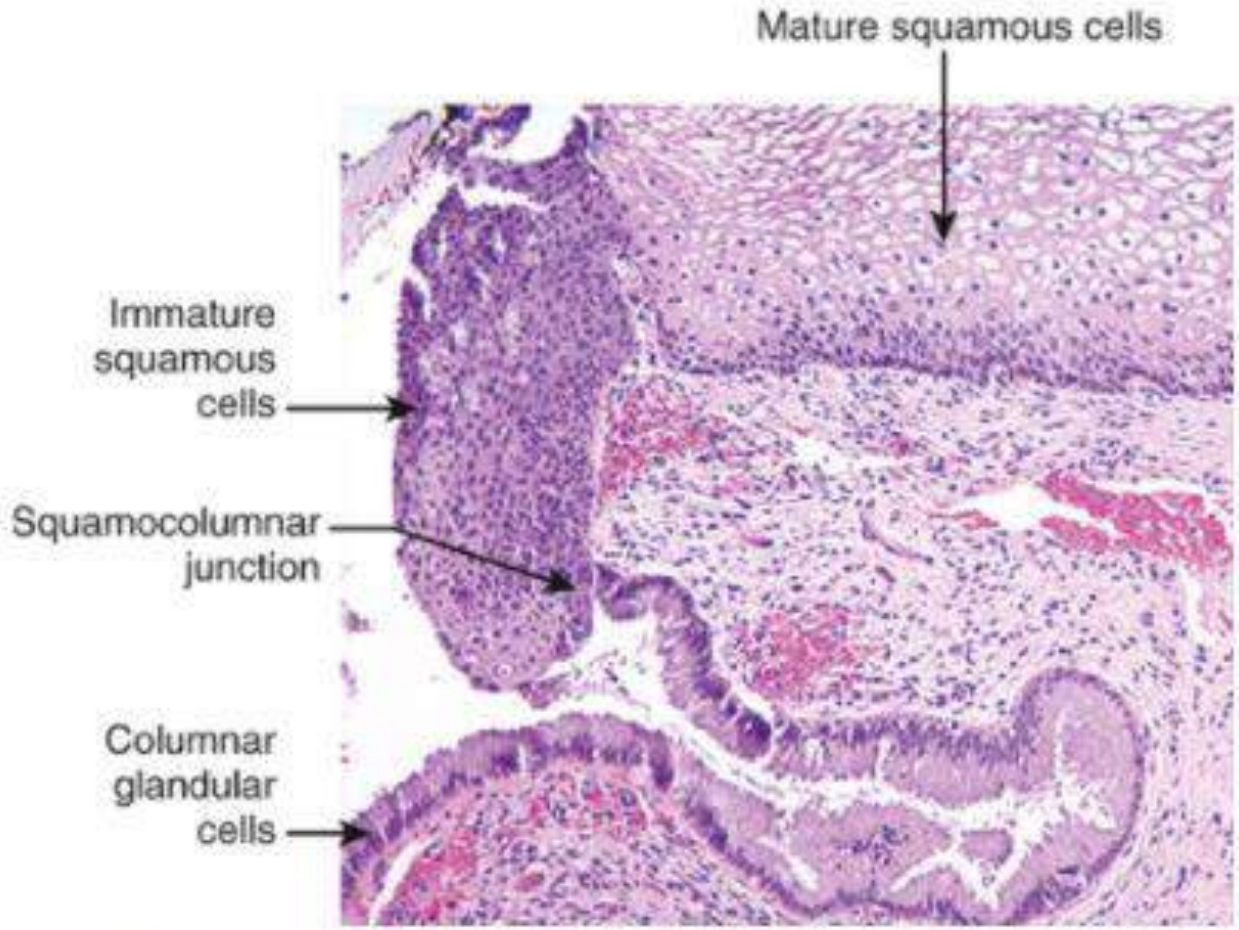


FIG. 19.4 Cervical transformation zone showing the transition from mature glycogenat...

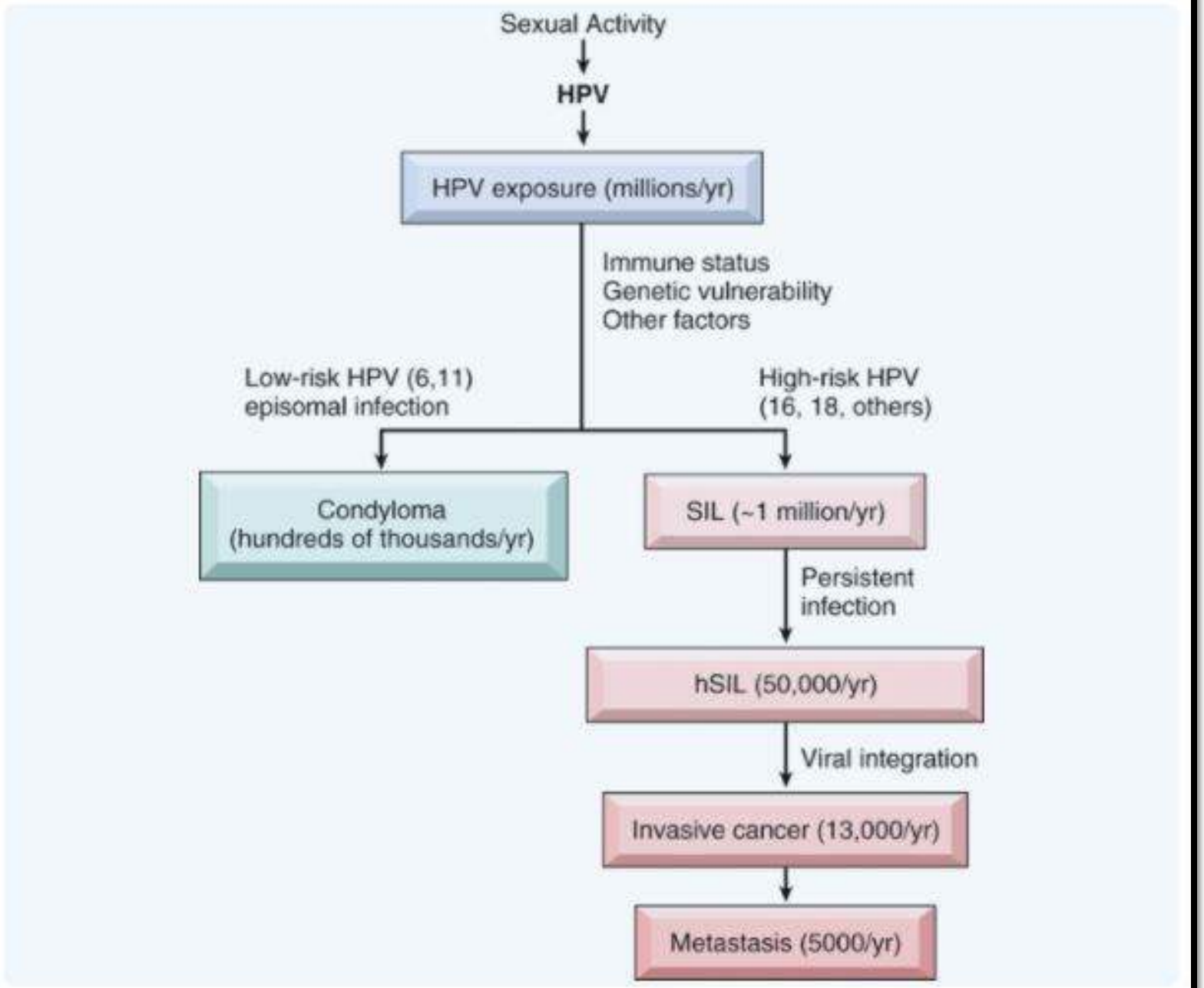
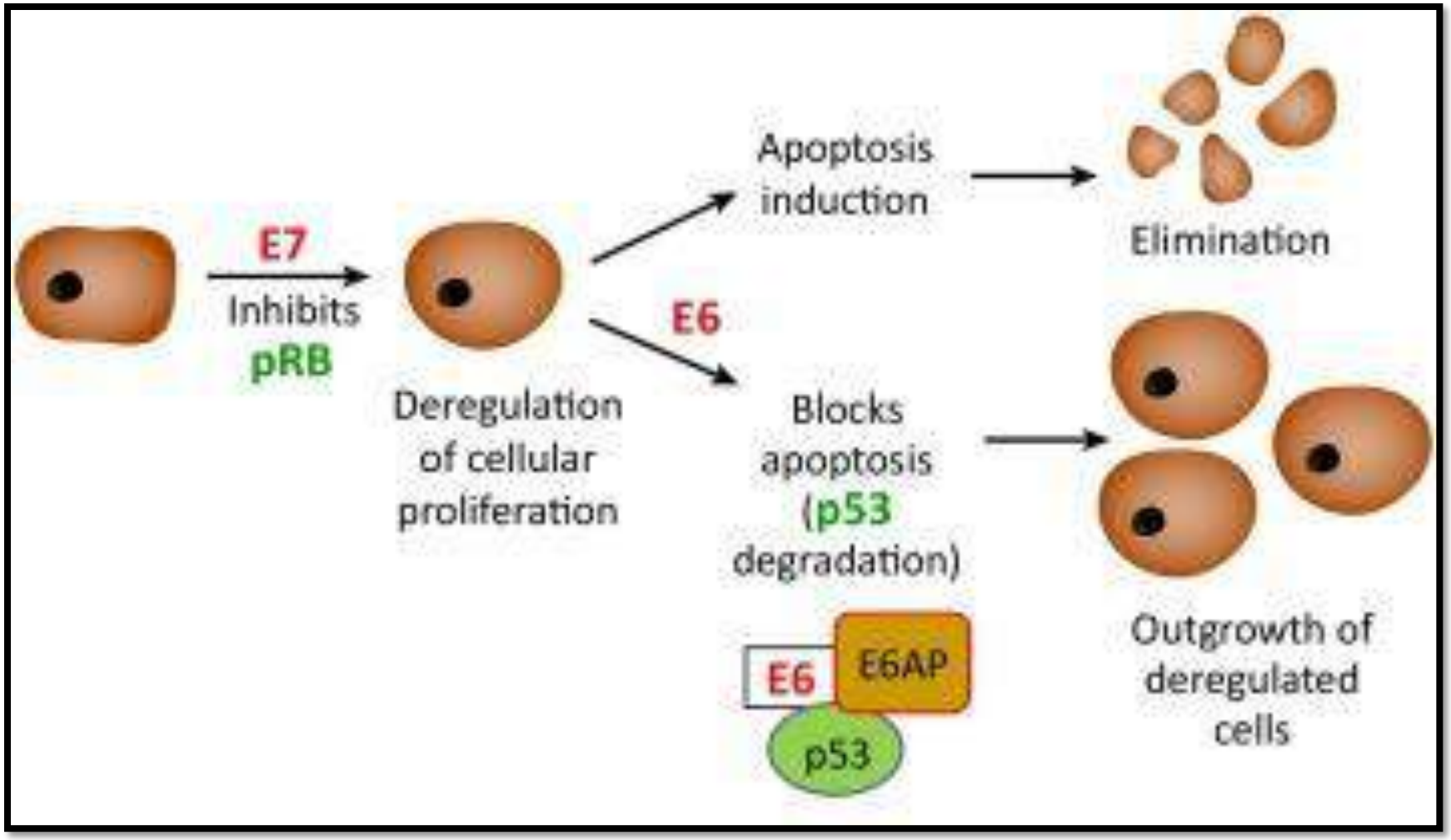


FIG. 19.5 Possible consequences of human papillomavirus (HPV) infection. Progressio…

HPV CARCINOGENESIS:



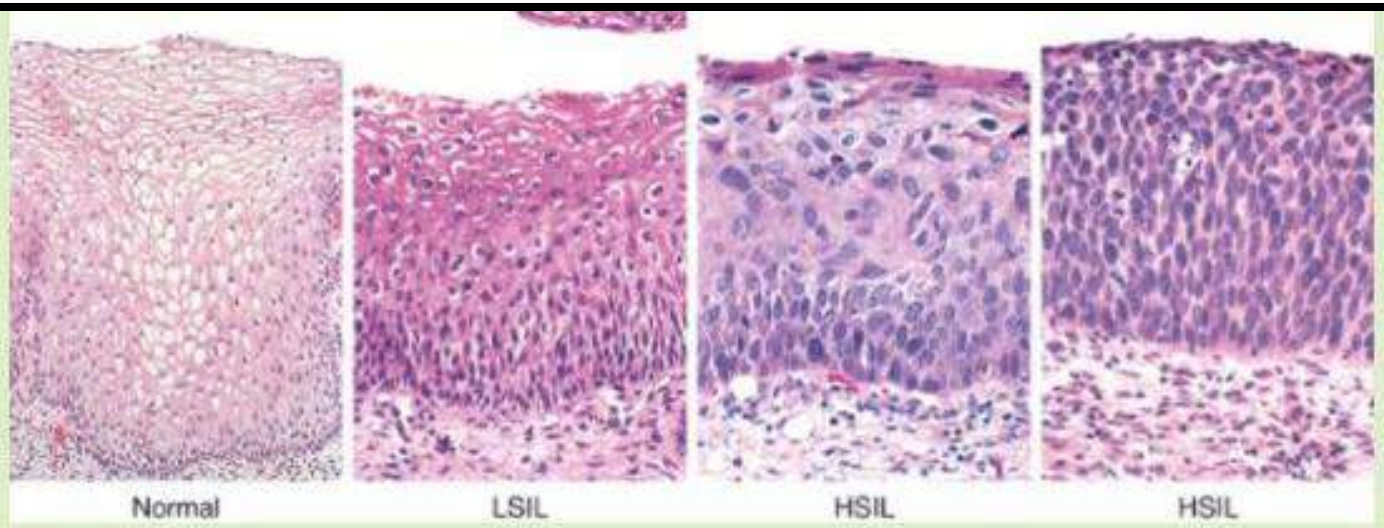


FIG. 19.6 Spectrum of squamous intraepithelial lesions (SIL) with normal squa…

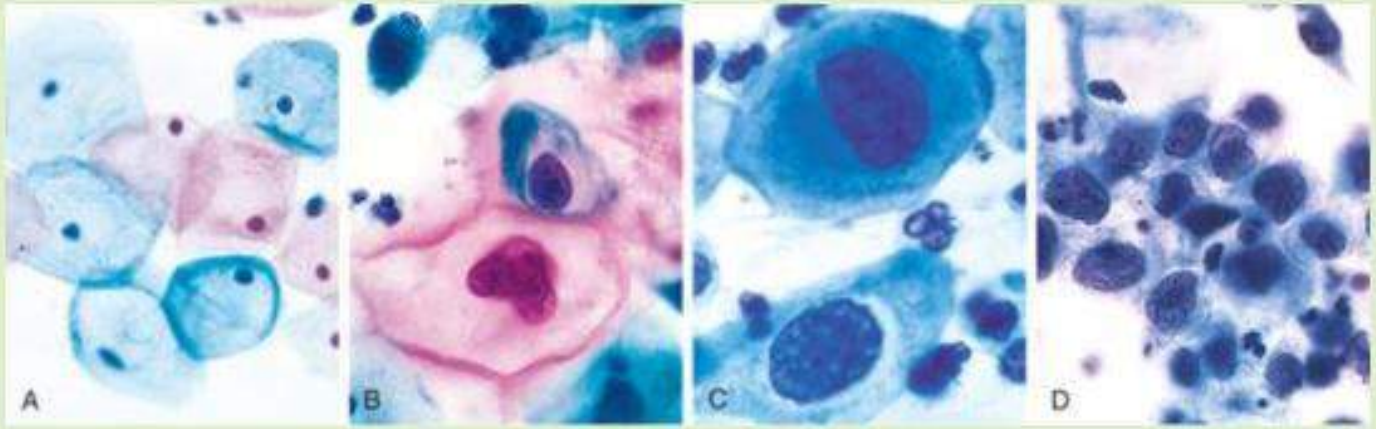


FIG. 19.7 Cytologic features of squamous intraepithelial lesion (SIL) in a Papani…

NATURAL HISTORY OF HPV INFECTION:

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]

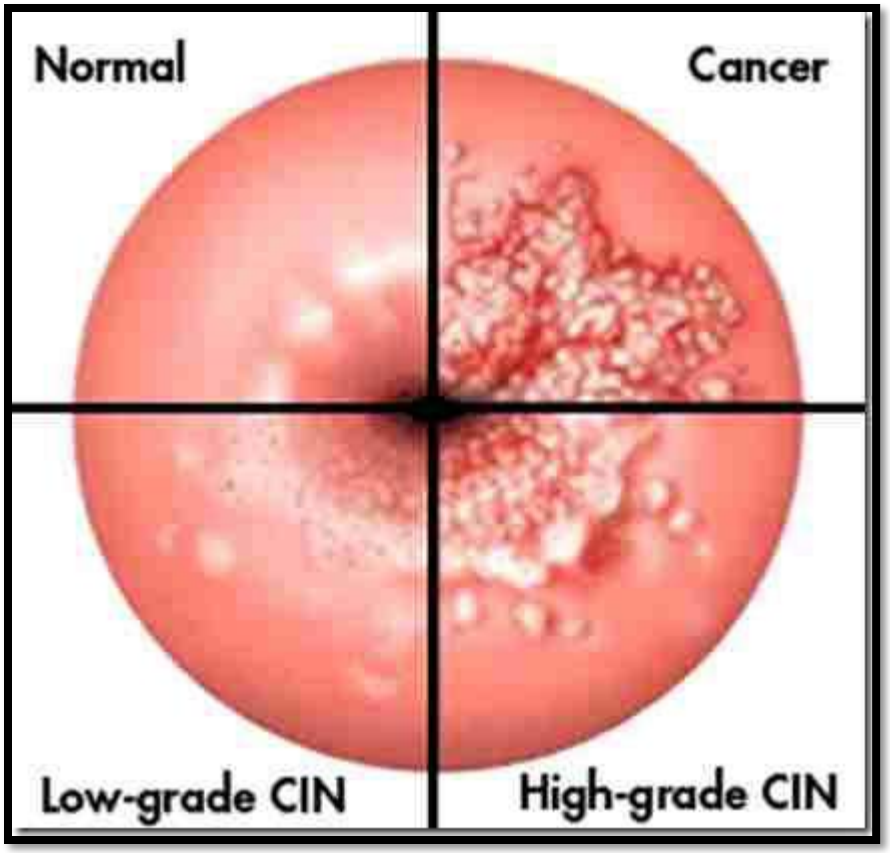
LSIL, Low-grade SIL; HSIL, high-grade SIL.

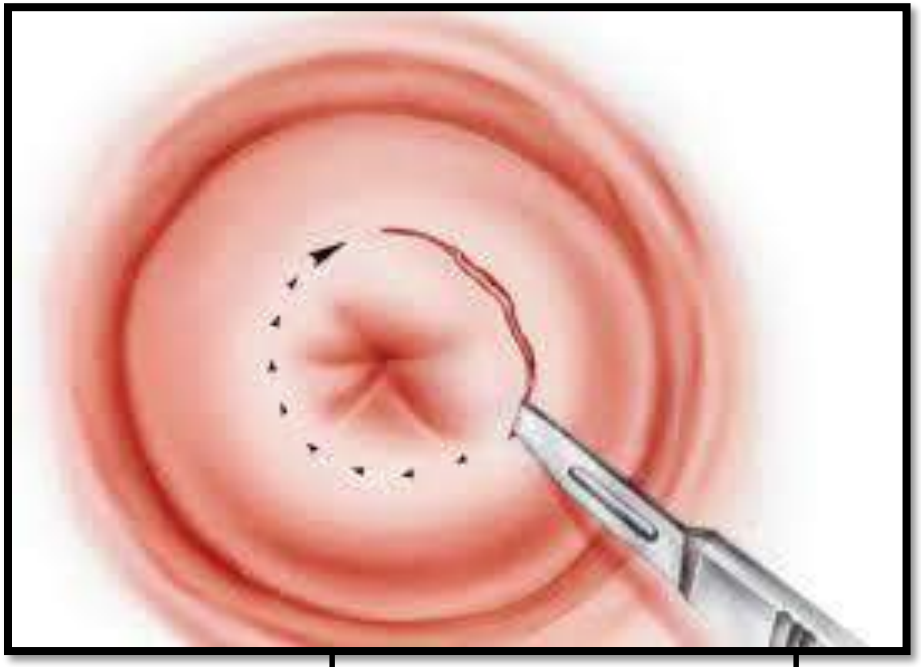
EARLY DETECTION AND THE PAP TEST:

- **The pap smear remains the most successful cancer-screening test ever developed**
- **Now, cancer death from cervix dropped dramatically (not of top ten)**
- **Smear (specific) morphology and HPV DNA (sensitive) testing are now used (co-testing)**
- **HPV vaccines: quadrivalent (HPV 6, 11, 16, 18) and more (divalent and 9 valent); are promising preventive measures**

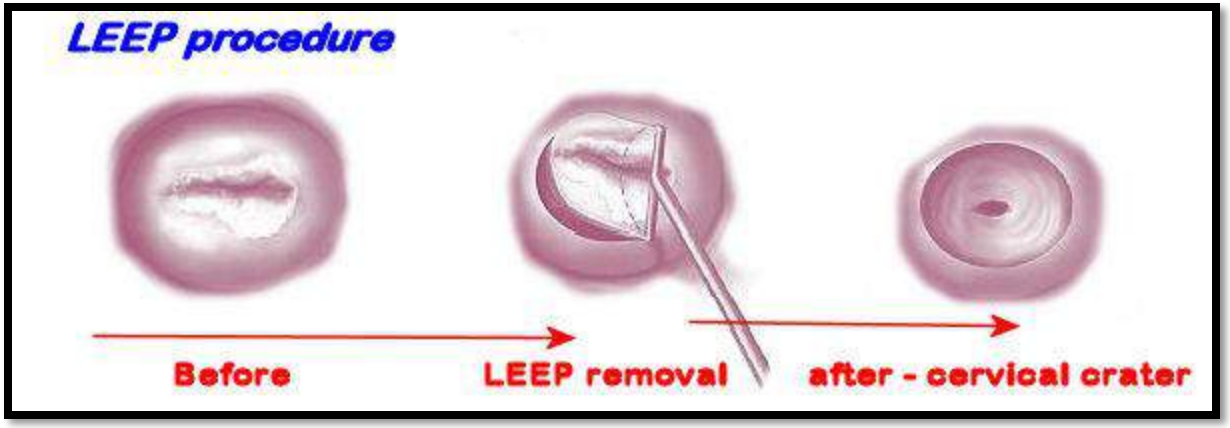
HGSIL DETECTION & TREATMENT:

- **The pap test (smear and HPV DNA test) is essential to detect early lesions before invasive carcinoma**
- **Specific guidelines are in place: colposcopy to see the lesions and biopsy them**
- **Confirm HGSIL by histology**
- **LEEP or cone excision of lesions**





Cone excision

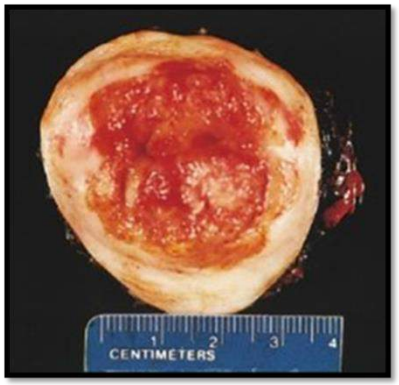


INVASIVE CERVICAL CARCINOMA:

- Squamous (75%), adenocarcinoma & adenosquamous (20%), and small cell NEC
- All are HPV associated
- Increase incidence of adenocarcinoma (better screening and early detection of squamous)
- SqCC peak at age 45 (10-15 years after HPV infection)
- Risk factors for invasion: smoking and HIV

INVASIVE CERVICAL CANCER:

- Often seen in unscreened women: vaginal bleeding, leukorrhea, and dyspareunia
- Biopsy dx needed before planning trx.
- Grading and depth of invasion are important predictors of stage and prognosis
- Depth of invasion 3 mm or more
- Spread: pelvic lymph nodes and surrounding structures
- Trx: radical hysterectomy + lymph node dissection, RT and CT

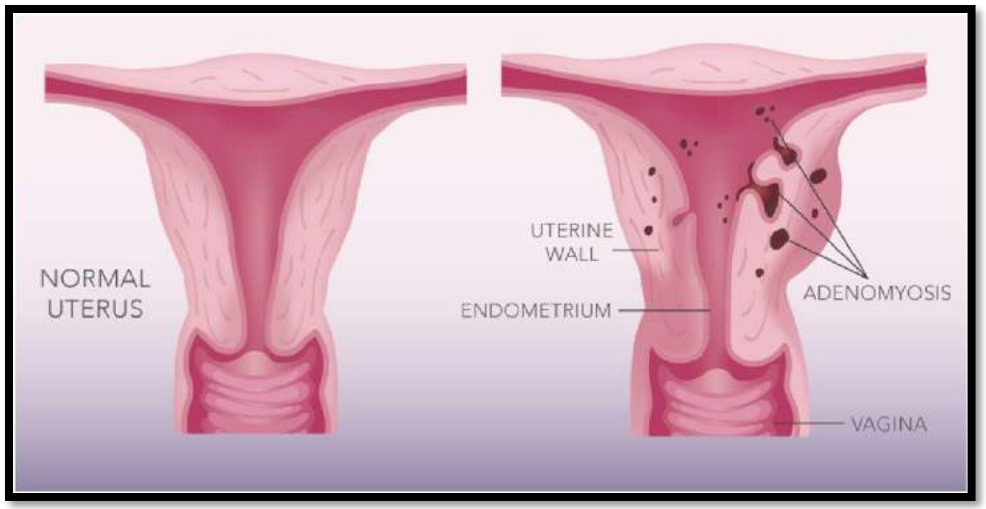


UTERINE PATHOLOGY:

- **Endometritis: acute (neutrophilic) or chronic (plasma cells)**
- **Can be part of pelvic inflammatory disease (*N. gonorrhoeae or C. trachomatis*)**
- **TB: granulomatous endometritis in endemic countries (+ TB salpingitis) or immunocompromised patients**
- **Retained POC and IOUCD associated**
- **Fever, abdominal pain and menstrual abnormalities**
- **Dx and trx: biopsy and antibiotics (removal of IUCD and POC)**

ADENOMYOSIS:

- Endometrial tissue deep in myometrium
- Functional tissue causing hypertrophy
- When extensive: menorrhagia, dysmenorrhea and pelvic pain (specially before menses)
- Can co-exist with endometriosis



ENDOMETRIOSIS:

- **Endometrial glands and stroma outside uterus**
- **Any where and multifocal: but common locations are ovaries, pouch of Douglas, uterine ligaments, cervix, tubes and rectovaginal septum).**
- **Theories:**
  - **Regurgitation (favored)**
  - **Benign metastases**
  - **Metaplasia**
  - **Extrauterine stem cell differentiation**

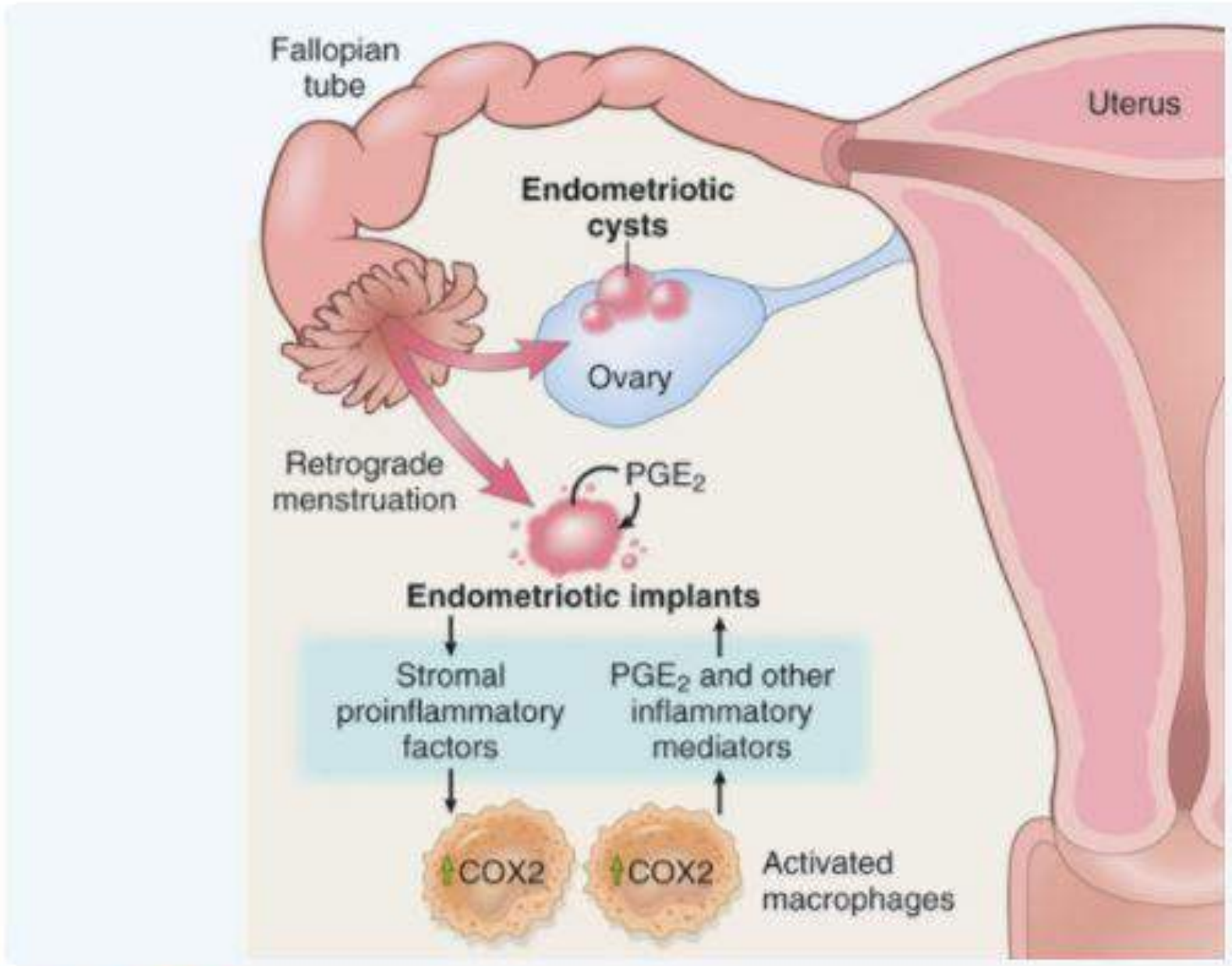
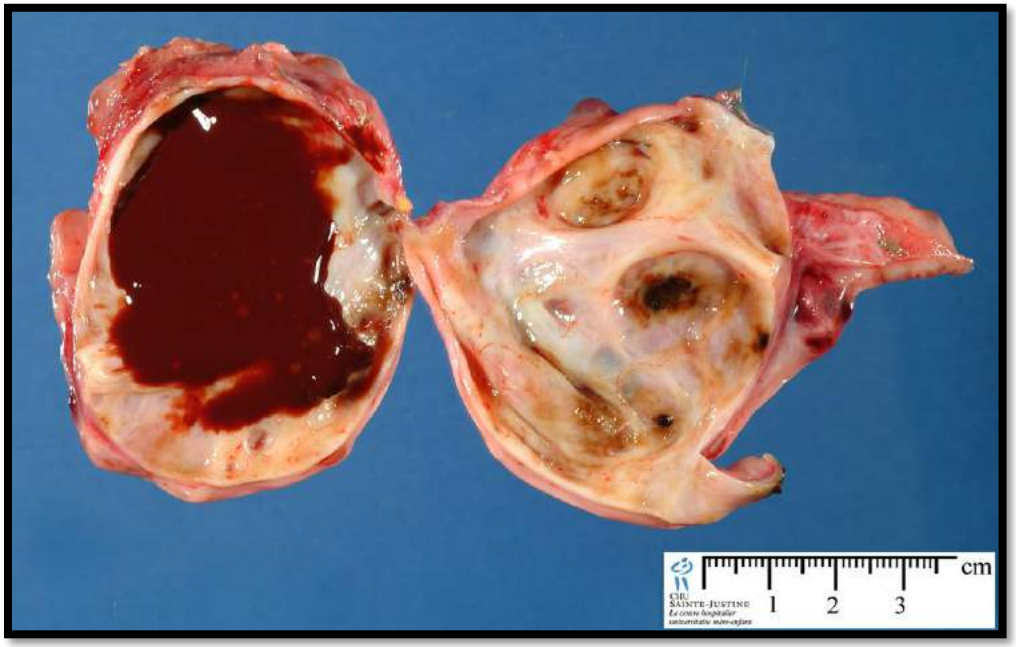
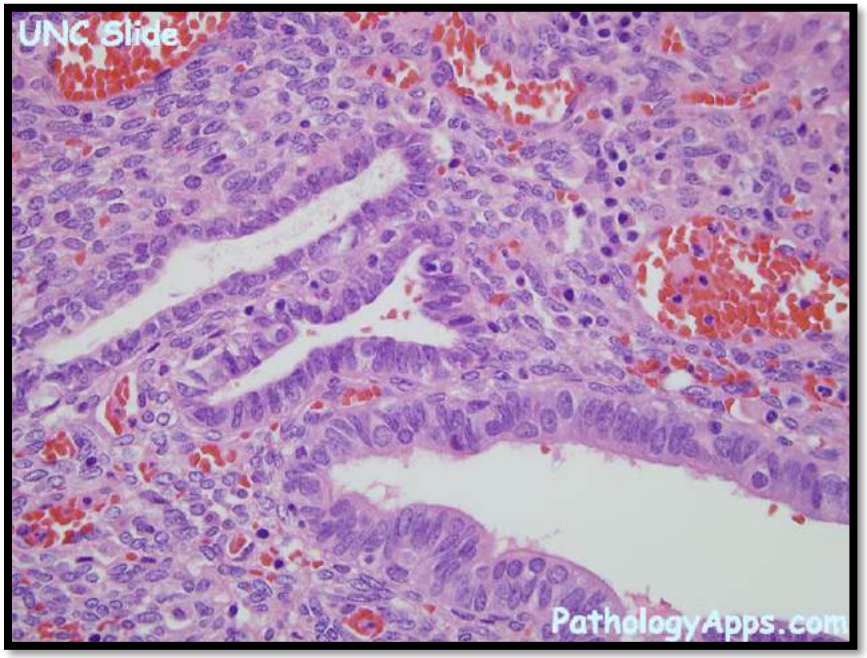
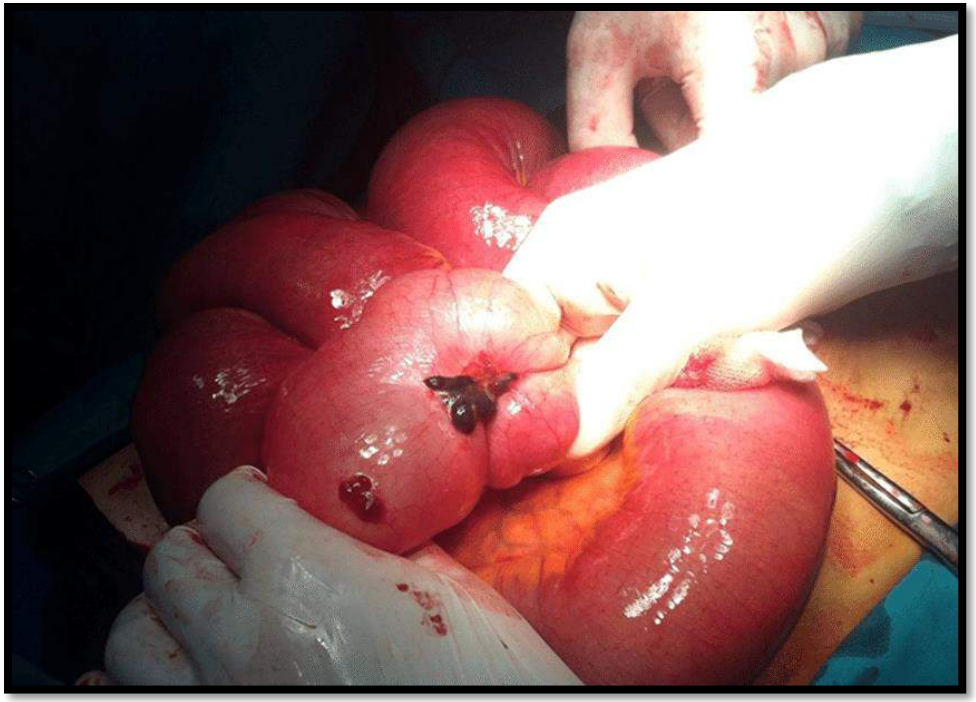
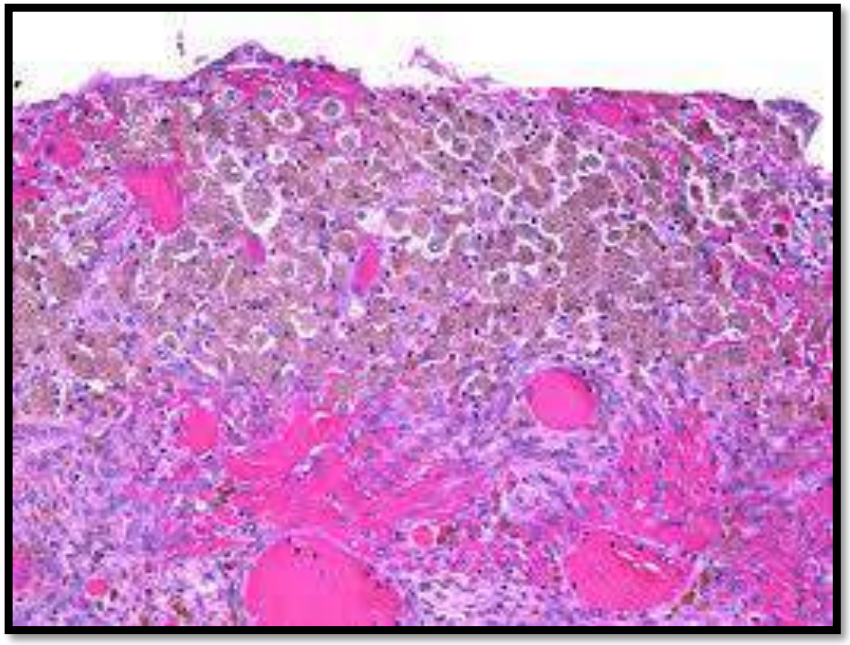


FIG. 19.9 Proposed origins of endometriosis.


cm
1
2
3

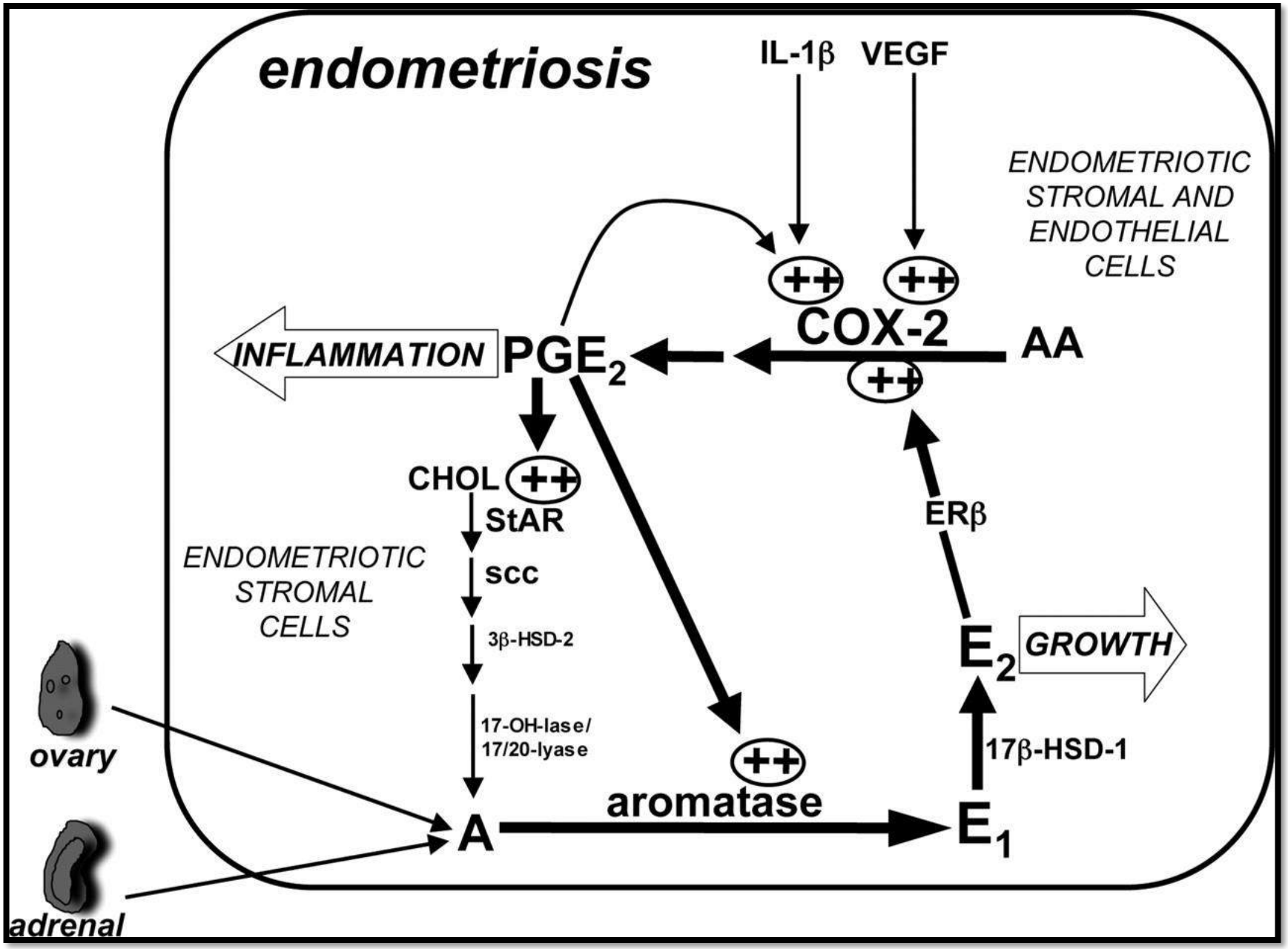

UNC Slide
PathologyApps.com





ENDOMETRIOSIS CLINICALLY

- 10% of women in reproductive age and 50% of infertile women
- S&S: depends on distribution and location
- Scarring of tubes and ovaries; pain and discomfort, infertility [red dots]
- Rectal (painful defecation), uterine and bladder serosa (dyspareunia and dysuria)
- Severe dysmenorrhea, pelvic pain (bleeding and adhesions)
- Trx: complex (surgical and / or medical)


endometriosis
IL-1β
VEGF
ENDOMETRIOTIC STROMAL AND ENDOTHELIAL CELLS
++
++
COX-2
AA
++
INFLAMMATION
PGE2
CHOL
++
StAR
ERβ
ENDOMETRIOTIC STROMAL CELLS
scc
3β-HSD-2
E2
GROWTH
17-OH-lase/ 17/20-lyase
17β-HSD-1
ovary
++
aromatase
A
E1
adrenal

ABNORMAL UTERINE BLEEDING (AUB):

- **Very common complaint for women**
- **Menorrhagia (heavy and / or long periods), metrorrhagia (irregular bleeding) or post menopausal bleeding**
- **Causes:**

Dysfunctional uterine bleeding (DUB)
Endometrial polyps
Leiomyomas (fibroids)
Endometrial hyperplasia
Endometrial carcinoma

TABLE 19.2 Causes of Abnormal Uterine Bleeding by Age Group

Age Group	Cause(s)
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy) Proliferations (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma) Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopause	Anovulatory cycle Irregular shedding Proliferations (carcinoma, hyperplasia, polyps)
Postmenopause	Proliferations (carcinoma, hyperplasia, polyps) Endometrial atrophy

DYSFUNCTIONAL UTERINE BLEEDING (DUB):

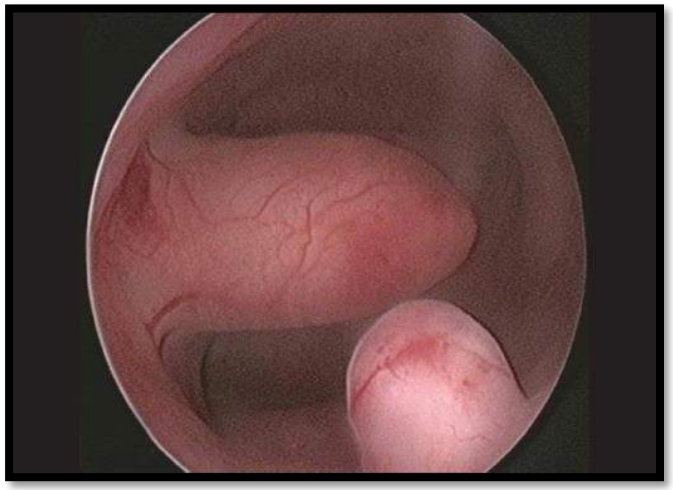
- Very common
- Abnormal bleeding with no organic uterine cause
- Many due to anovulation around menarche and perimenopause because of hormonal imbalances
- Less common causes: endocrine diseases; ovarian tumors (GCT) and PCOS, obesity, malnutrition, chronic diseases, inadequate luteal phase

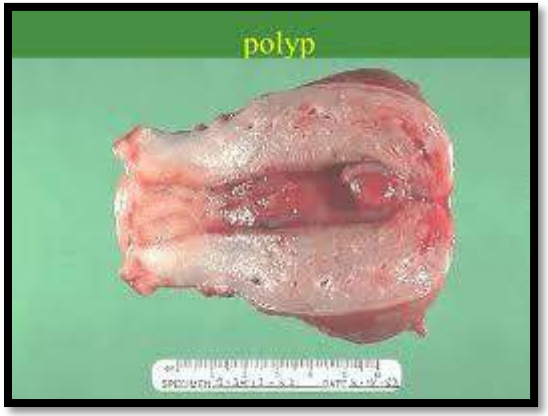
PROLIFERATIVE LESIONS OF ENDOMETRIUM AND MYOMETRIUM:

- Endometrial polyps
- Leiomyomas “fibroids”
- Endometrial hyperplasia
- Endometrial carcinoma

ENDOMETRIAL POLYPS:

- Common finding in endometrial curettings
- Cause abnormal uterine bleeding
- Almost all are benign
- Most common around menopause

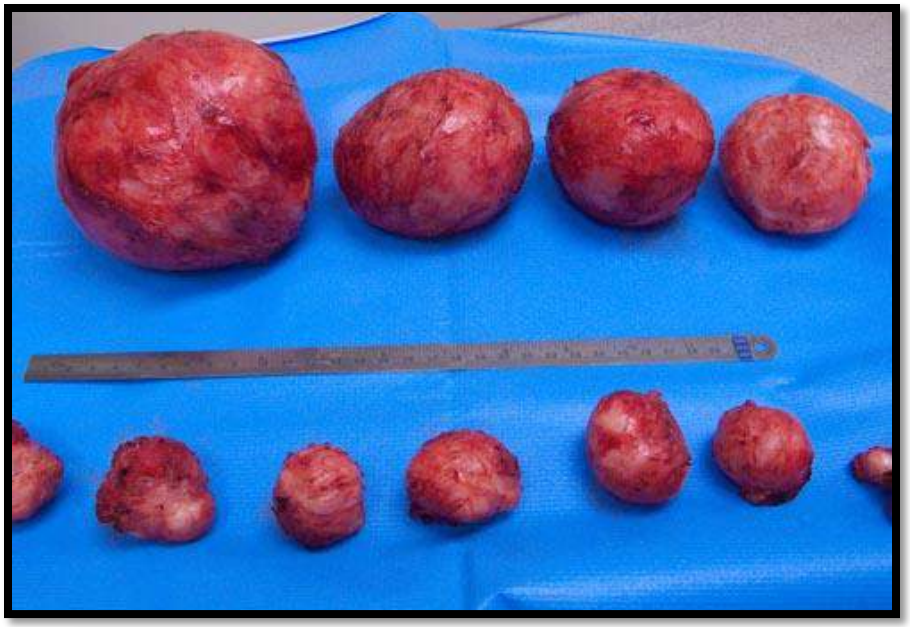


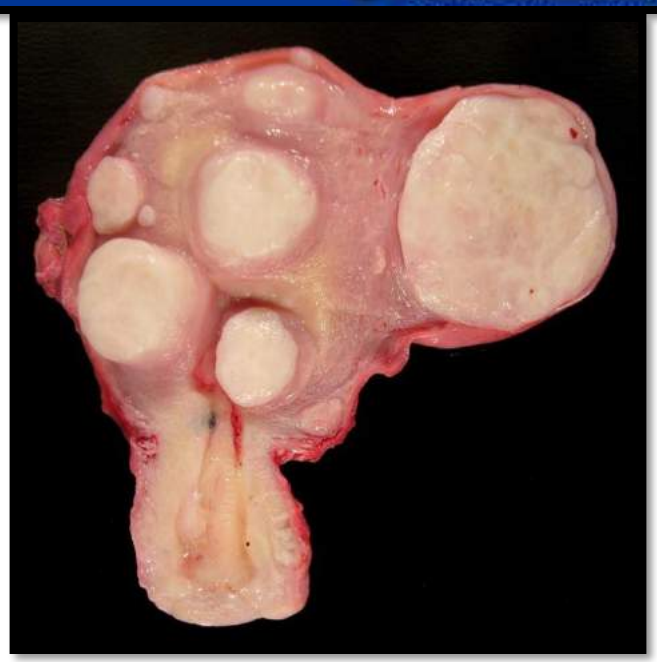


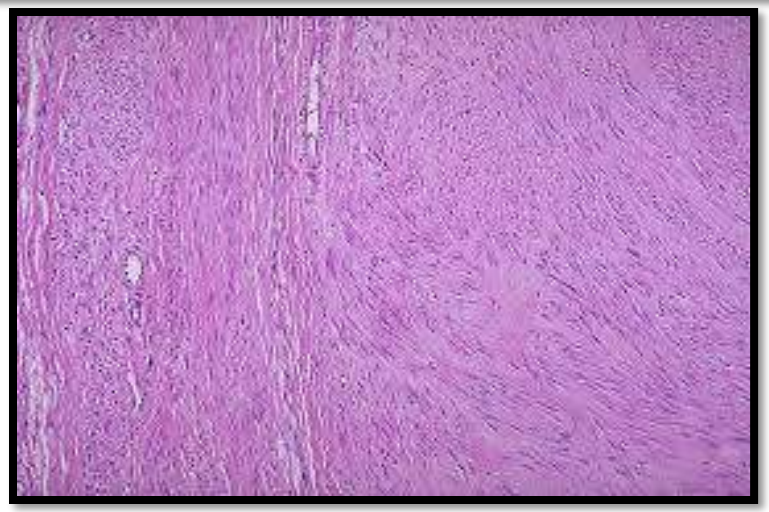
LEIOMYOMAS “FIBROIDS”:

- **Benign smooth muscle tumor of myometrium**
- **Most common tumors of females, 30-50% of women in reproductive age, > in Blacks**
- **Chromosomal abnormalities (Ch 6 and 12 rearrangements) and *MED12* gene mutations**
- **Grow with estrogens and OCP and shrink postmenopausally**
- **Asymptomatic; menorrhagia**

PATHOLOGIC FEATURES:



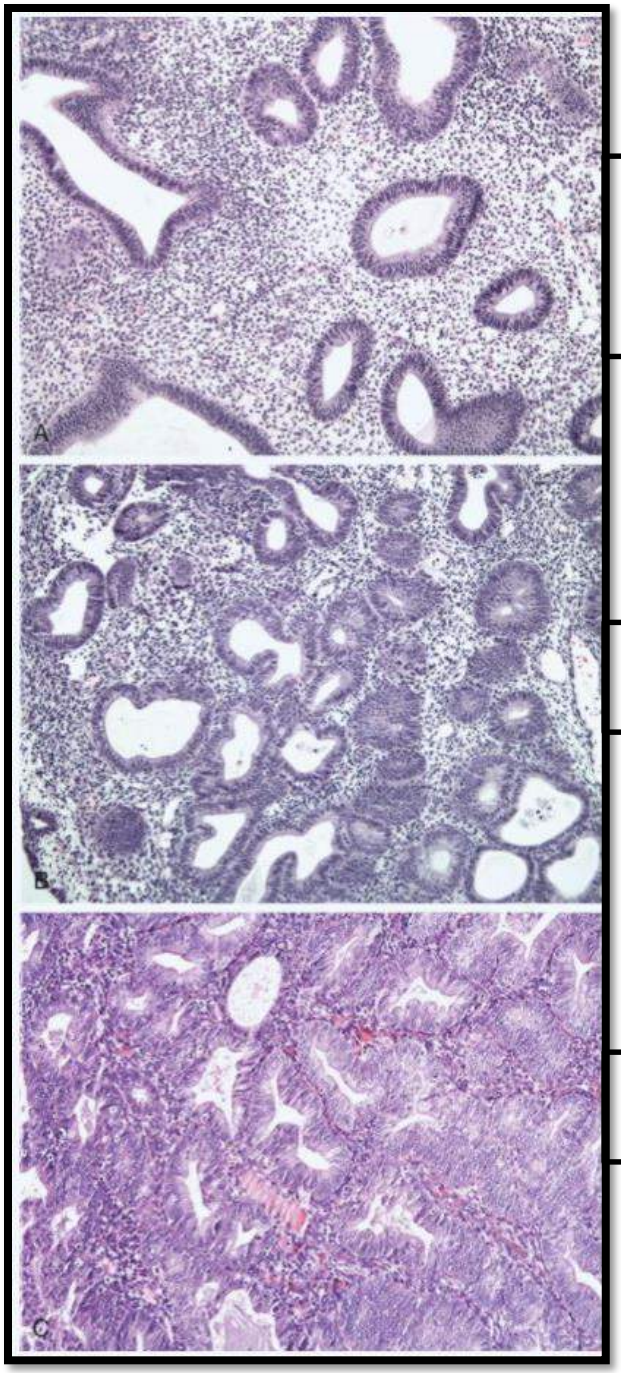




ENDOMETRIAL HYPERPLASIA:

- **Excess estrogen in relation to progestins**
- **Causes: obesity, anovulation, unopposed estrogen intake, estrogen producing ovarian tumors**

Hyperplasia without atypia	Hyperplasia with atypia (EIN)
- No atypical cellular features - Less complex, more cystic - Risk of carcinoma is 1-3% - No PTEN tumor suppressor gene abnormalities	- Atypical cellular features present - More complex glands - Risk of carcinoma is 20-50% - Inactivation of PTEN tumor suppressor gene



Disordered proliferative endometrium

Hyperplasia without atypia

Atypical hyperplasia

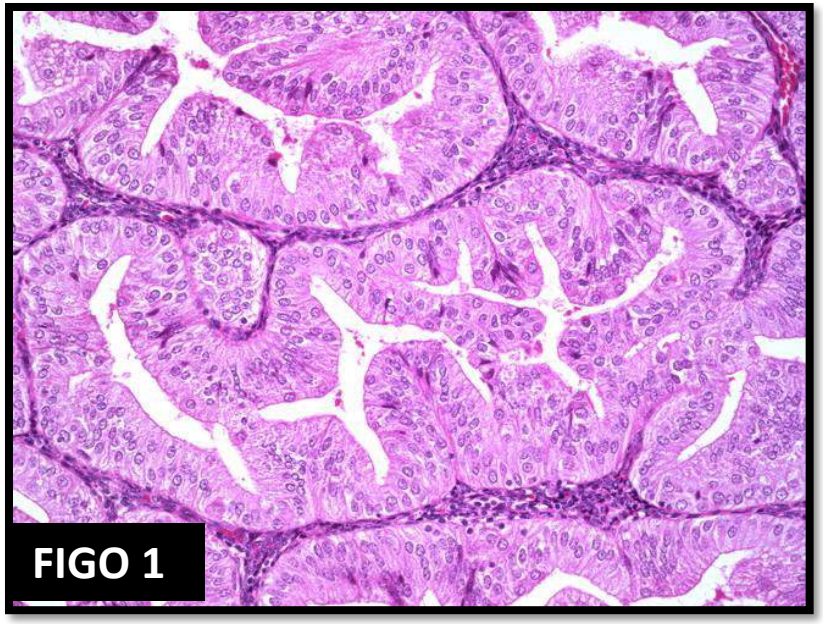
ENDOMETRIAL CARCINOMA:

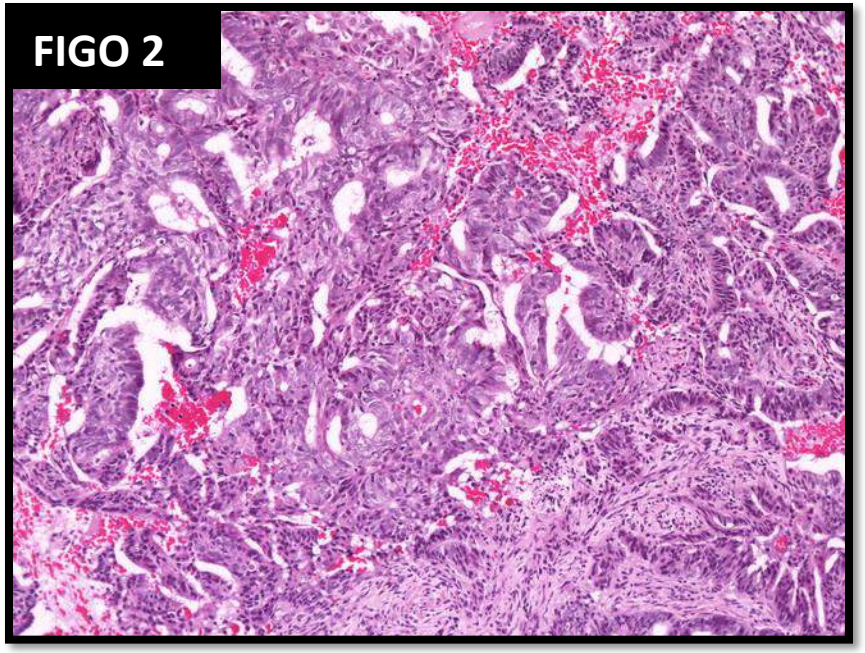
- **Most frequent cancer in FGT**
- **Age: 55-65 years**
- **2 main types:**
  - **1. Endometrioid carcinoma (80%)**
  - **2. Serous carcinoma (15%)**
- **Others less common: clear cell Ca and MMT (carcinosarcoma)**

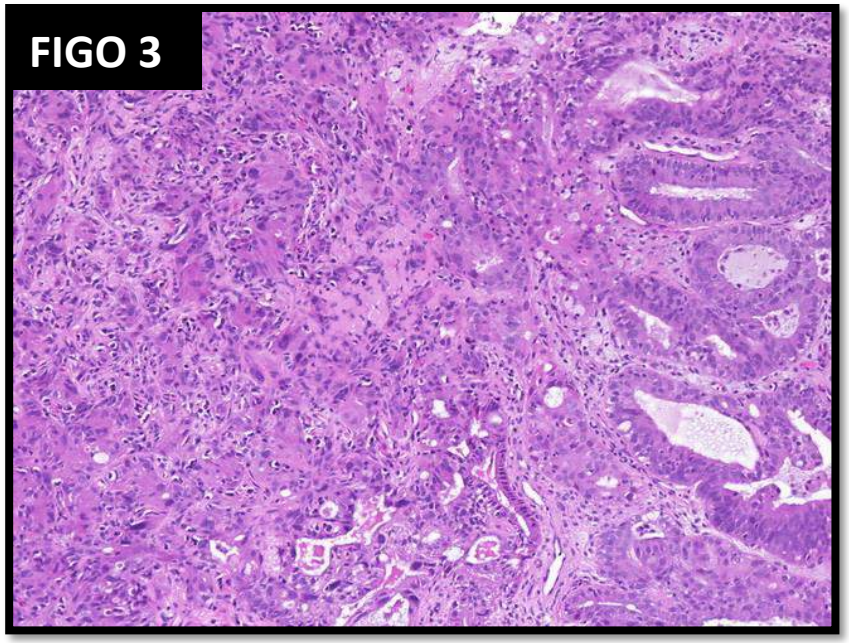
ENDOMETRIOID CARCINOMA:

- **Histology similar to normal endometrium**
- **Risk factors: Obesity, HT, DM, infertility, & unopposed estrogen exposure**
- **Associated and preceded by atypical hyperplasia**
- **Mutations:**
  - **Early: mismatch DNA repair genes (Lynch syndrome) and *PTEN* tumor suppressor gene (Cowden syndrome)**
  - **Late: *TP53*, less common and late event**

MORPHOLOGY & FIGO GRADE ENDOMETRIOID CARCINOMA



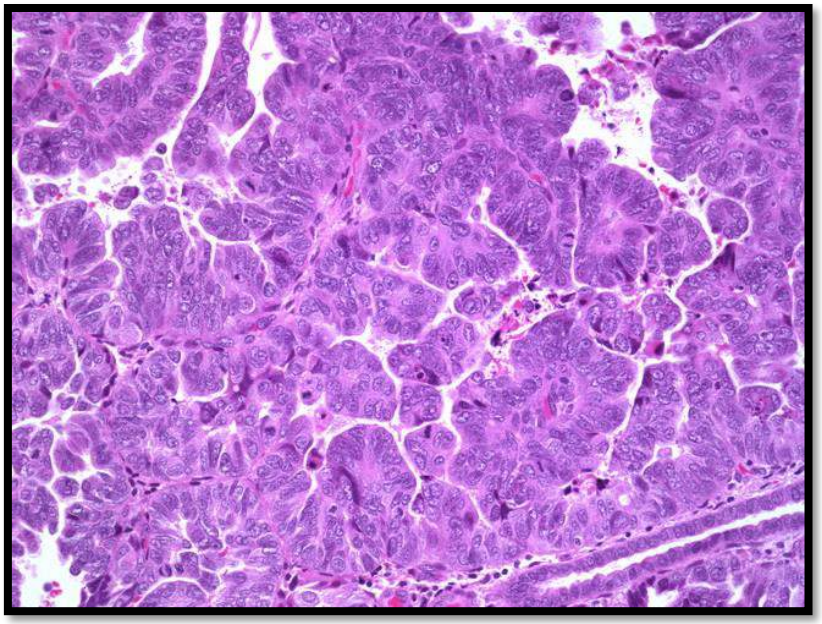


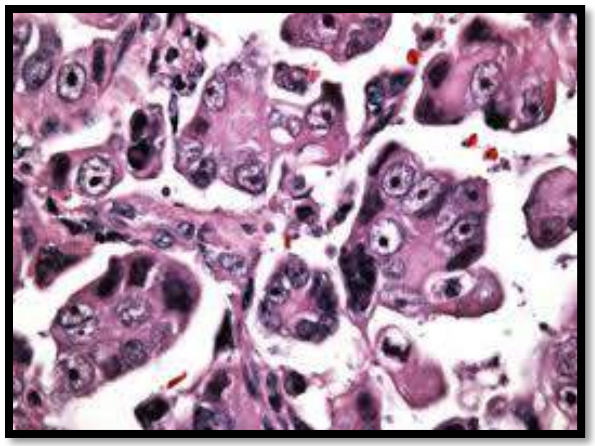


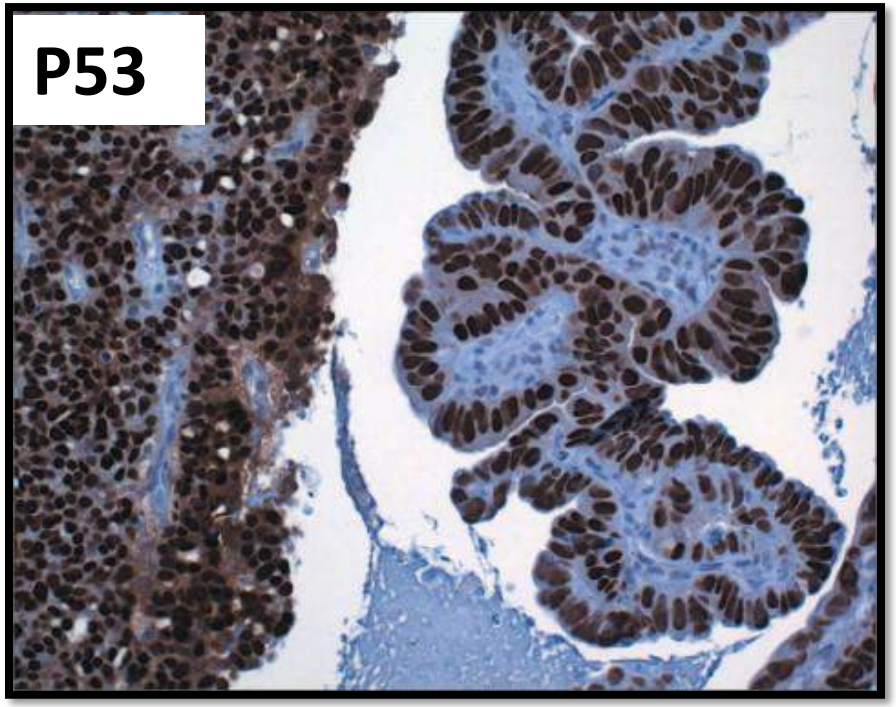
SEROUS CARCINOMA:

- **Serous is serious “Dr. Samir Amr”, aggressive carcinoma**
- **Not associated with hyperplasia or unopposed estrogen exposure**
- **Mutations in *TP53***
- **Maybe preceded by serous endometrial intraepithelial carcinoma (SIEC) with *TP53* mutations**

MORPHOLOGY: SEROUS CARCINOMA







FIGO STAGING:

Table 1: 2009 FIGO staging system for carcinoma of the endometrium

Stage I[a]	Tumor contained to the corpus uteri		
	IA	No or less than half myometrial invasion	
	IB	Invasion equal to or more than half of the myometrium	
Stage II		Tumor invades the cervical stroma but does not extend beyond the uterus[b]	
Stage III[a]		Local and/or regional spread of tumor[c]	
	IIIA	Tumor invades the serosa of the corpus uteri and/or adnexas	
	IIIB	Vaginal and/or parametrial involvement	
	IIIC	Metastases to pelvis and/or para-aortic lymph nodes	
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV[a]			Tumor invades bladder and/or bowel mucosa and/or distant metastases
	IVA		Tumor invasion of bladder and/or bowel mucosa
	IVB		Disant metastases, including intra-abdominal metastases and or inguinal lymph nodes

FIGO = International Federation of Gynecology and Obstetrics

[a] Includes grades 1, 2, or 3

[b] Endocervical glandular involvement only should be considered as stage I and no longer as stage II.

[c] Positive cytology has to be reported separately without changing the stage.

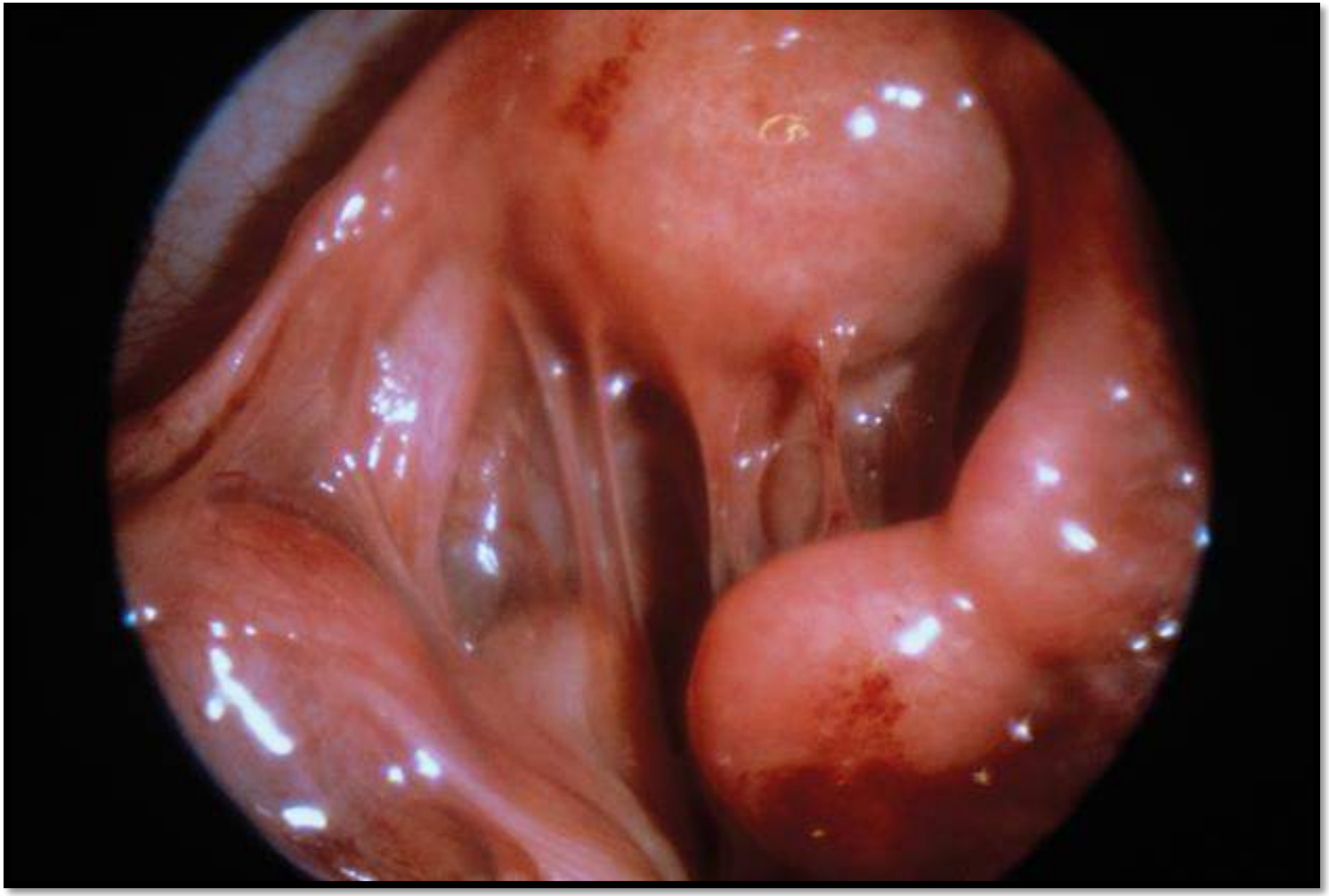
ENDOMETRIAL CARCINOMA: CLINICALLY

- Irregular or postmenopausal bleeding
- Endometrioid carcinoma is slow growing, late progression with no treatment
- Early stage, 5-year survival is >90%
- Untreated: metastasis to lymph nodes and surrounding structures
- Serous carcinoma is more aggressive, present with advanced stage and have bad prognosis

FALLOPIAN TUBE PATHOLOGY:

- Salpingitis is the commonest significant pathology; almost part of PID
- Gonorrhea, Chlamydia, Mycoplasma, coliforms, Strept and staph
- TB salpingitis is less common but occurs with TB endometritis
- Fever, abd. Pain and sometimes masses (abscess formation = tubo-ovarian abscesses)
- May lead to adhesions, infertility and ectopic pregnancy

PID



FALLOPIAN TUBE CARCINOMA:

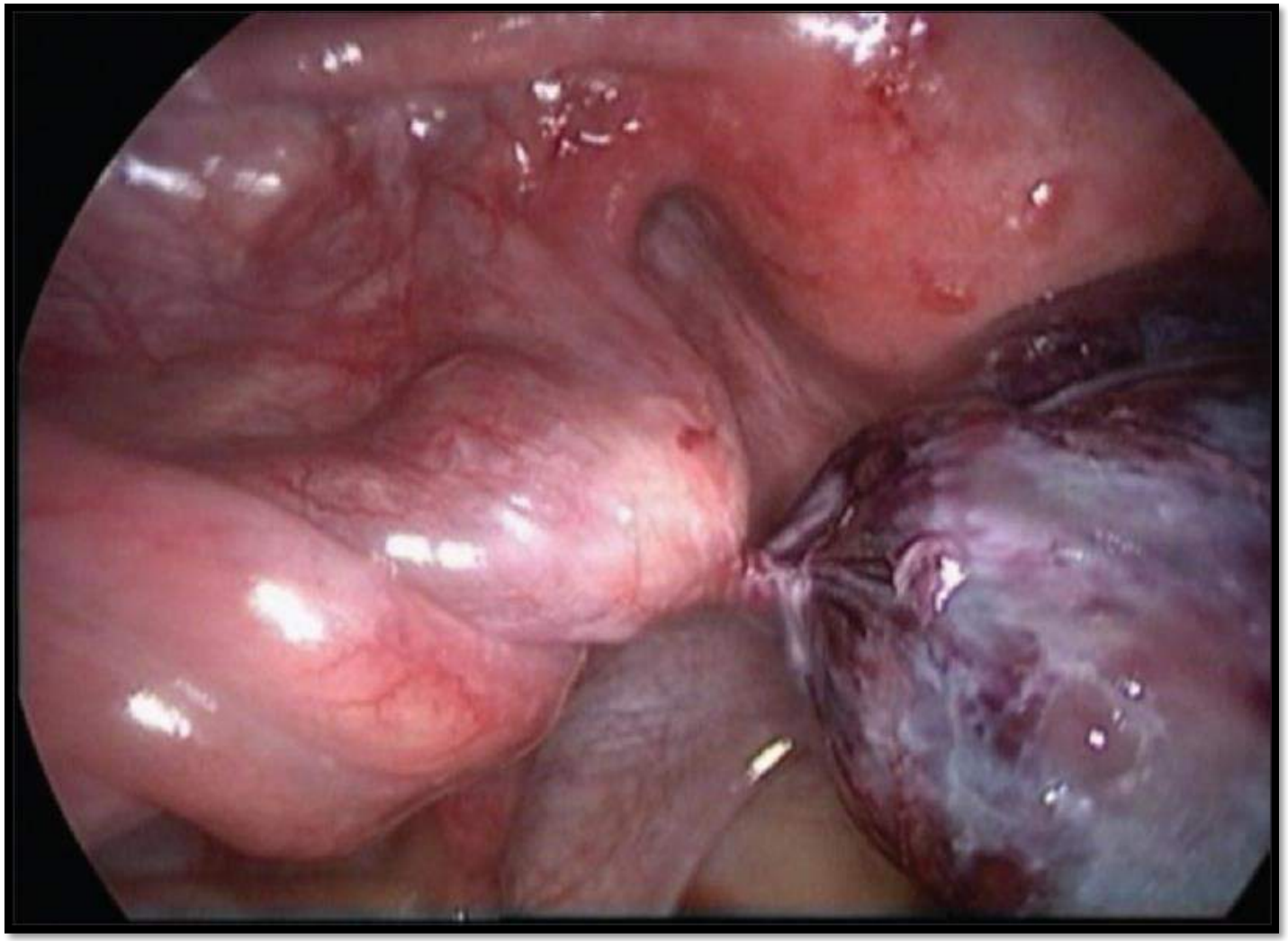
- **Rare but can occur**
- **Usually high grade serous type carcinoma**
- **Can be preceded by serous tubal intraepithelial carcinoma (STIC)**
- **Seen in patients with *BRCA1* and *BRCA2* mutations**
- **Many have *TP53* mutations**
- **They usually present late (mets to ovaries and peritoneal cavity)**

OVARIAN PATHOLOGY

FOLLICULAR AND LUTEAL CYSTS:

- Very common and benign
- Unruptured graafian follicle
- Single or multiple; variable in size
- May rupture causing acute abdomen and intraperitoneal bleeding
- May twist and cause acute abdomen “torsion”

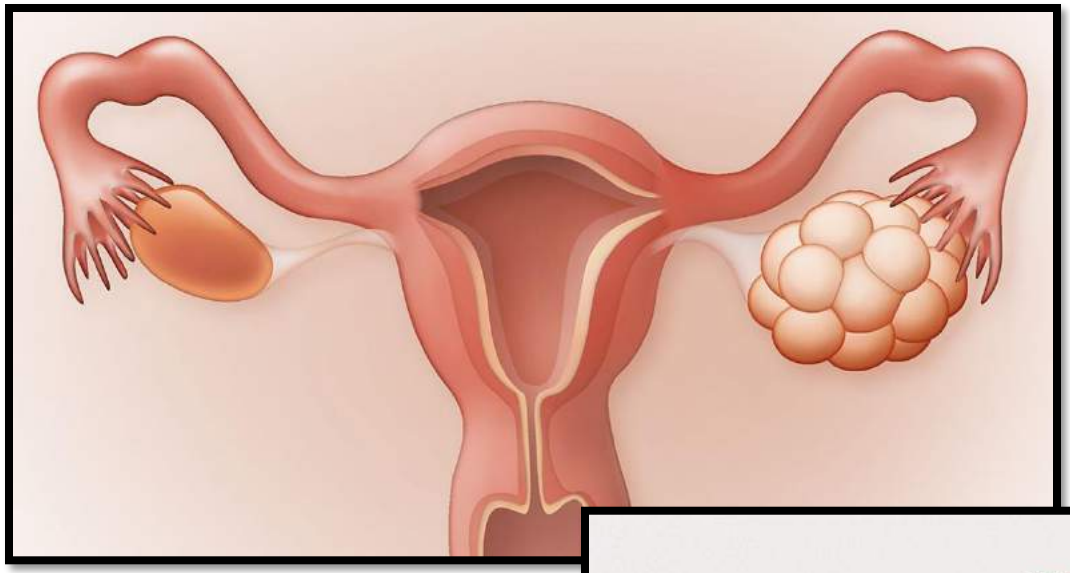
TORSION OVARIAN CYST:

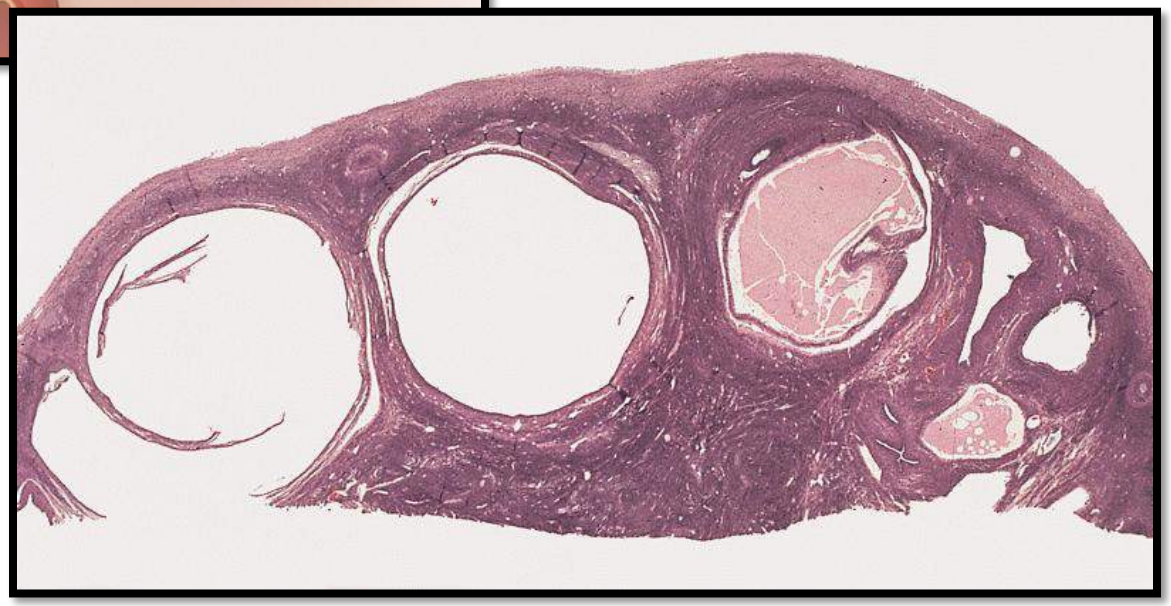


POLYCYSTIC OVARIAN SYNDROME:

- **Old name: *Stein-leventhal syndrome***
- **Hyperandrogenism+menstrual abnormalities+PCO+chronic anovulation & decreased fertility**
- **Unknown cause (? Imbalance of LH/FSH ratio)**
- **Young females after menarche; oligomenorrhea, hirsutism, infertility and obesity**

PATHOLOGIC FEATURES:





OVARIAN TUMORS: GENERAL FACTS

- Relatively common tumors; many are lethal
- Mortality ranks fifth in women
- Can arise from 3 cell lines: 1. multipotent coelomic epithelium (70-80%) 2. totipotent germ cells 3. sex cord-stromal cells
- 90% of malignant ovarian cancer are epithelial
- They tend to present late (stage IV) with peritoneal involvement

SURFACE EPITHELIAL TUMORS:

- **Thought to arise from fallopian tube epithelium and cysts**
- **Benign ones are usually cystic (cystadenoma or cystadenofibroma)**
- **Malignant ones maybe cystic (cystadenocarcinoma) or solid (carcinoma)**
- **Some are borderline malignancy (borderline tumors)**

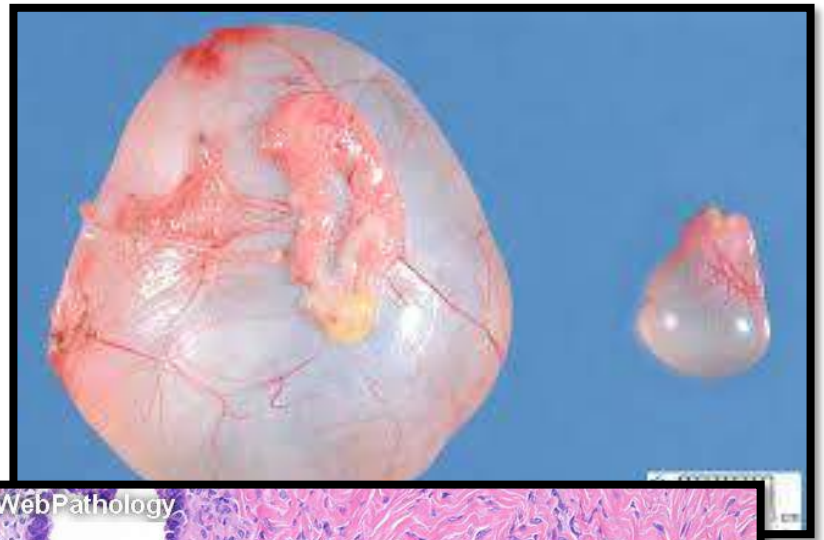
RISK FACTORS FOR OVARIAN CANCER:

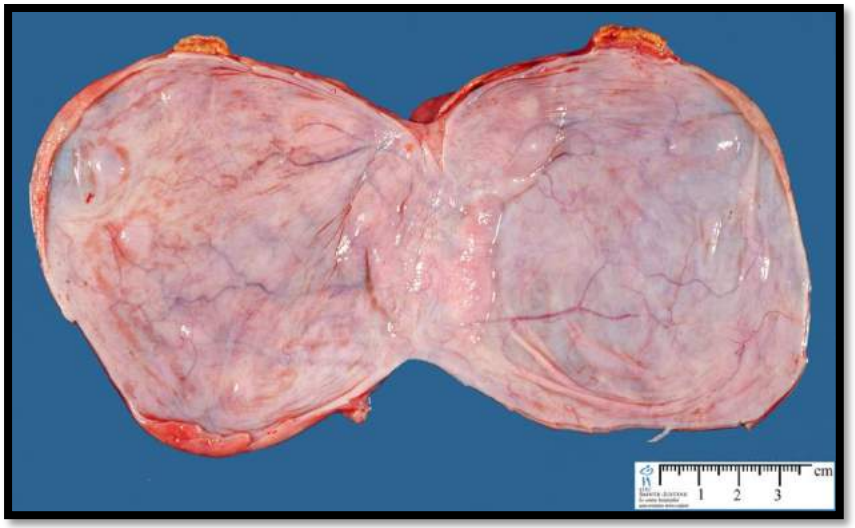
- **Nulliparity**
- **Family history**
- **Germline mutations in TS genes**
- **Unmarried women and women with low parity**
- **Prolonged use of OCP reduces the risk**
- **5-10% are familial and most have mutations in *BRCA1* & *BRCA2***
- **Life risk in *BRCA1* 30%; but *BRCA2* is lower**
- **Sporadic ovarian cancer only 10% have mutations in *BRCA1* & *BRCA2***

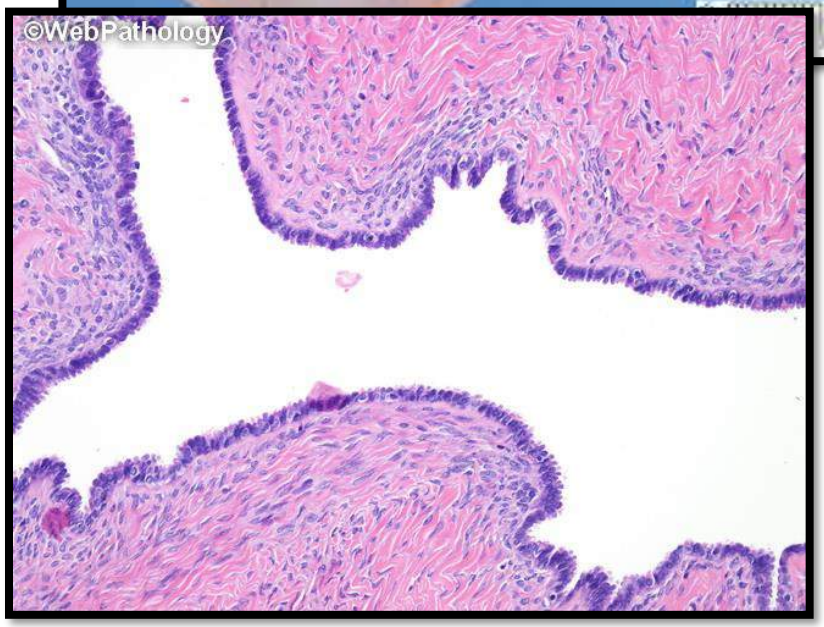
TABLE 19.3 Frequency of Major Ovarian Tumors

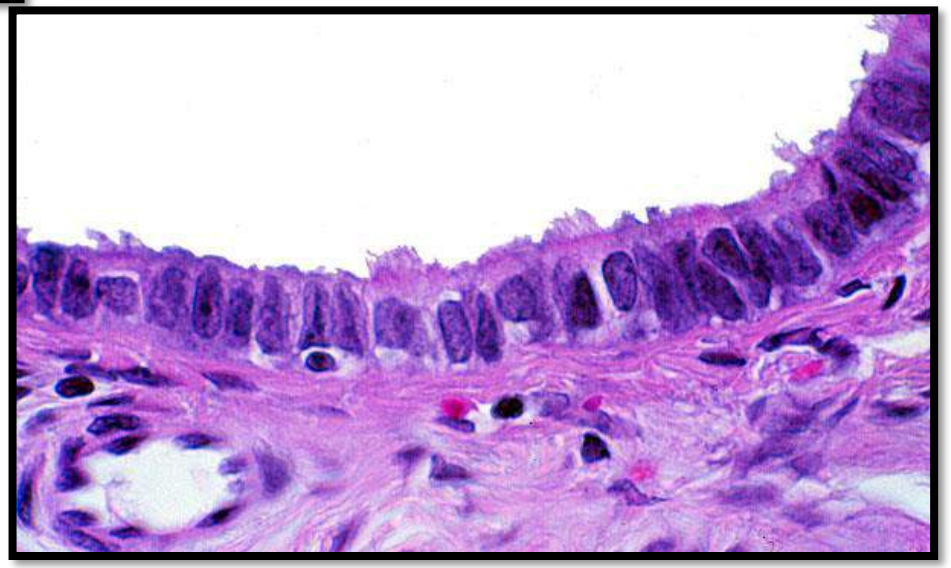
Type	Percentage of Malignant Ovarian Tumors	Percentage That Are Bilateral
Serous	47	
Benign (60%)		25
Borderline (15%)		30
Malignant (25%)		65
Mucinous	3	
Benign (80%)		5
Borderline (10%)		10
Malignant (10%)		<5
Endometrioid carcinoma	20	30
Undifferentiated carcinoma	10	—
Clear cell carcinoma	6	40
Granulosa cell tumor	5	5
Teratoma	1	
Benign (96%)		15
Malignant (4%)		Rare
Metastatic	5	>50
Others	3	—

SEROUS CYSTADENOMA FEATURES:

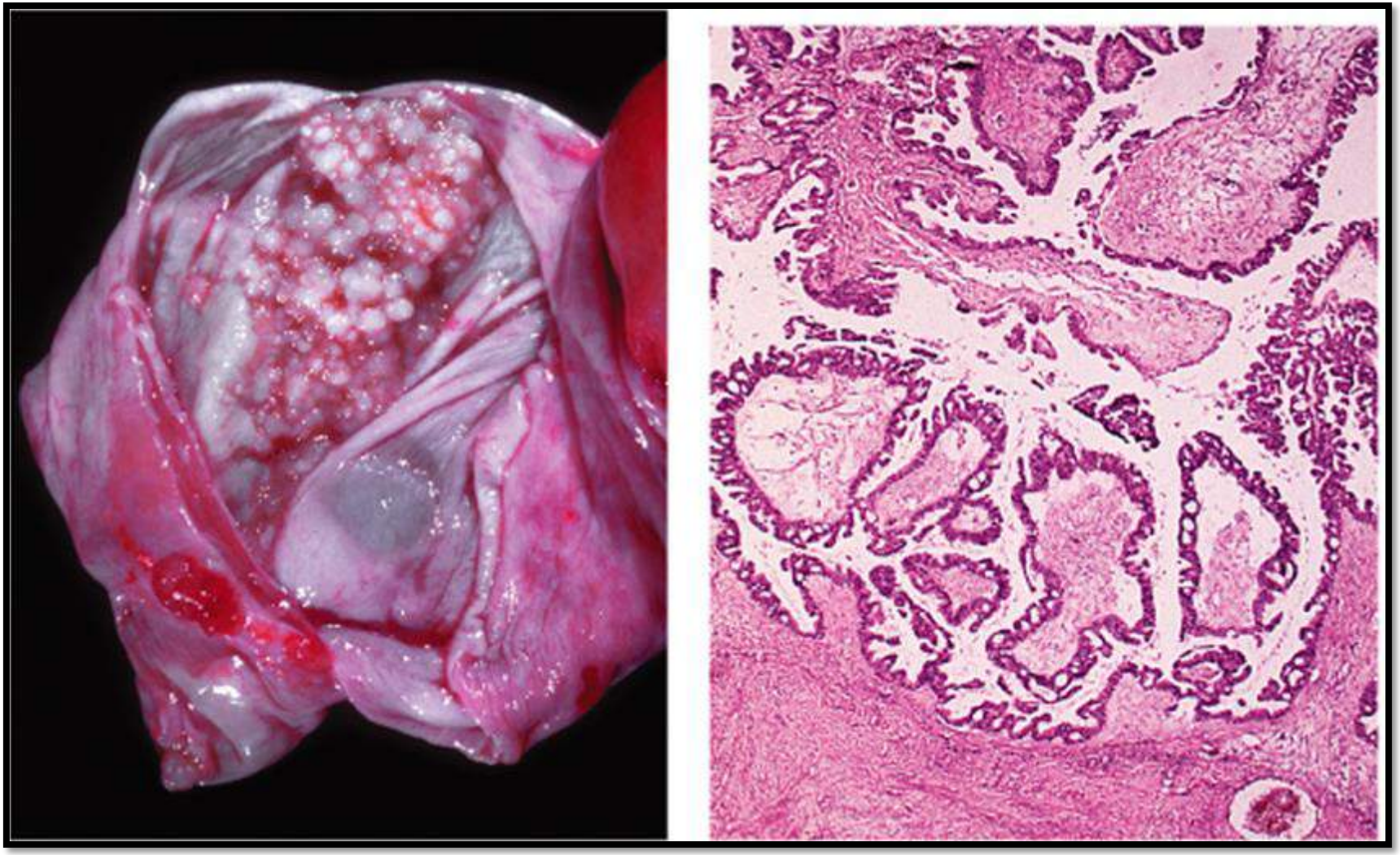








BORDERLINE SEROUS TUMORS:



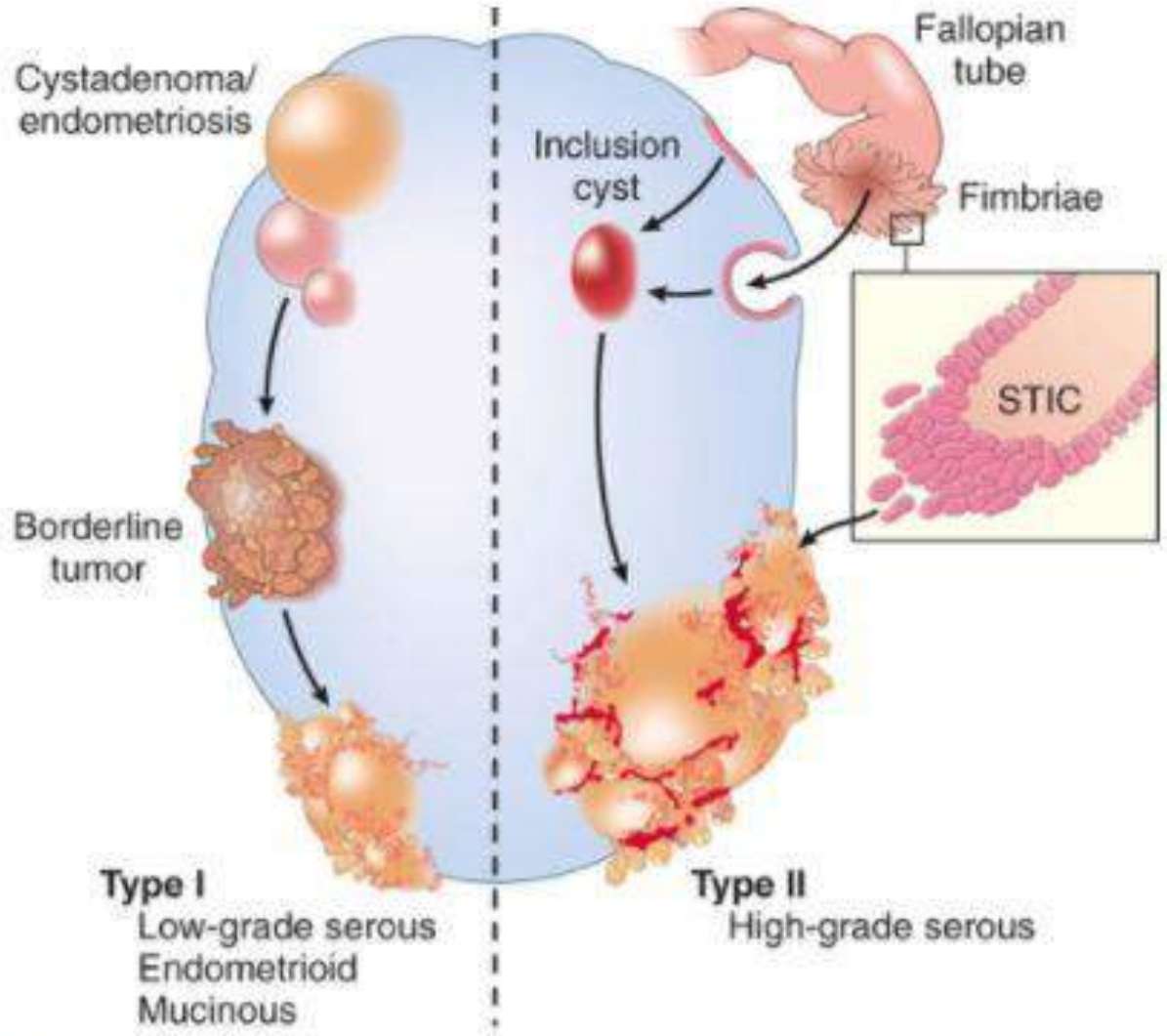
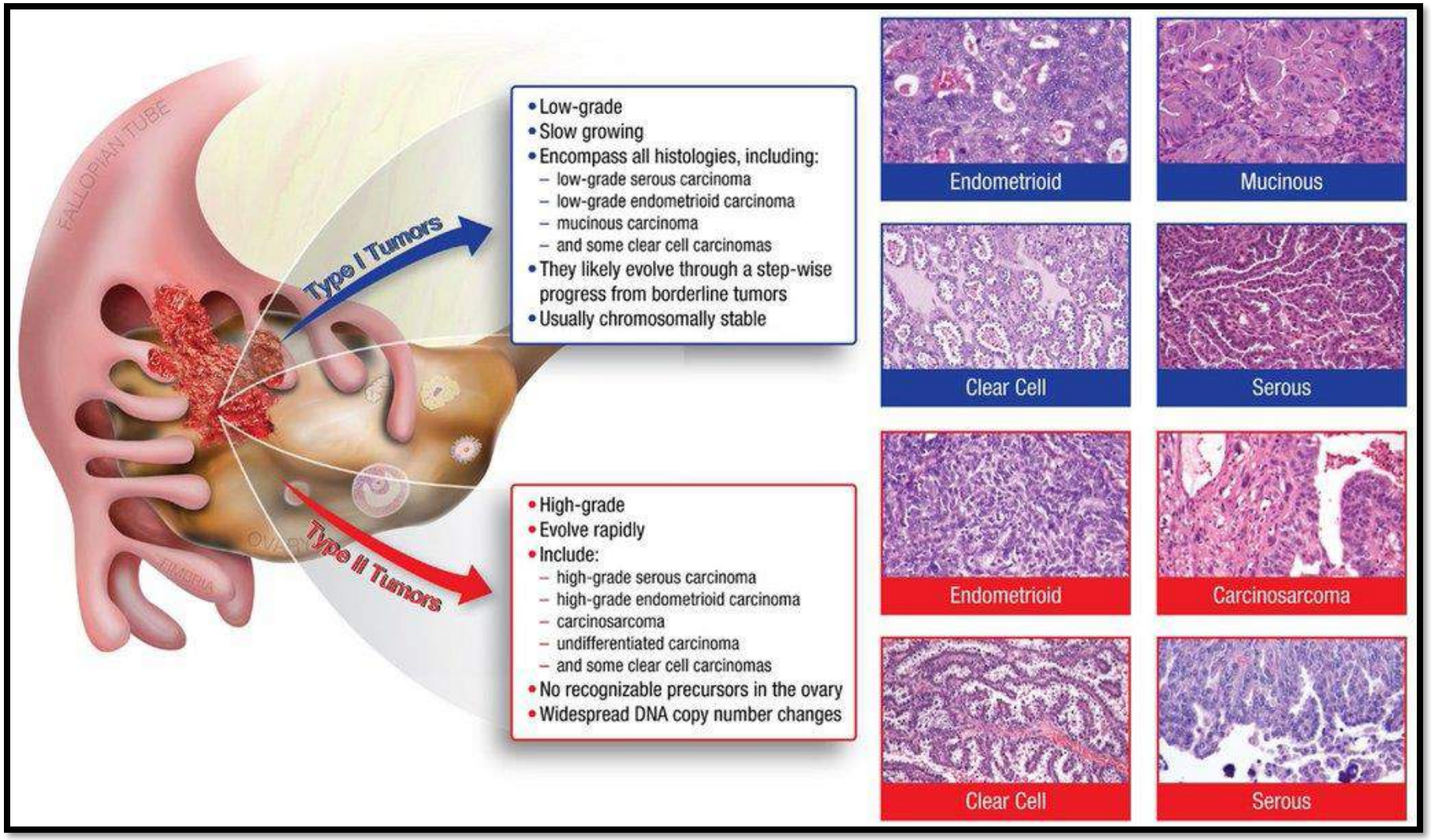
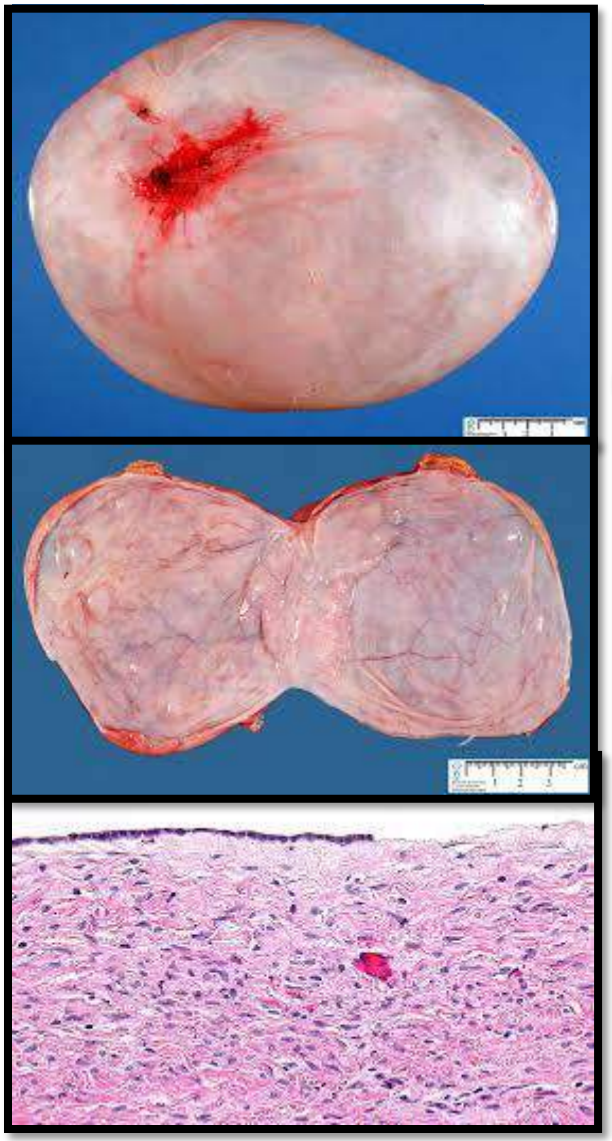


FIG. 19.15 Derivation, of various ovarian neoplasms. Type I tumors progress from beni...

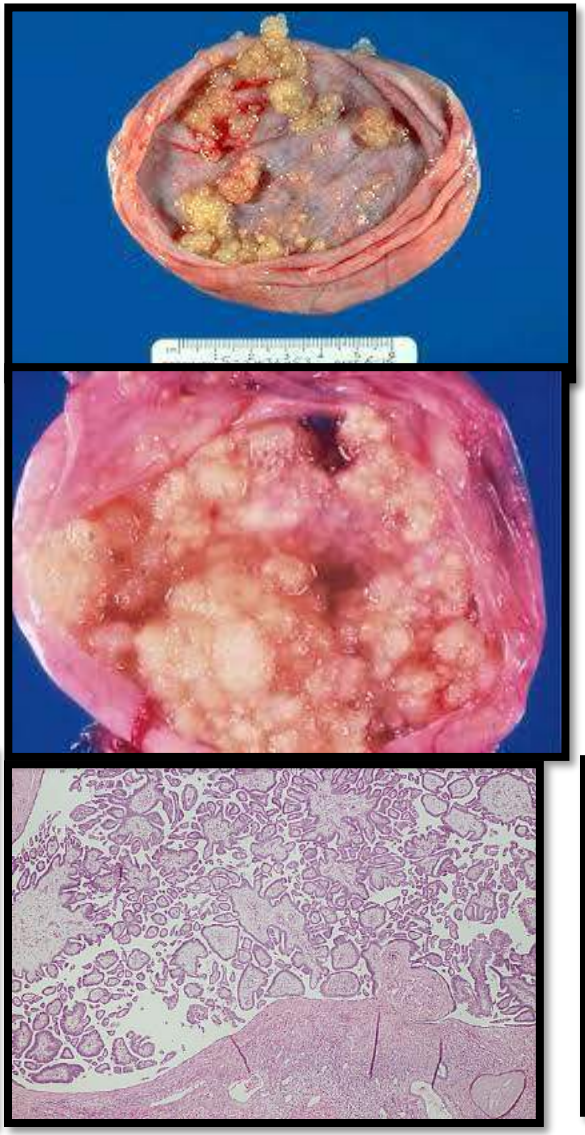
TYPE I & II OVARIAN TUMORS



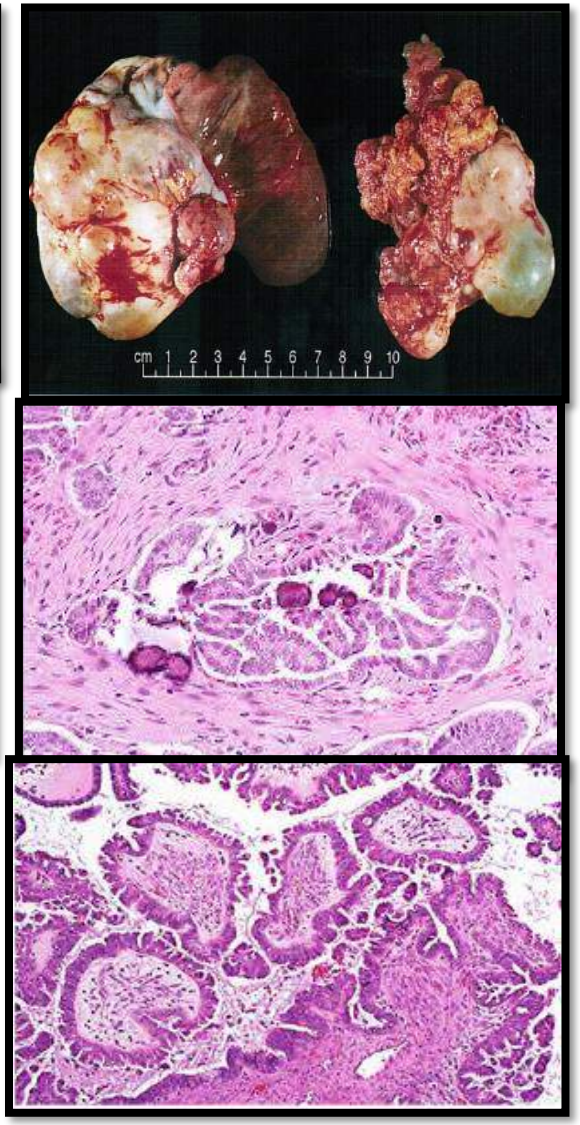
SCA



SBT



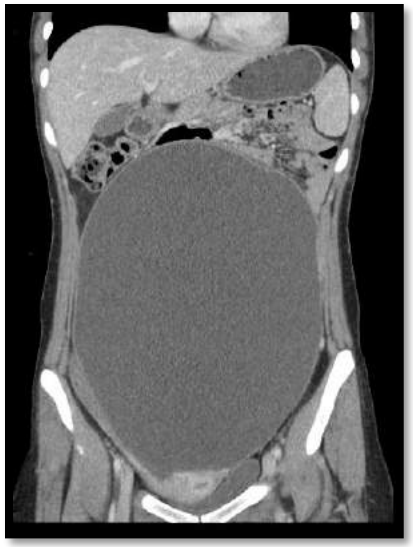
SCarcinoma

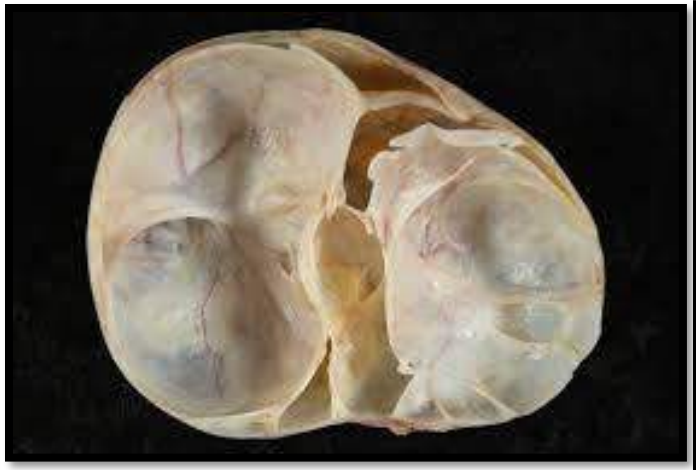


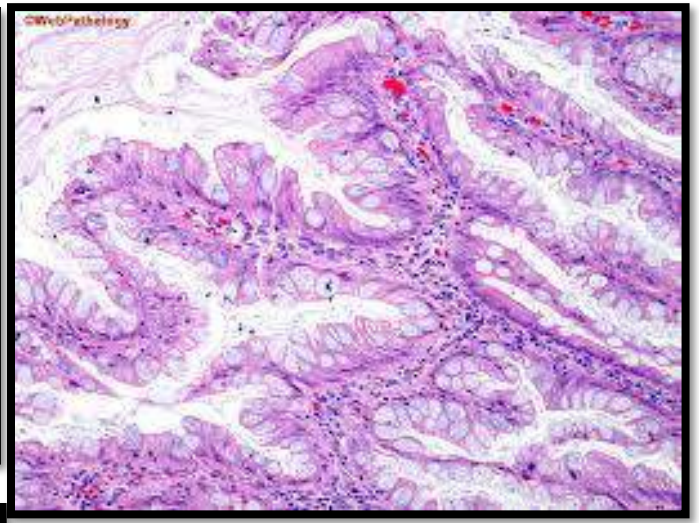
MUCINOUS TUMORS:

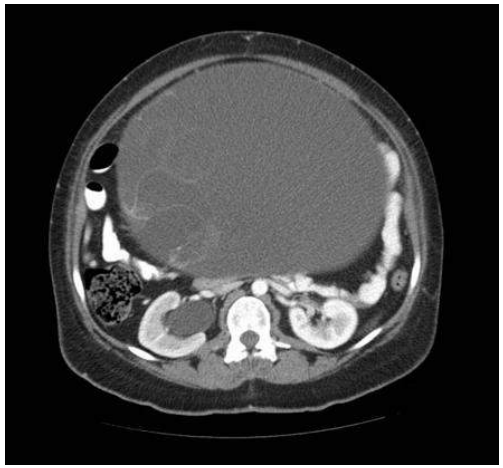
- **Cells contain mucin**
- **Less likely to be malignant than serous (10% malignant, 10% Borderline & 80% B9)**
- **More likely larger and multicystic than serous but less likely bilateral**
- **Bilateral mucinous ovarian tumors are more likely metastatic from GI tract "Krukenberg tumor"**
- **Peritoneal mucinous carcinoma "pseudomyxoma peritonei"…more GI primary**
- ***KRAS* mutations are common like GIT (50%)**
- **Stage for stage, better prognosis than serous**

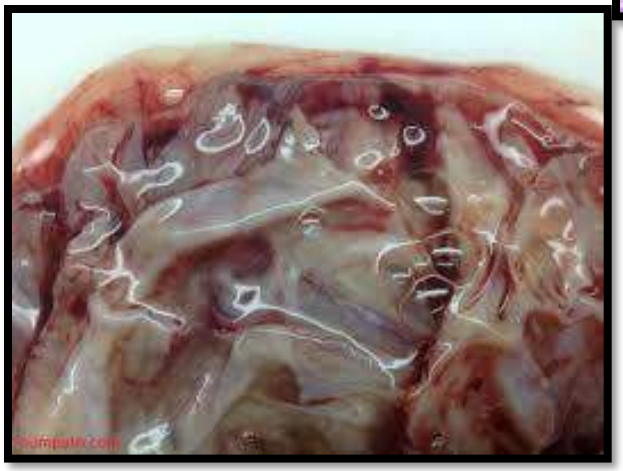
MCA: PATHOLOGIC FEATURES



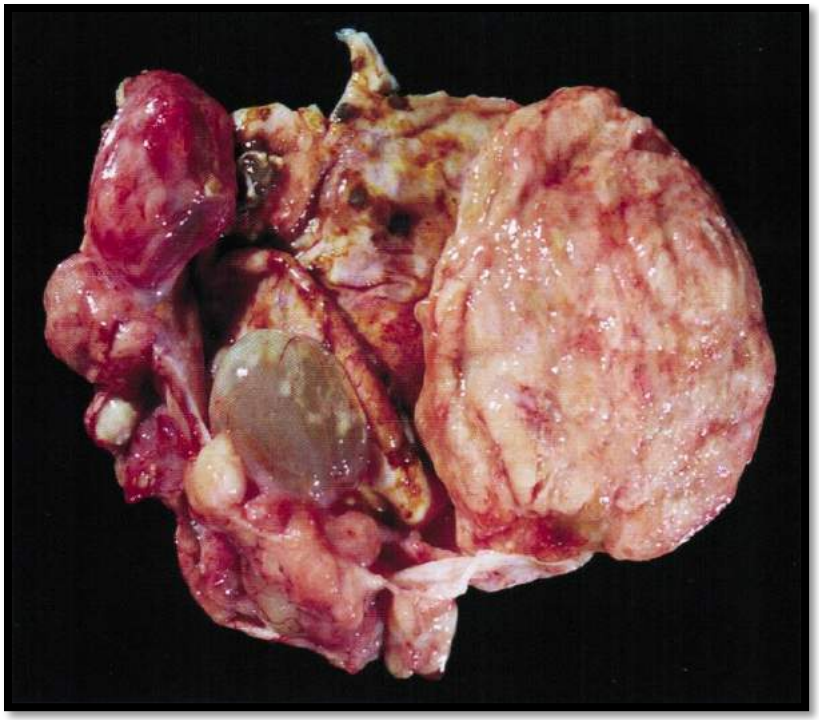


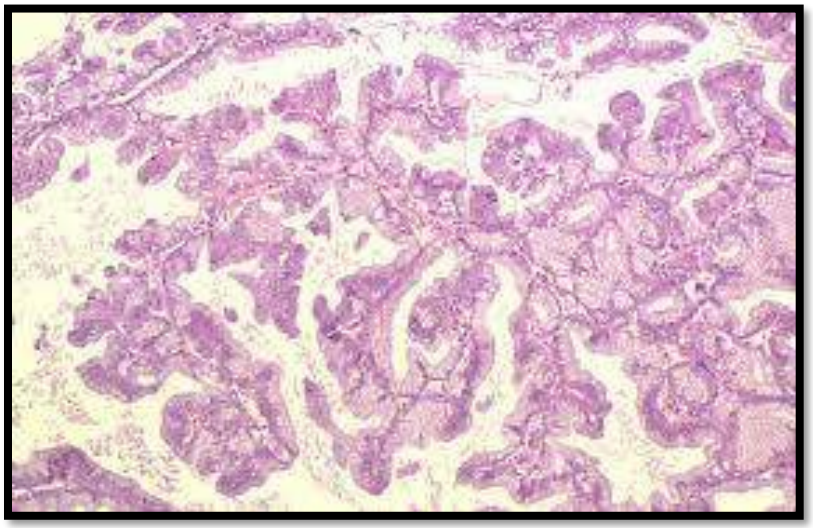


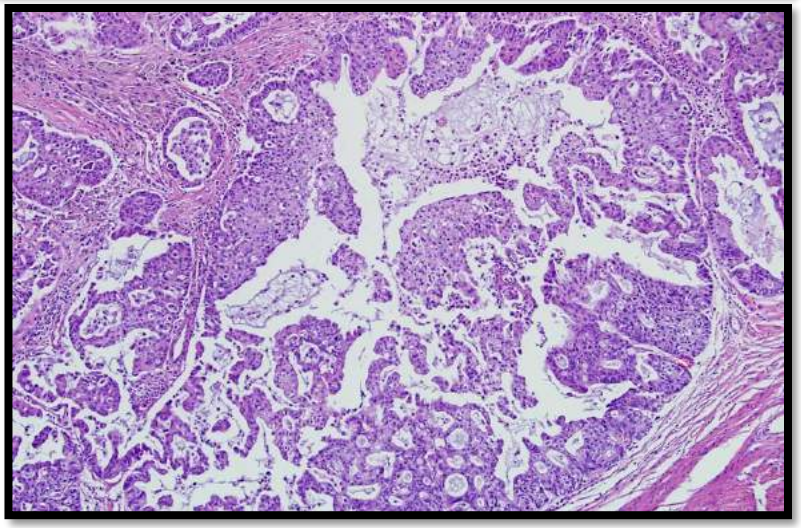




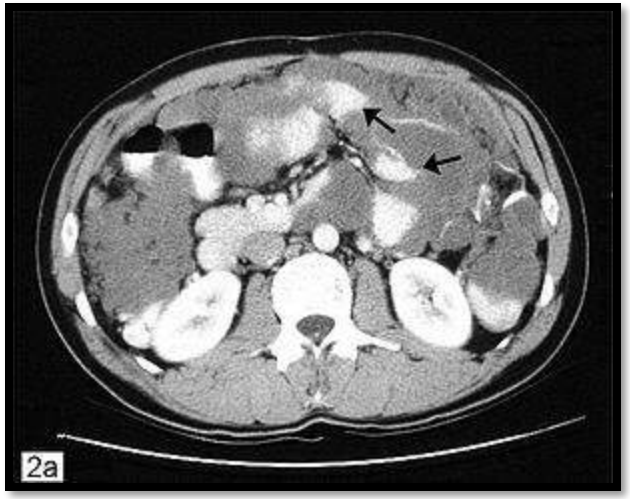
MUCINOUS CARCINOMA FEATURES:

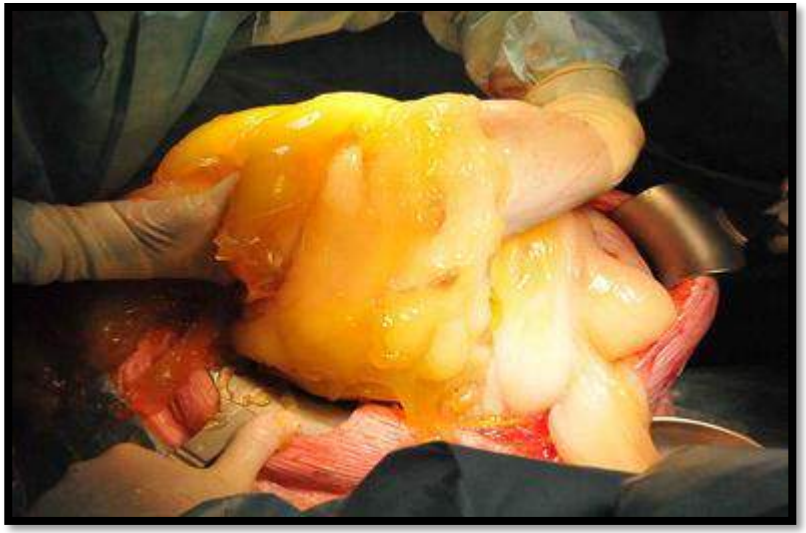


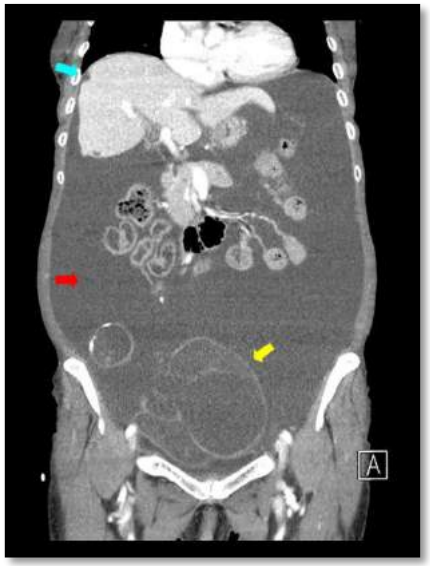


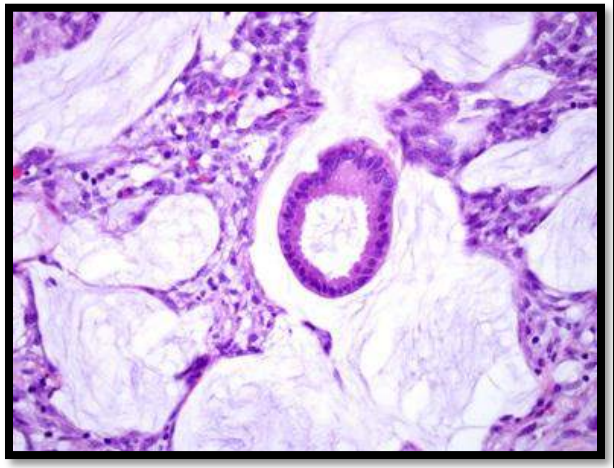


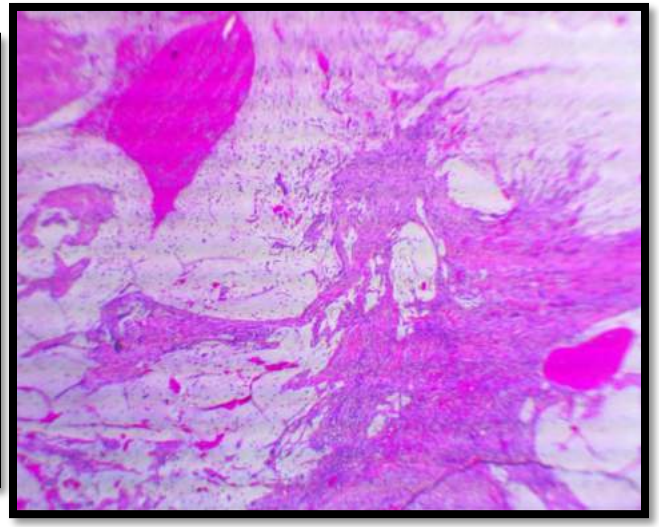
PSEUDOMYXOMA PERITONEIT FEATURES:





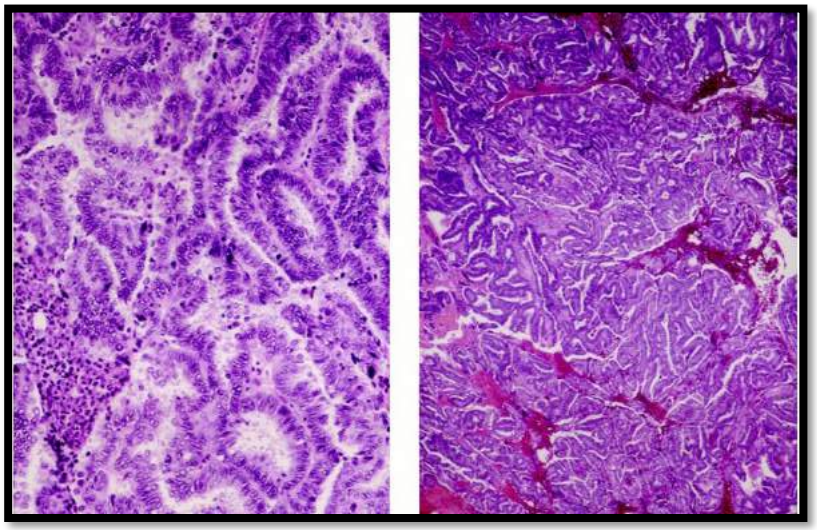






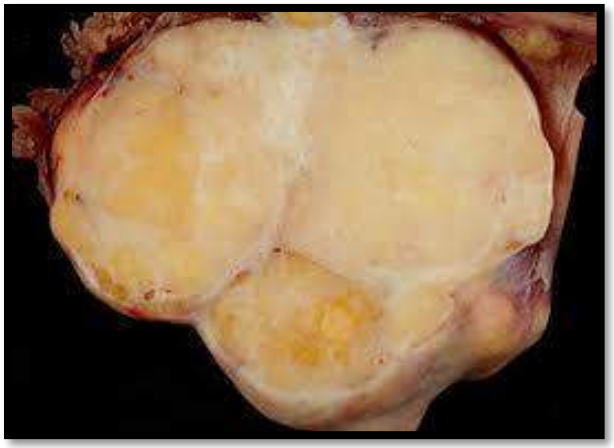
ENDOMETIOID CARCINOMA:

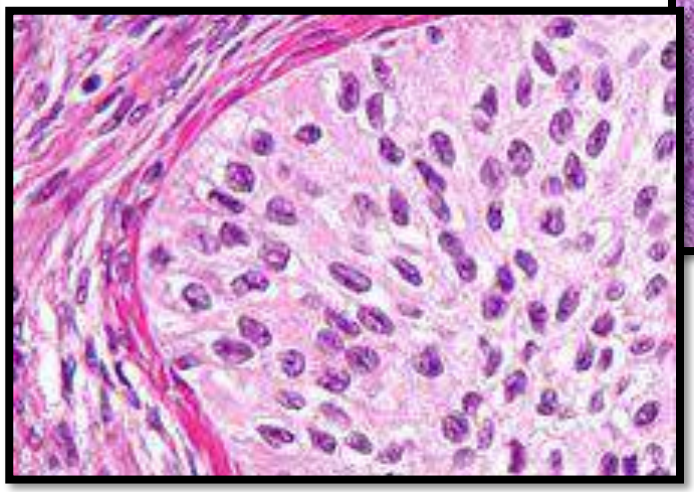
- Solid or cystic
- Arise from endometriosis
- Similar histology to endometrial carcinoma
- Bilateral in 30%
- 15-30% have concomitant endometrial Ca
- *PTEN* TS gene mutations and those with upregulation of P13-AKT signaling pathway



BRENNER TUMOR:

- Uncommon; solid, unilateral tumor
- Nests of bland transitional-type epithelium
- Most are benign; few can be malignant





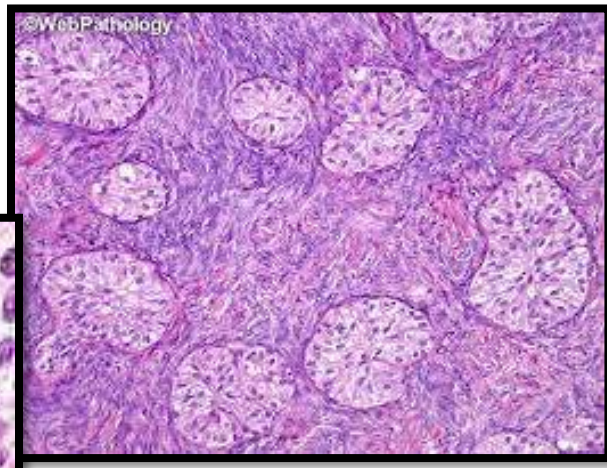


TABLE 19.4 Salient Features of Ovarian Germ Cell and Sex Cord Neoplasms

Neoplasm	Peak Incidence	Usual Location	Morphologic Features	Behavior
Germ Cell Origin				
Dysgerminoma	Second to third decade of life Occur with gonadal dysgenesis	Unilateral in 80%–90%	Counterpart of testicular seminoma Sheets or cords of large clear cells Stroma may contain lymphocytes and occasional granulomas	All malignant but only one-third metastasize; all radiosensitive; 80% cure rate
Choriocarcinoma	First 3 decades of life	Unilateral	Identical to placental tumor Two types of epithelial cells: cytotrophoblast and syncytiotrophoblast	Metastasizes early and widely Primary focus may degenerate, leaving only metastases Resistant to chemotherapy
Sex Cord Tumors				
Granulosa-theca cell	Most postmenopausal, but may occur at any age	Unilateral	Composed of mixture of cuboidal granulosa cells and spindled or plump lipid-laden theca cells Granulosa elements may recapitulate ovarian follicle as Call-Exner bodies	May elaborate large amounts of estrogen Granulosa element may be malignant (5%–25%)
Thecoma-fibroma	Any age	Unilateral	Yellow (lipid-laden) plump thecal cells	Most hormonally inactive About 40% produce ascites and hydrothorax (Meigs syndrome) Rarely malignant

Sertoli-Leydig cell	All ages	Unilateral	Recapitulates development of testis with tubules or cords and plump pink Sertoli cells	Many masculinizing or defeminizing Rarely malignant
Metastases to Ovary				
	Older ages	Mostly bilateral	Anaplastic tumor cells, cords, glands, dispersed through fibrous background Cells may be "signet ring" mucin-secreting	Primaries are gastrointestinal tract (Krukenberg tumors), breast, and lung

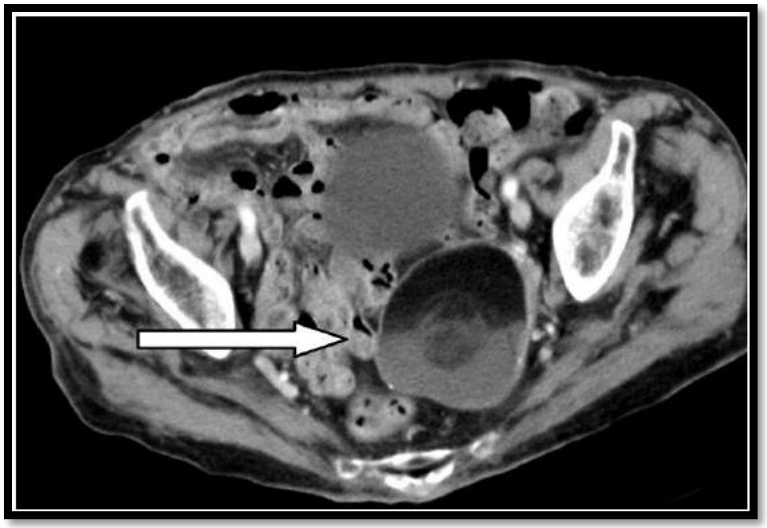
TERATOMAS:

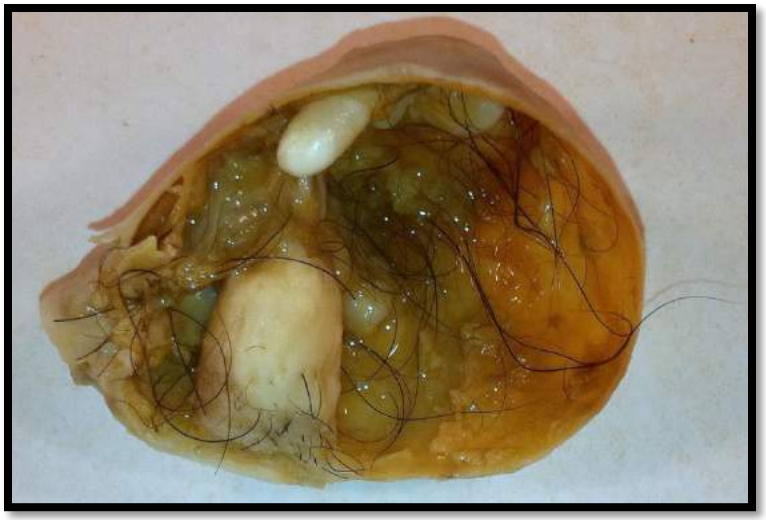
- Germ cell tumors, arise from totipotent germ cells
- Forming mature cell lines Ectoderm, endoderm and mesoderm
- Usually midline or para-axial location
- 90% are benign
- First 2 decades of life

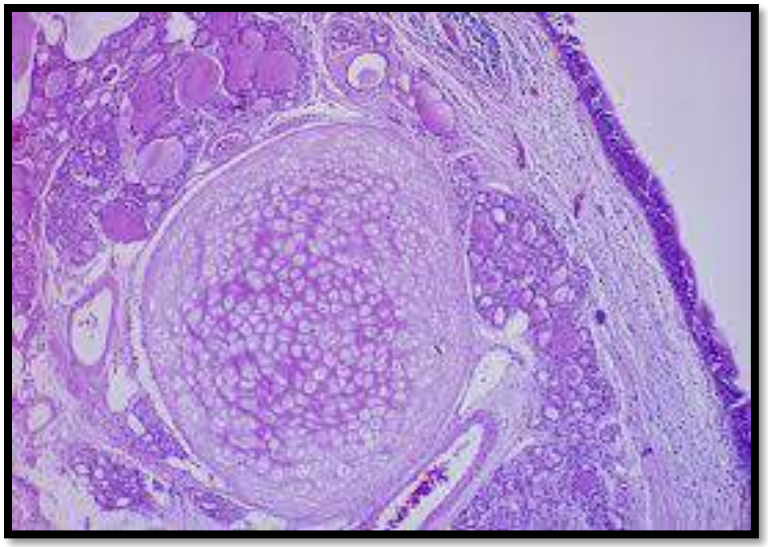
MATURE CYSTIC TERATOMA (DERMOID CYST)

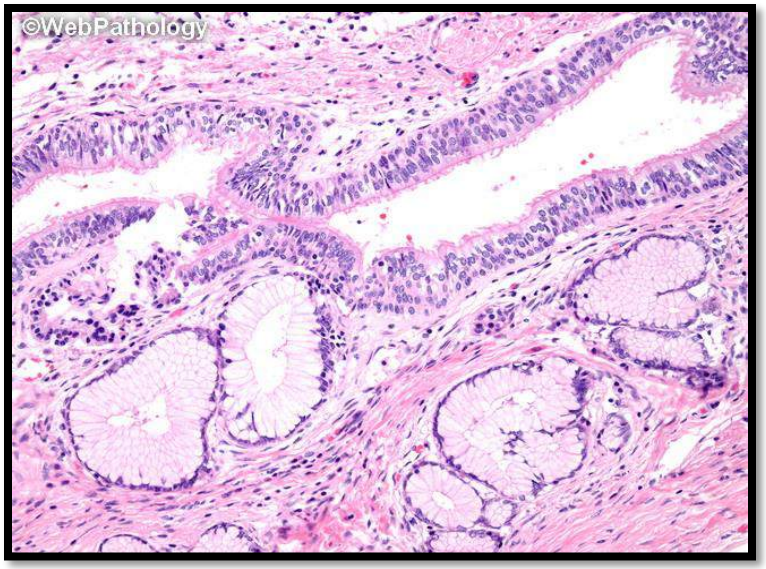
- Mature tissue from different all germ cells (skin, hair, teeth, bone, glands…etc.)
- Young women (10-30); unilateral, incidental
- Less than 10 cm
- Can undergo torsion and cause infertility
- Rare malignant transformation
- Surgical removal is the treatment

FEATURES OF MATURE TERATOMA:





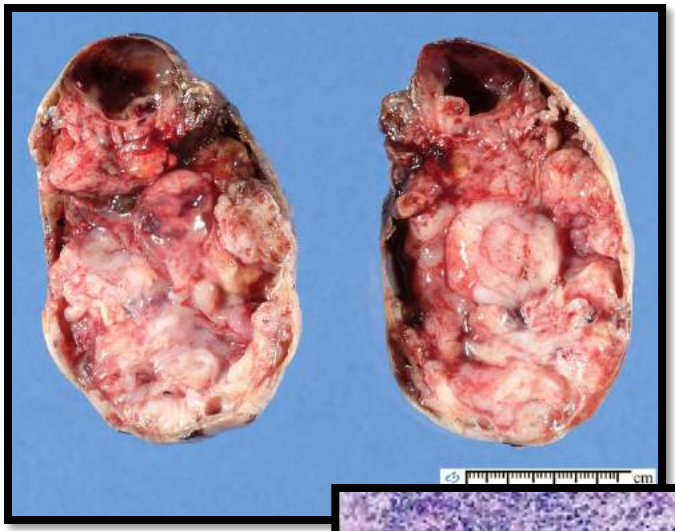


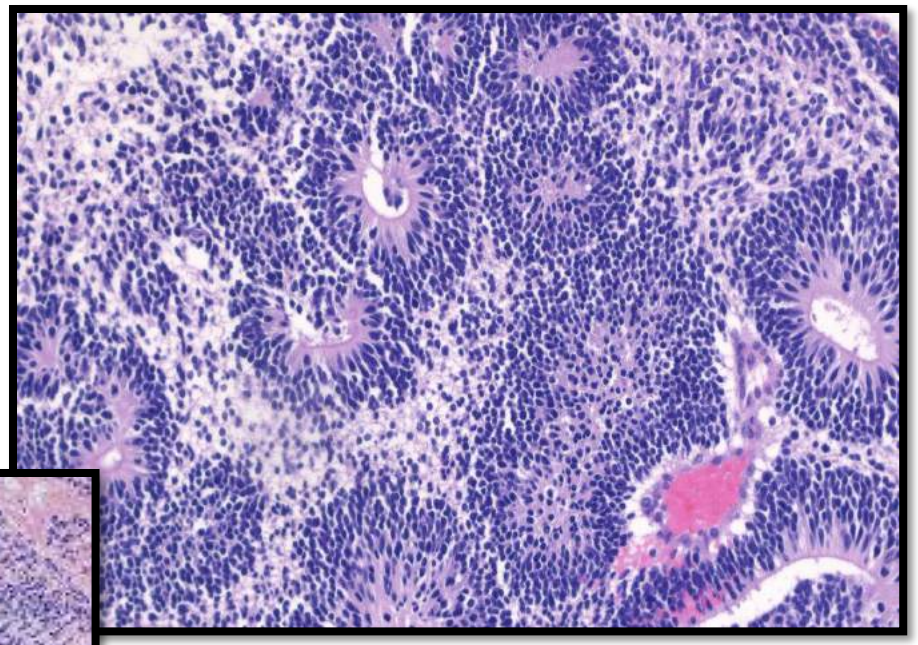


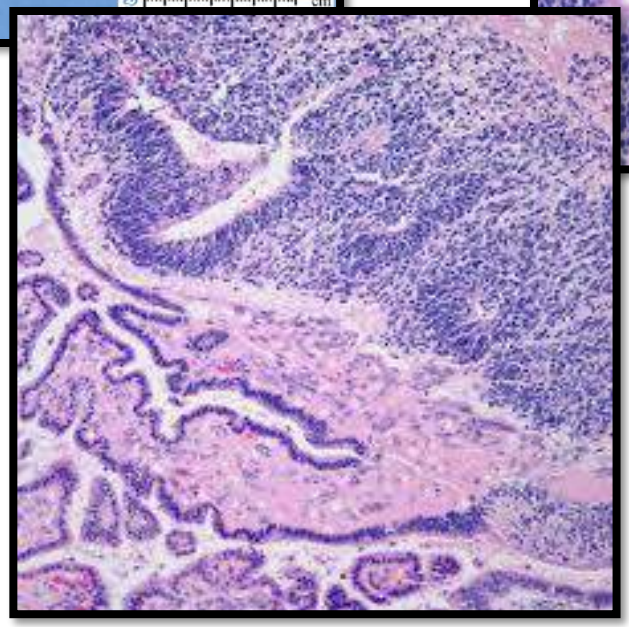
IMMATURE (MALIGNANT) TERATOMA:

- **Early presentation (< 20 years)**
- **Bulky and more solid**
- **Necrosis on cut section +basic mature elements**
- **The diagnostic feature is finding immature elements (neural, mesenchymal..etc..), has to be sampled very well**
- **Prognosis depends on grade and stage**

IMMATURE TERATOMA FEATURES:

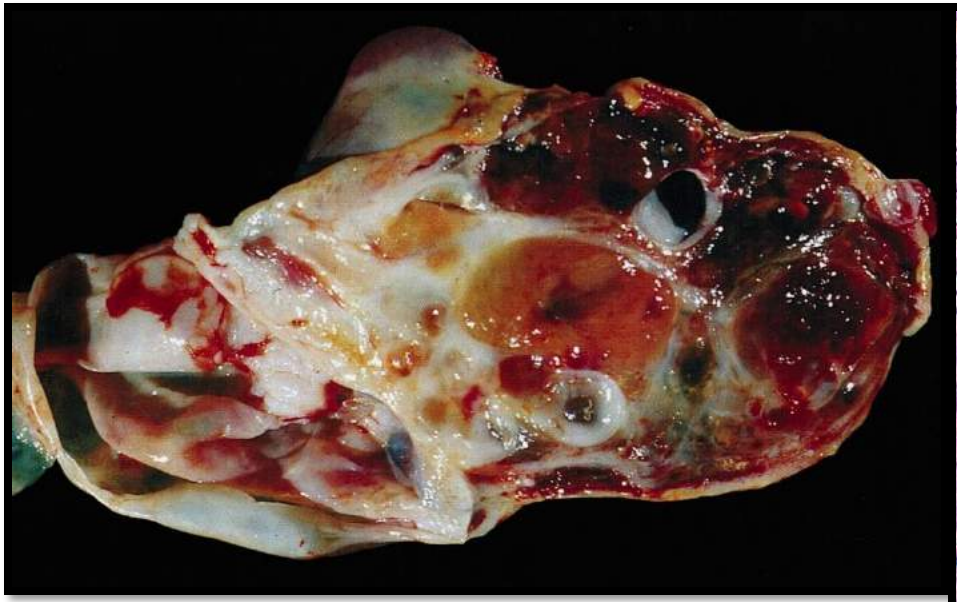


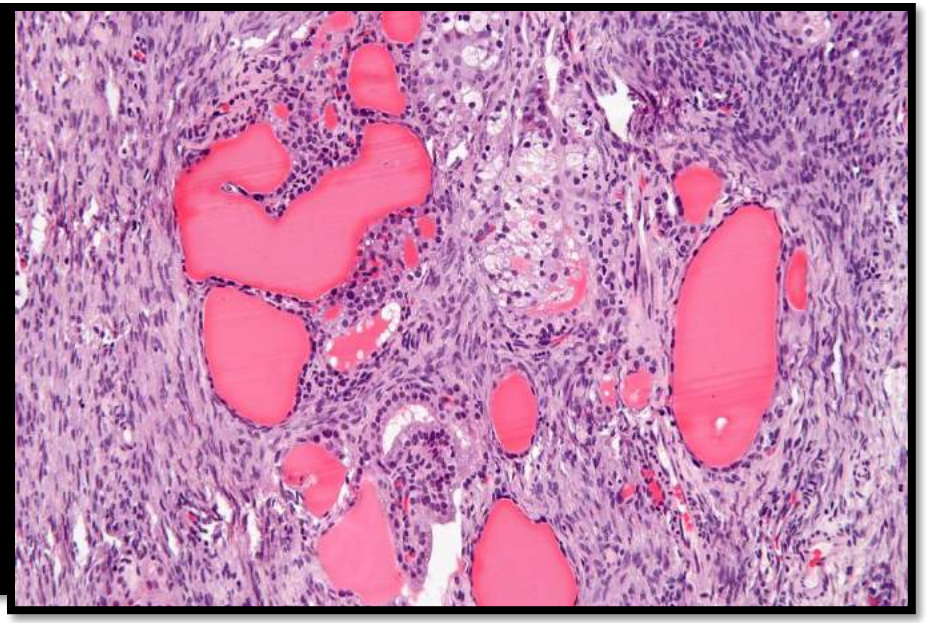




STRUMA OVARII:

- Very specialized benign teratoma
- Contains mature thyroid tissue (maybe functional)

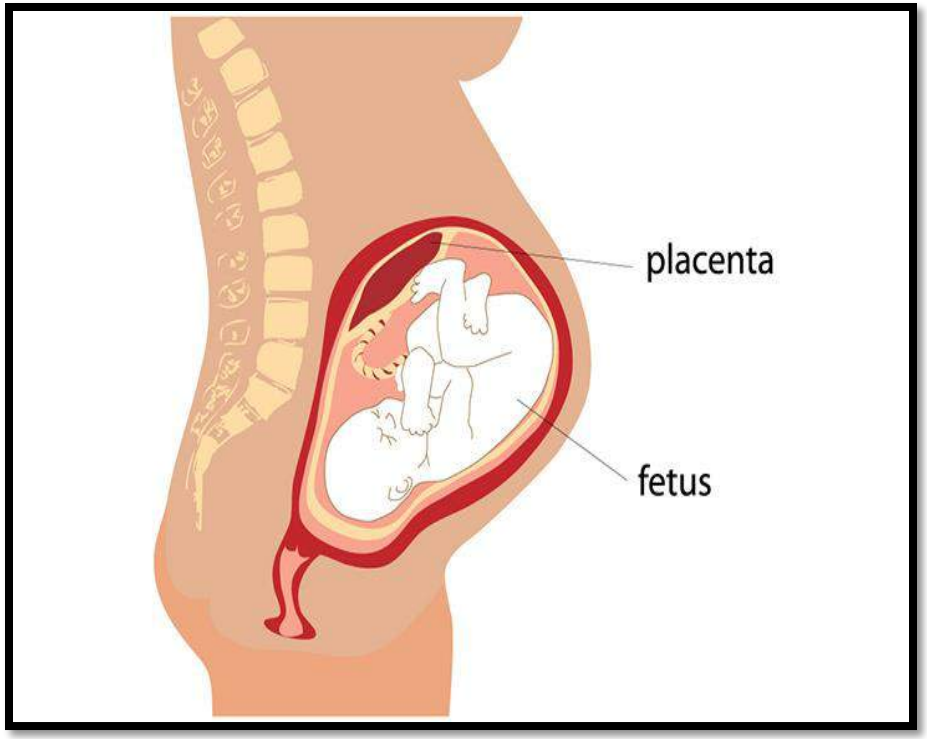




CLINICAL FEATURES OF OVARIAN TUMORS:

- Late presentation (stage IV; malignant ascites, serous carcinoma)
- Pose diagnostic challenges
- Still carry high mortality and bad prognosis
- Survival improvement is modest
- 30% discovered incidentally
- No “good” screening test (CA125 ?)

DISEASES OF PLACENTA AND PREGNANCY



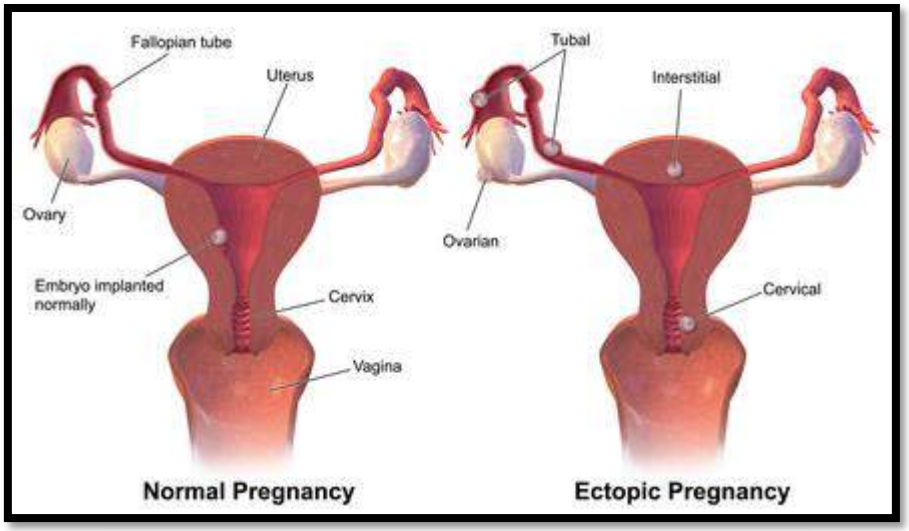
PLACENTAL INFLAMMATION AND INFECTIONS:

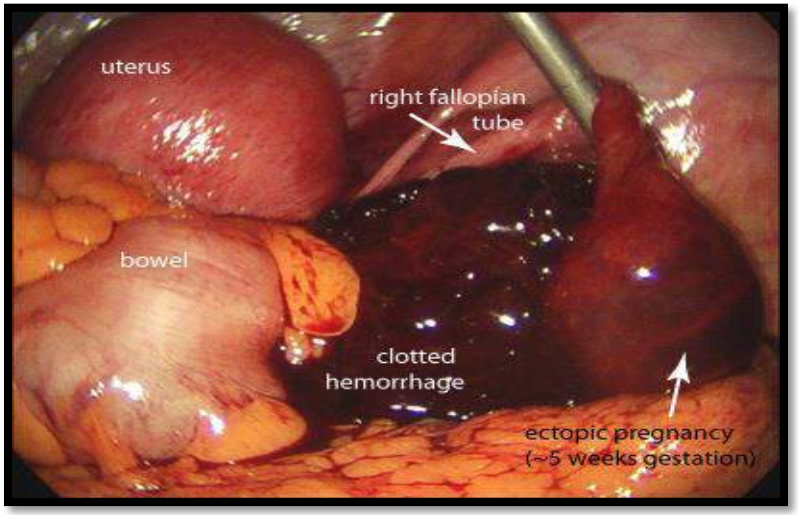
ASCENDING INFECTIONS:	HEMATOGENOUS:
• More common • Mostly bacterial and cause premature membrane rupture (histology show acute chorioamnionitis, neutrophils), may extend to umbilicus (acute funisitis) • Mycoplasma, candida and vaginal flora bacteria	• Less common • Bacteria via blood stream • Histology: villitis • TB, Listeria, Syphilis, Toxoplasma, viruses (Rubella, CMV, HSV) • May affect fetus causing “TORCH” complex

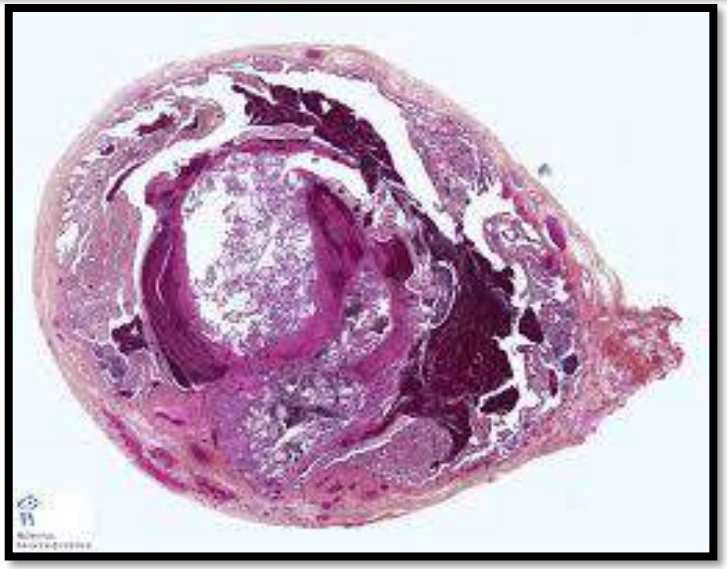
ECTOPIC PREGNANCY:

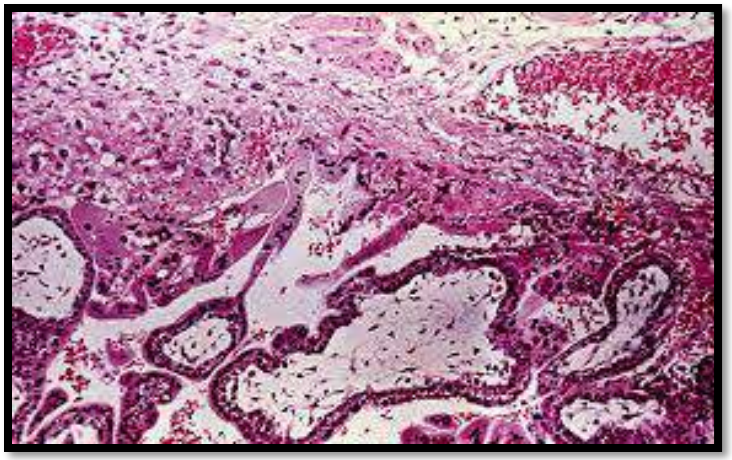
- **Fertilization of ova outside uterus, 1%, mostly fallopian tube (90%)**
- **Causes (slow ova move): salpingitis, uterine tumors and endometriosis**
- **50% no anatomic cause found**
- **Tubal ectopic: hemosalpinx, enlargement, may rupture (acute abdomen and sometimes fatal bleeding)**

TUBAL ECTOPIC PREGNANCY FEATURES:









GESTATIONAL TROPHOBLASTIC DISEASES:

- Abnormal proliferation of fetal trophoblasts
- Molar and nonmolar diseases
- Molar: Partial, complete or invasive hydatidiform mole
- Nonmolar: choriocarcinoma
- All have high levels of hCG in serum and urine
- Level is important for dx and monitoring of therapy

HYDATIDIFORM MOLE:

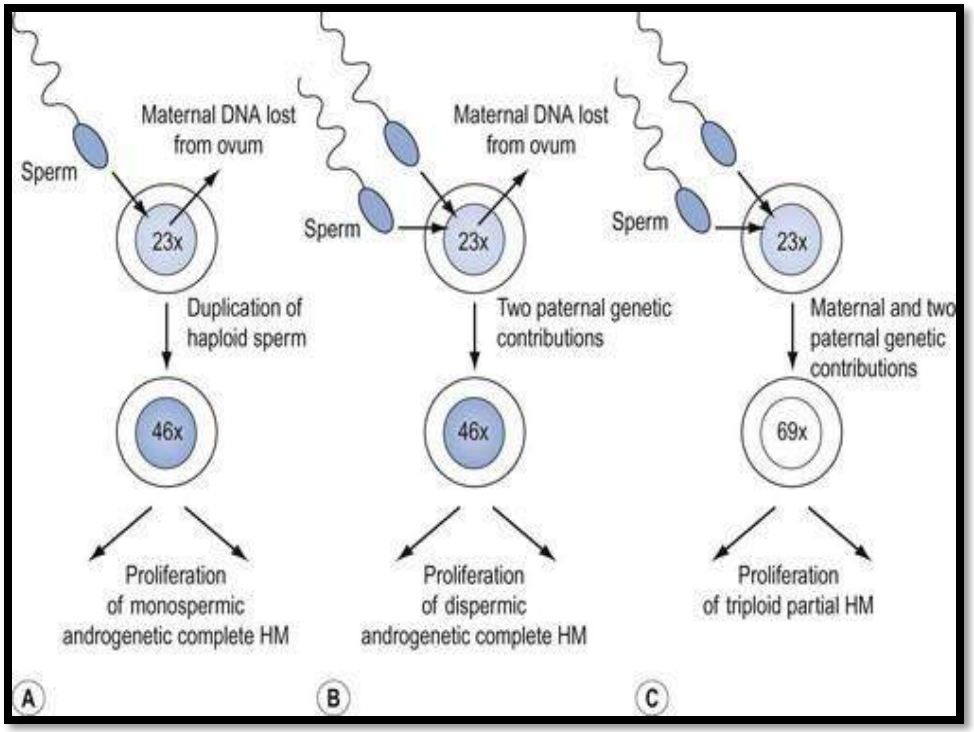
COMPLETE MOLE:

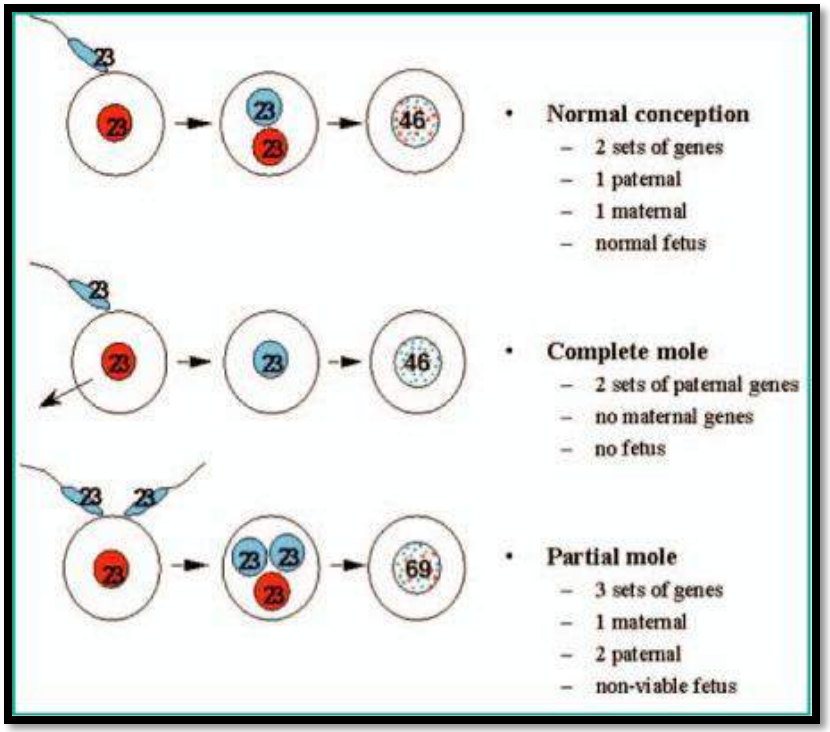
- Large mass of swollen cystically dilated villi
- Normal or atypical chorionic epithelium
- No fetal tissue
- Diploid (46XX or 46XY) two spermatozoa1/2000 pregnancies (> in Asia)
- "Large for date"
- Antepartum care increased early detection (U/S exam)
- Before 20 and after 40 yr of age
- 10% invasive after curetting, 2-3% develop into choriocarcinoma

PARTIAL MOLE:

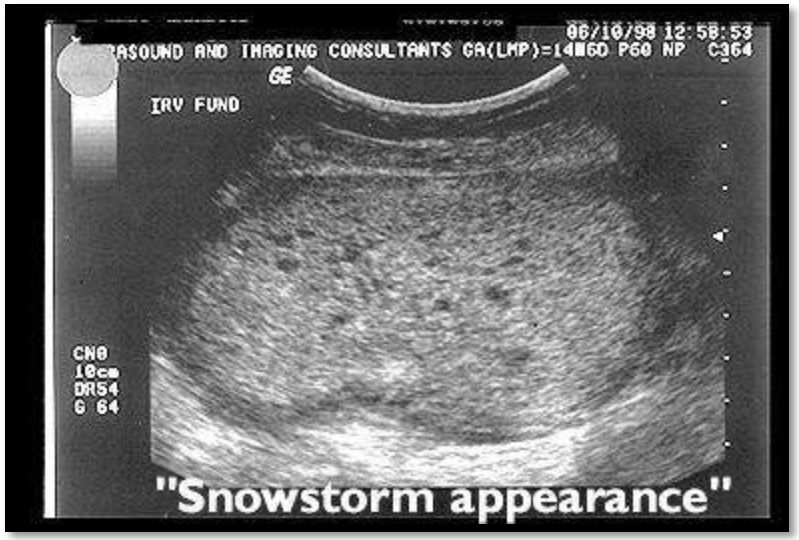
- Less swollen and less proliferation or incomplete proliferation
- Can have fetal tissue
- Triploid (i.e. 69XXY); one egg fertilized by 2 spermatozoa

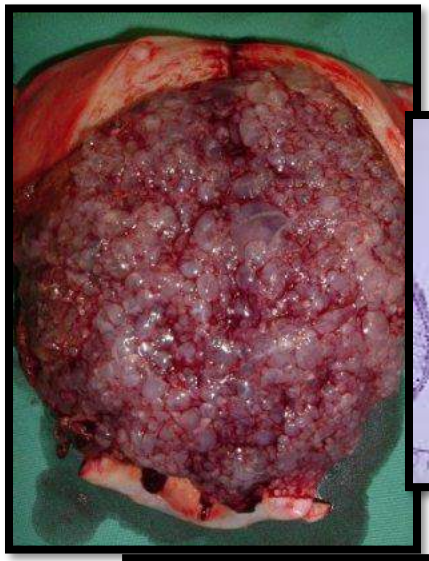
PATHOGENESIS OF MOLE:

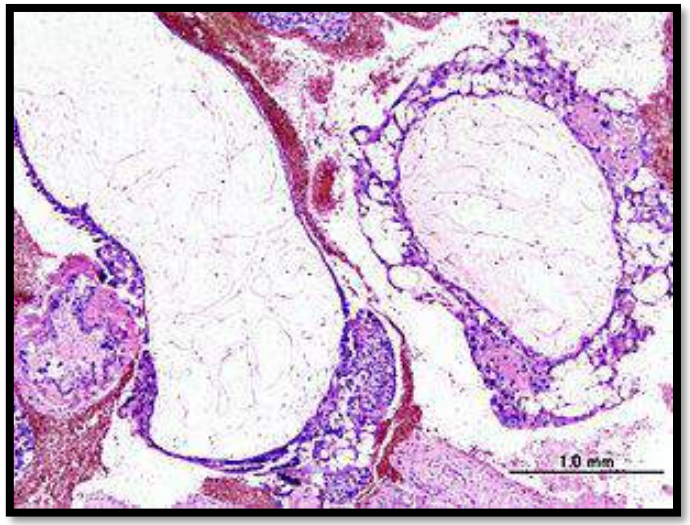




COMPLETE MOLE FEATURES:







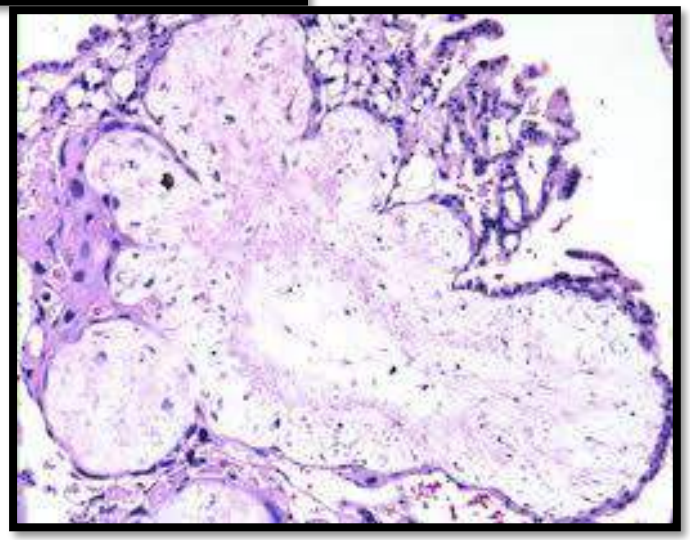


TABLE 19.5 Features of Complete and Partial Hydatidiform Mole

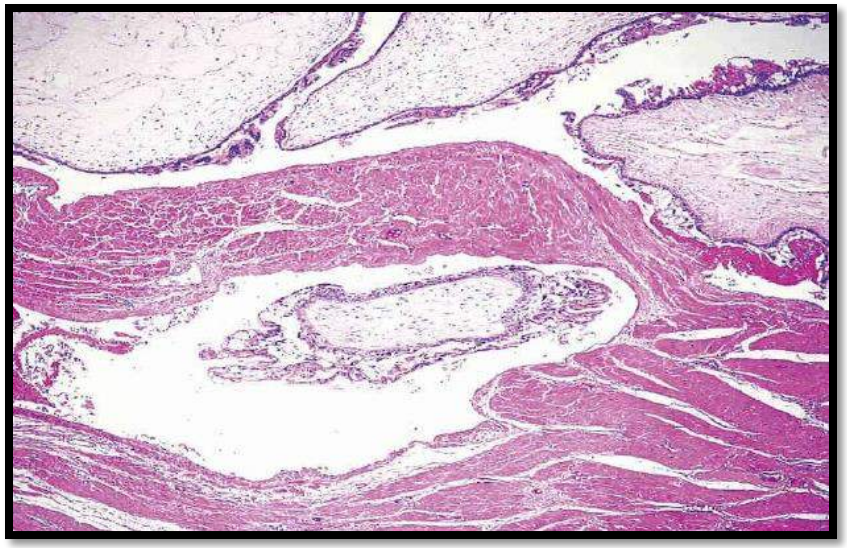
Feature	Complete Mole	Partial Mole
Karyotype	46,XX (46,XY)	Triploid (69,XXY)
Villous edema	All villi	Some villi
Trophoblast proliferation	Diffuse; circumferential	Focal; slight
Serum hCG	Elevated	Less elevated
Tissue hCG	++++	+
Risk of subsequent choriocarcinoma	2%	Rare

hCG, Human chorionic gonadotropin.

INVASIVE MOLE:

- **Complete mole invading uterine myometrium and sometimes causing rupture (life-threatening hemorrhage)**
- **No metastasis**
- **Atypia on histology with invasion to myometrium; may cause distant emboli**
- **Treatment:**

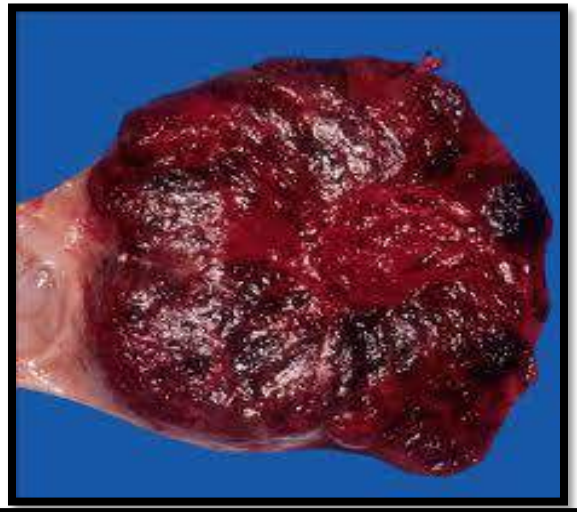
surgery and CT

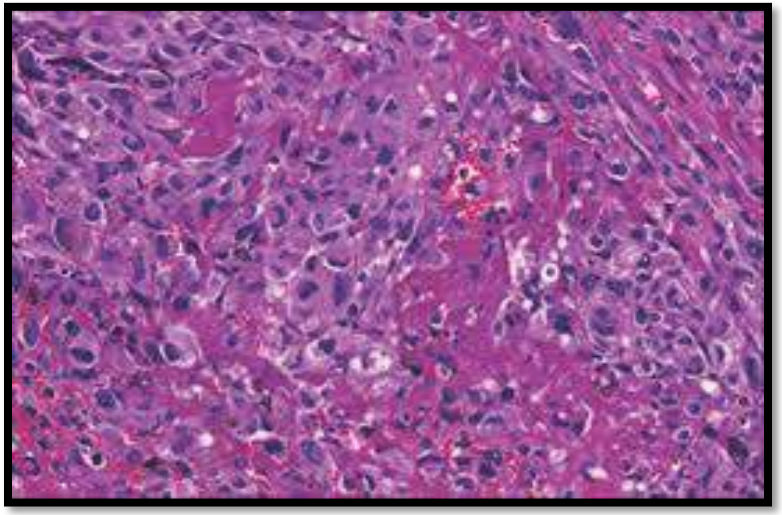


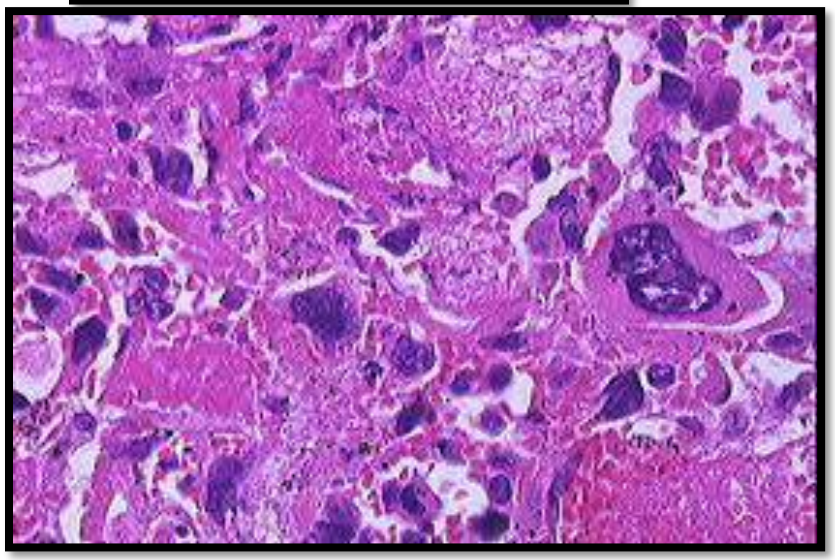
CHORIOCARCINOMA:

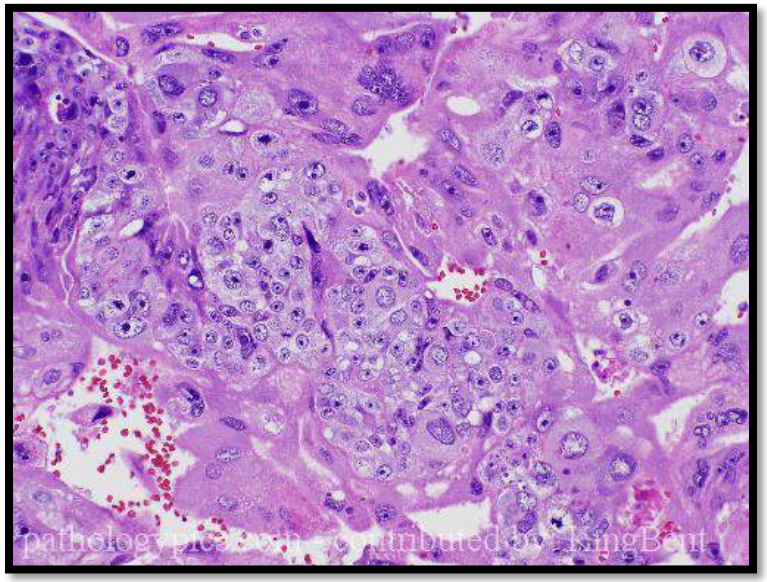
- Aggressive malignant neoplasms
- Arise from gestational chorionic epithelium or less commonly totipotent germ cells
- 1/30,000 in USA; but more common in Asia & Africa
- 50% arise from complete mole; 25% after abortions; 25% after normal pregnancies
- Bloody vaginal discharge with rising serum β-HCG
- No chorionic villi; anaplastic tumor cells

CHORIOCARCINOMA FEATURES:









CLINICAL FEATURES OF CHORIOCARCINOMA (Ch Ca):

- **Gestational Ch Ca 100% sensitive to CT (cure rate is very high) even after metastasis**
- **However; non gestational Ch Ca (testicular and ovarian) DON'T respond well to CT (maybe paternal antigens make these sensitive to CT) & maternal immunity against foreign paternal antigens**

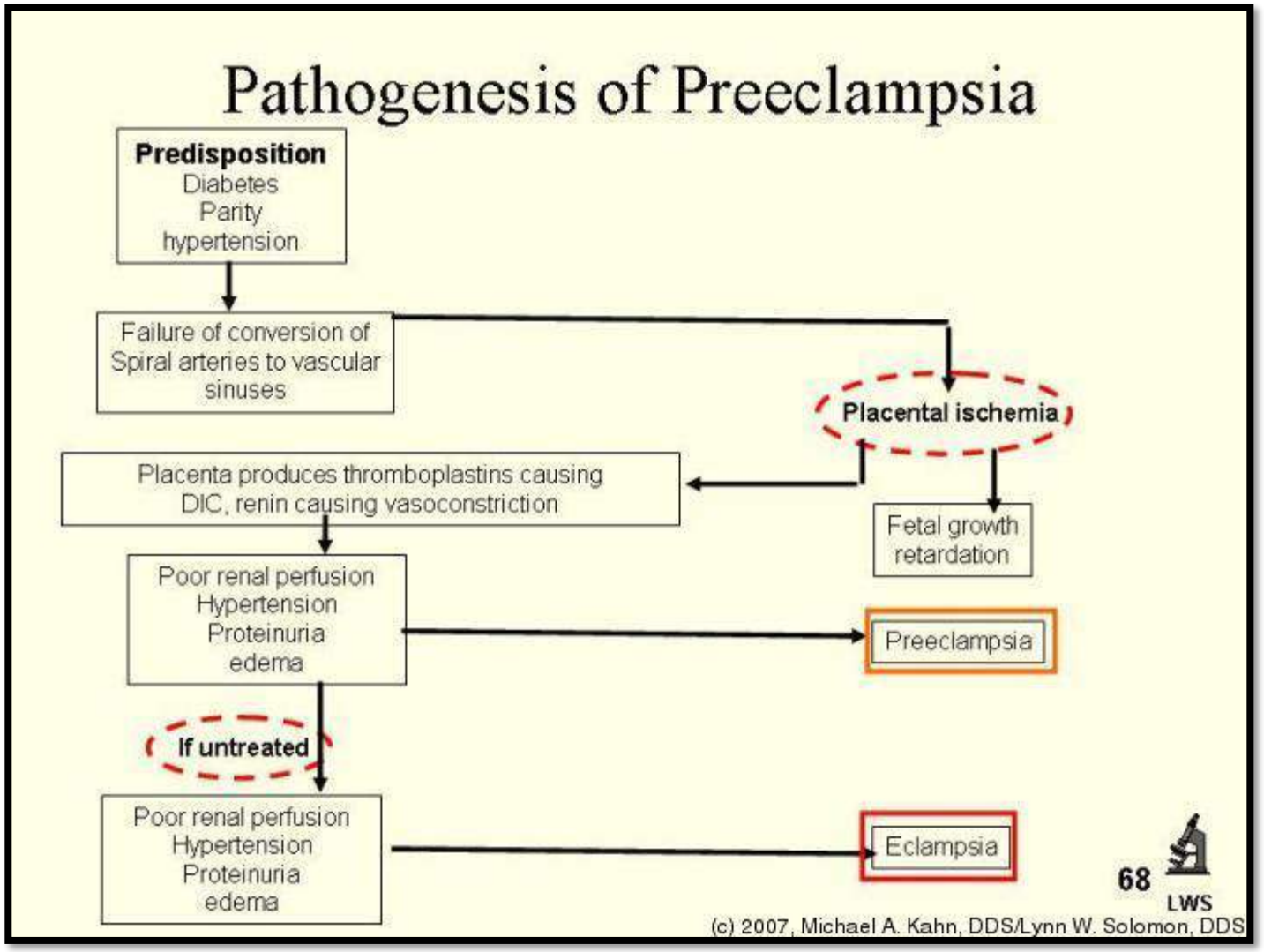
PLACENTAL SITE TROPHOBLASTIC TUMOR:

- Arise from intermediate trophoblastic cells
- Diploid XX karyotype
- Arise few months after pregnancy
- Serum β-HCG normal or slightly elevated
- Human placental lactogen
- Favorable prognosis if confined to uterus
- Not sensitive to CT like Ch Ca

PREECLAMPSIA/ECLAMPSIA (TOXEMIA OF PREGNANCY/TOP):

- **HT + PU + edema in 3rd trimester = PreECL**
- **5-10% of pregnancies; primi, >35 yrs**
- **Severe = seizures (eclampsia)**
- **No blood toxin identified (misnomer)**
- **Early detection now; eclampsia is rare**
- **Etiology is unknown (abnormal uteroplacental vascular bed causing insufficient blood flow)**

PATHOGENESIS OF TOP:



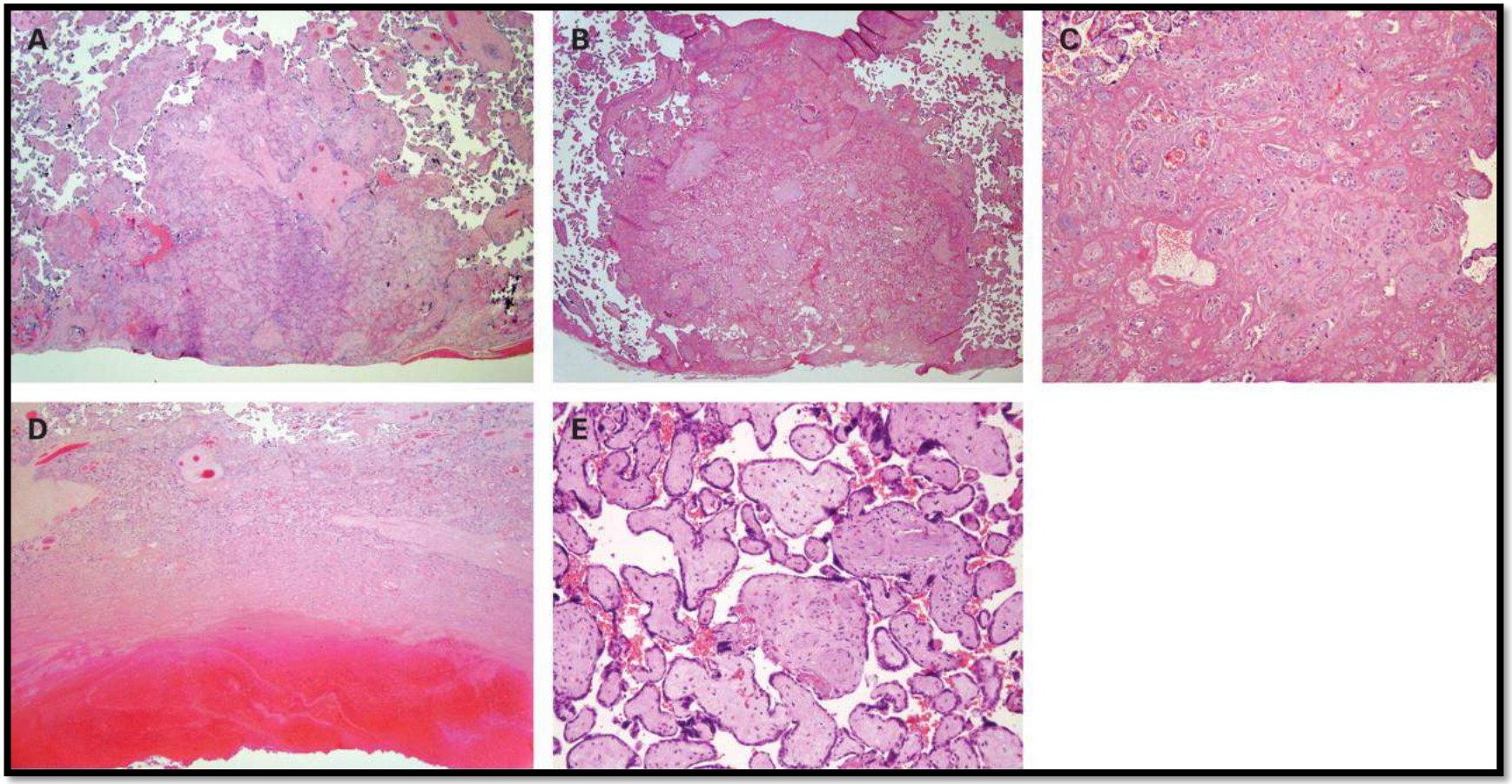
CONSEQUENCES OF TOP:

- **Placental infarction**
- **HT: ⇩ Vasodilators (PCY & PGE2); ⇧ Vasoconstrictors (TBX A2)**
- **Hypercoagulability: endothelial injury**
- **End-organ failure: kidney & liver**
- **10% of severe eclampsia develop “HELLP” syndrome [microangiopathic HA, increased liver enzymes,, thrombocytopenia, DIC]**

PLACENTAL CHANGES:

- Variable and depends on severity
- Infarcts: increase in number & volume
- Retroplacental hemorrhage
- Villi premature maturation: knots, hypovascularity & edema
- Fibrinoid necrosis of villi and acute atherosis (lipid filled macrophages) of decidual vessels
- Trx: early trx is best. Changes gone after delivery

MORPHOLOGICAL PLACENTAL CHANGES :



Summary

Nonneoplastic Epithelial Disorders

- Lichen sclerosus is characterized by atrophic epithelium, subepithelial dermal fibrosis, and bandlike chronic inflammation.
- Lichen sclerosus carries a slightly increased risk for development of squamous cell carcinoma.
- Lichen simplex chronicus is characterized by thickened epithelium (hyperplasia), usually with a dermal inflammatory infiltrate.
- The lesions of lichen sclerosus and lichen simplex chronicus must be biopsied to distinguish them definitively from other causes of leukoplakia, such as squamous cell carcinoma of the vulva.

Summary

Tumors of the Vulva

- HPV-related vulvar squamous cell carcinomas usually are poorly differentiated lesions and sometimes are multifocal. They often evolve from vulvar intraepithelial neoplasia.
- Non–HPV-related vulvar squamous cell carcinomas occur in older women and usually are well differentiated and unifocal. They are often preceded by "differentiated" vulvar intraepithelial neoplasia associated with lichen sclerosus.
- Vulvar Paget disease is characterized by a red, scaly plaque caused by proliferation of epithelial cells within the epidermis; usually, there is no underlying carcinoma, unlike Paget disease of the nipple.

Summary

Cervical Neoplasia

- Risk factors for cervical carcinoma are related to HPV exposure, such as early age at first intercourse, multiple sexual partners, and other factors including cigarette smoking and immunodeficiency.
- Nearly all cervical carcinomas are caused by HPV infections, particularly high-risk HPV types 16, 18, 31, and 33; the HPV vaccine is effective in preventing infection resulting from the HPV types most commonly associated with carcinoma.
- HPV expresses E6 and E7 proteins that inactivate the p53 and RB tumor suppressors, respectively, resulting in increased cell proliferation and suppression of DNA damage–induced apoptosis.
- In cervical cancer, high-risk HPV is integrated in the host genome, an event that increases the expression of E6 and E7 and contributes to progression to cancer.
- The Pap smear is a highly effective screening tool for the detection of SIL and carcinoma and has significantly reduced the incidence of cervical carcinoma. HPV testing is currently being used in conjunction with the Pap smear.

Summary

Nonneoplastic Disorders of Endometrium

- Adenomyosis refers to growth of endometrium into the myometrium often with uterine enlargement.
- Endometriosis refers to endometrial glands and stroma located outside the uterus and most often involves the pelvic or abdominal peritoneum. Rarely, distant sites such as the lymph nodes and the lungs also are involved.
- The ectopic endometrium in endometriosis undergoes cyclic bleeding, and the condition is a common cause of dysmenorrhea and pelvic pain.

Summary

Endometrial Hyperplasia and Endometrial Carcinoma

- Endometrial hyperplasia results from unopposed endogenous or exogenous estrogen.
- Risk factors for developing endometrial hyperplasia include anovulatory cycles, polycystic ovary syndrome, estrogen-producing ovarian tumor, obesity, and estrogen therapy without counterbalancing progestin.
- Hyperplasia is classified based on cytologic atypia, which determines the risk of developing endometrioid carcinoma.
- On the basis of clinical and molecular data, two major types of endometrial carcinoma are recognized:
  - *Endometrioid carcinoma* is associated with estrogen excess and endometrial hyperplasia. Early molecular changes include inactivation of DNA mismatch repair genes and the *PTEN* gene.
  - *Serous carcinoma* of the endometrium arises in older women and usually is associated with endometrial atrophy and a distinct precursor lesion, serous intraepithelial carcinoma. Mutations in the *TP53* gene are an early event, usually being present in serous endometrial intraepithelial carcinoma as well as invasive serous carcinoma.
- Stage is the major determinant of survival in both types. Serous tumors tend to manifest more frequently with extrauterine extension and therefore have a worse prognosis than endometrioid carcinomas.

Summary

Ovarian Tumors

- Tumors may arise from epithelium, sex cord–stromal cells, or germ cells.
- Epithelial tumors are the most common malignant ovarian tumor and are more common in women older than 40 years of age.
- The major types of epithelial tumors are serous, mucinous, and endometrioid. Each has a benign, malignant, and borderline counterpart.
- Serous carcinoma is the most common and many arise in the distal fallopian tube.
- Sex cord–stromal tumors may display differentiation toward granulosa, Sertoli, Leydig, or ovarian stromal cell type. Depending on differentiation, they may produce estrogens or androgens.
- Germ cell tumors (mostly cystic teratomas) are the most common ovarian tumor in young women; the vast majority are benign.
- Germ cell tumors may differentiate toward oogonia (dysgerminoma), primitive embryonal tissue (embryonal), yolk sac (endodermal sinus tumor), placental tissue (choriocarcinoma), or multiple tissue types (teratoma).

Summary

Ectopic Pregnancy

- Ectopic pregnancy is defined as implantation of the fertilized ovum outside of the uterine corpus. Approximately 1% of pregnancies implant ectopically; the most common site is the fallopian tube.
- Chronic salpingitis with scarring is a major risk factor for tubal ectopic pregnancy.
- Rupture of an ectopic pregnancy is a medical emergency that, if left untreated, may result in exsanguination and death.

Summary

Gestational Trophoblastic Disease

- Molar disease is a result of an abnormal contribution of paternal chromosomes to the conceptus.
- Partial moles are triploid and have two sets of paternal chromosomes. They typically are accompanied by fetal tissue. There is a low rate of persistent disease.
- Complete moles are diploid, and all chromosomes are paternal. Rarely are embryonic or fetal tissues associated with a complete mole.
- Among complete moles, 10% to 15% are associated with persistent disease that usually takes the form of an invasive mole. Only 2% of complete moles progress to choriocarcinoma.
- Gestational choriocarcinoma is a highly invasive and frequently metastatic tumor that, in contrast with ovarian choriocarcinoma, is responsive to chemotherapy and curable in most cases.
- Placental site trophoblastic tumor is an indolent tumor of intermediate trophoblast that produces human placental lactogen. It can be cured surgically but once it spreads it does not respond well to chemotherapy.

Summary

Clinical Presentations of Breast Disease

- Symptoms affecting the breasts are evaluated primarily to determine if malignancy is present.
- Regardless of the symptom, the underlying cause is benign in the majority of cases.
- Breast cancer is most commonly detected by palpation of a mass in younger women and in unscreened populations and by mammographic screening in older women.

Summary

Breast Carcinoma

- The lifetime risk of developing breast cancer for an American woman is 1 in 8.
- A majority (75%) of breast cancers are diagnosed after the age of 50.
- The major risk factors for developing breast cancer are related to hormonal factors and inherited susceptibility.
- About 12% of all breast cancers are caused by identified germline mutations; *BRCA1* and *BRCA2* genes account for one-half of the cases associated with single-gene mutations.
- DCIS is a precursor to invasive ductal carcinoma and is most often found on mammographic screening as calcifications. When carcinoma develops in a woman with a previous diagnosis of untreated DCIS, it is usually is an invasive ductal carcinoma in the same breast.
- LCIS is both a marker of increased risk and a precursor lesion. When carcinoma develops in a woman with a previous diagnosis of LCIS, two-thirds are in the same breast and one-third is in the contralateral breast.
- Invasive carcinomas are classified according to histologic type and biologic type: ER-positive/HER2-negative, HER2-positive, and ER/PR/HER2-negative (triple-negative). The biologic types of cancer have important differences in patient characteristics, grade, mutation profile, metastatic pattern, response to therapy, time to recurrence, and prognosis.
- Prognosis is dependent on the biologic type of tumor, stage, and the availability of treatment modalities.

AL-ABBADI