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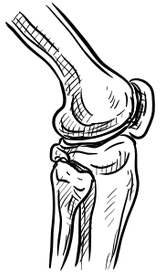

PATHOLOGY

Final | Lecture 5

MSS & skin tumors pt.10

Written by: Sadeel Al-hawawsheh

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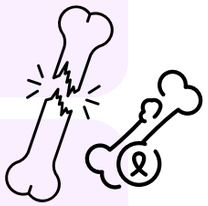

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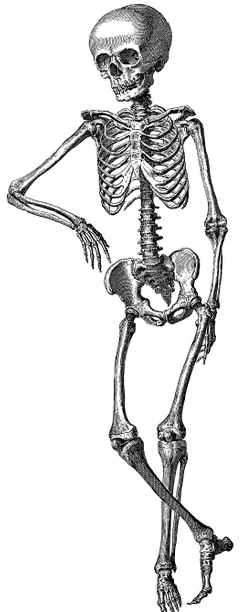
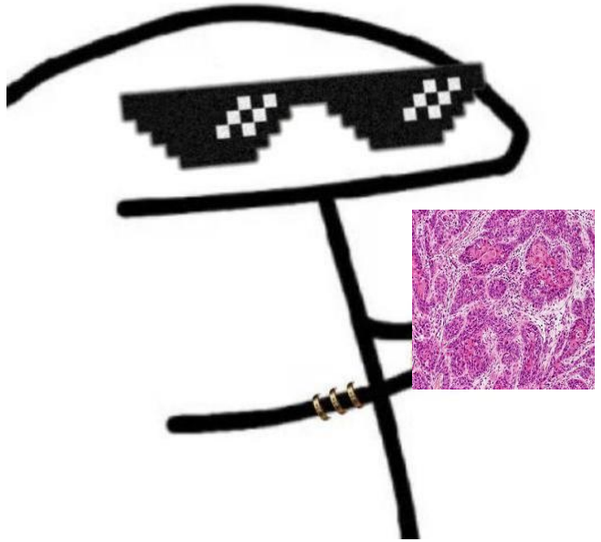
اللهم استعملنا ولا تستبدلنا



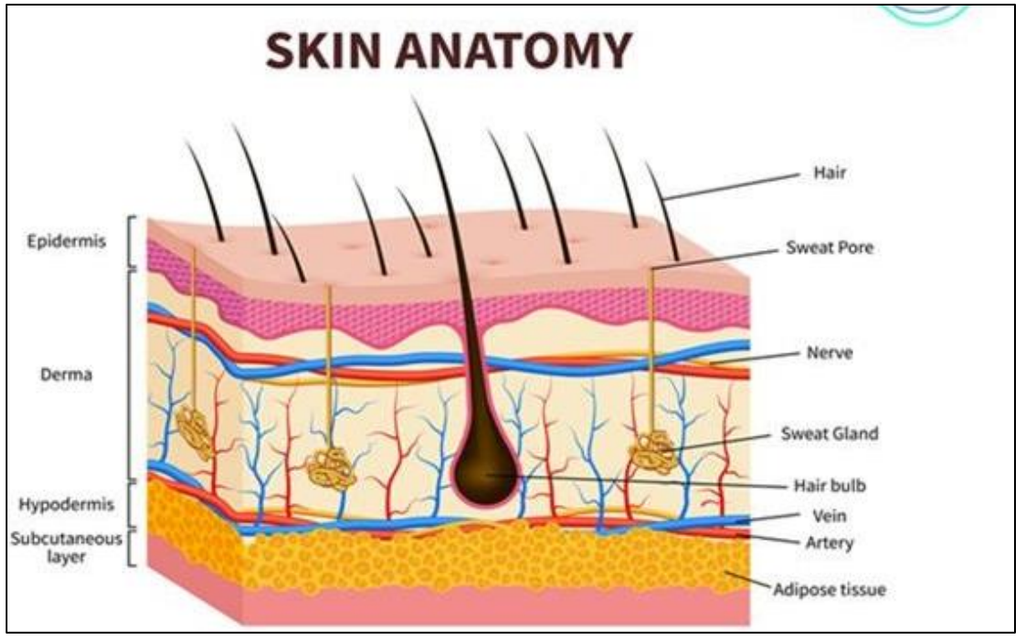
Capture the specimen….

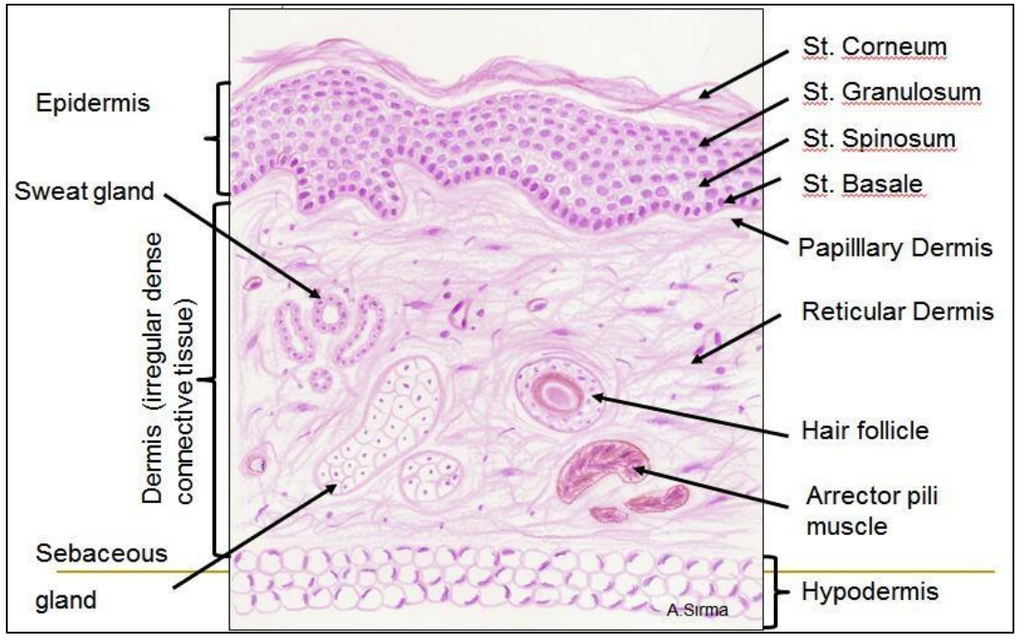


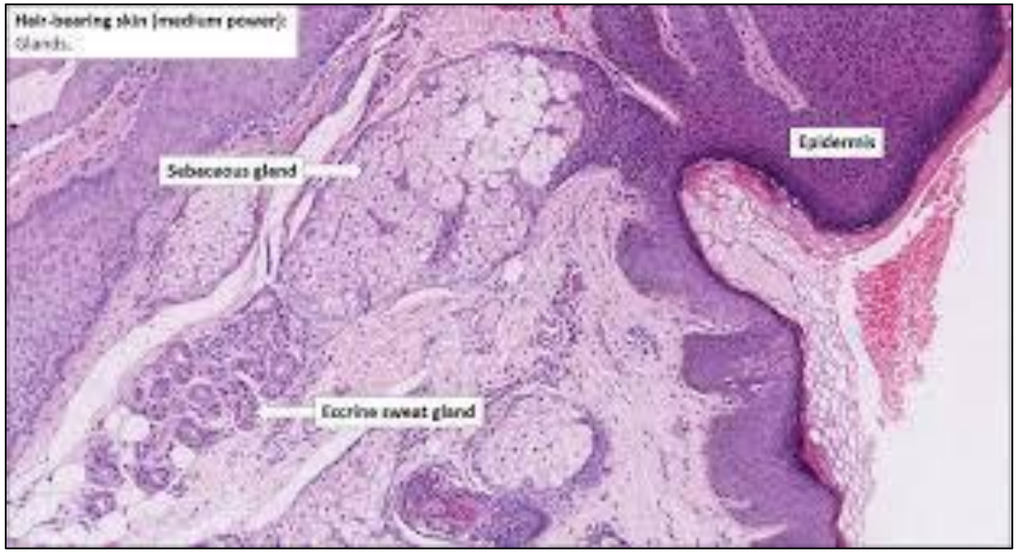
Skin Pathology: cysts and (neoplasms)

- **Inflammatory and infectious dermatosis (dermatology rotation)**
- **Very common lesions**
- **Increase with increasing age**
- **Rarely fatal (except melanomas)**
- **More common in sun exposed areas**
- **Associated with sun damage (solar elastosis)**

Ultraviolet (UV) radiation from sun exposure is one of the most significant predisposing and high-risk etiological factors for the development of skin tumors, including squamous cell carcinoma, basal cell carcinoma, and the more aggressive melanoma.


SKIN ANATOMY
Hair
Sweat Pore
Nerve
Sweat Gland
Hair bulb
Vein
Artery
Adipose tissue
Epidermis
Derma
Hypodermis
Subcutaneous layer


Epidermis
Sweat gland
Dermis (irregular dense connective tissue)
Sebaceous gland
St. Corneum
St. Granulosum
St. Spinosum
St. Basale
Papilllary Dermis
Reticular Dermis
Hair follicle
Arrector pili muscle
Hypodermis
A Sirma

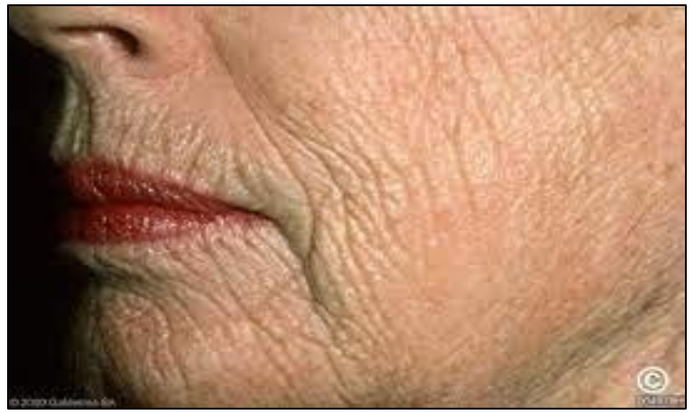

Sebaceous gland
Epidermis
Eccrine sweat gland

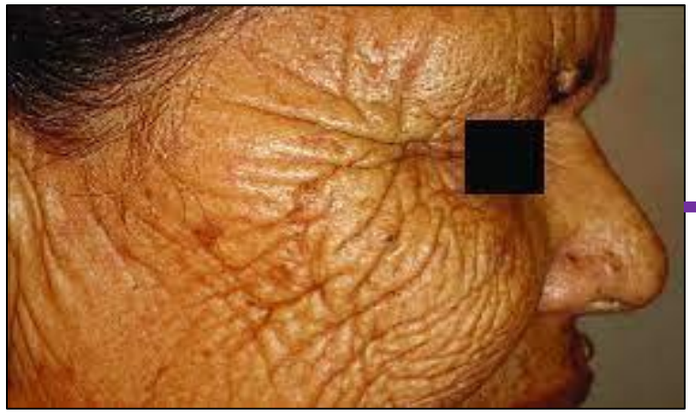
Solar (actinic) elastosis

- Chronic sun damage leading to: thickened and yellow skin
- "Damage to skin elasticity (tissue components) from sun exposure"
- Preventable disease
- (One of the early histological changes observed in sun-damaged skin)
- UV rays damage collagen and elastic fibers of the skin
- While solar elastosis itself is not cancerous, it will increase the risk of many skin pre-malignancies (Actinic keratosis) and malignancies (melanomas, squamous cell carcinomas, basal cell carcinomas)

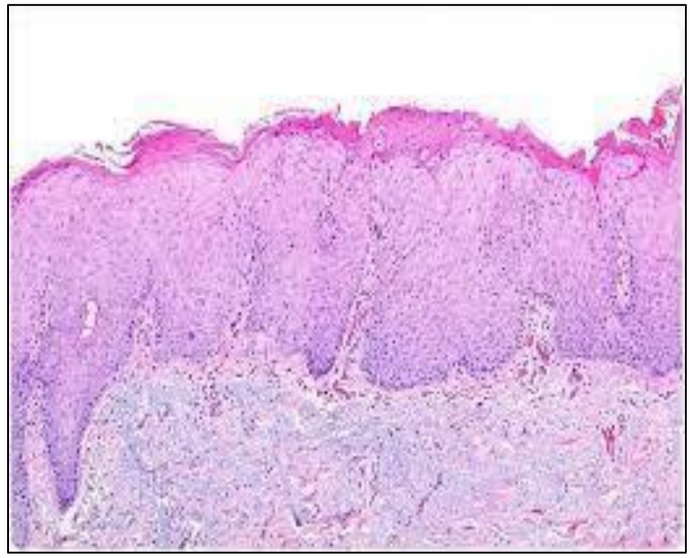
It is common to observe basal cell carcinoma arising in tissue that shows background solar elastosis, indicating the chronic UV damage that predisposed to tumor development.

Morphology





Clinically, solar elastosis presents as skin changes due to chronic sun exposure and may precede the onset of malignancies.

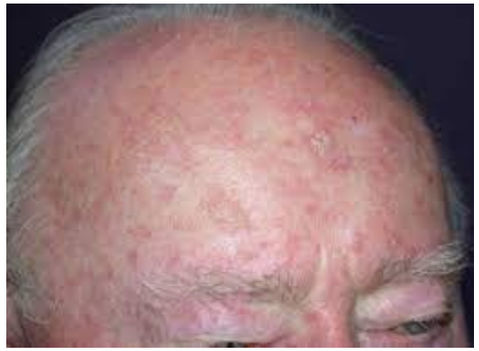


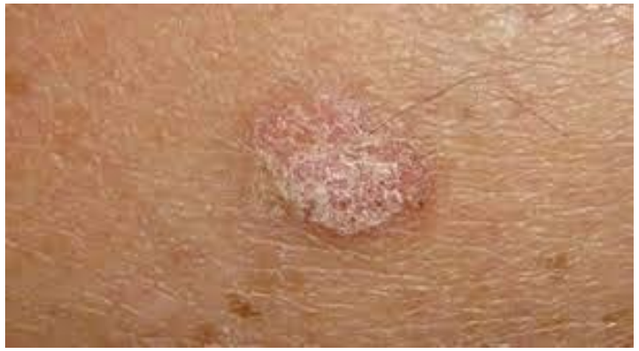
When a skin biopsy is taken from sun-exposed areas, the squamous epithelium may appear histologically normal, but the superficial dermis often shows prominent changes. One of the these is garish discoloration and degeneration of elastic fibers (solar elastosis).

Actinic keratosis

- **Premalignant skin disease due to sun damage**

It is characterized by epithelial atypia within the squamous epithelium, including an increased nuclear-to-cytoplasmic (N:C) ratio, nuclear hyperchromasia, and prominent nucleoli. Despite these atypical changes, it is not considered an invasive carcinoma, as the atypical cells do not breach the basement membrane, which comprises collagen IV and the lamina.

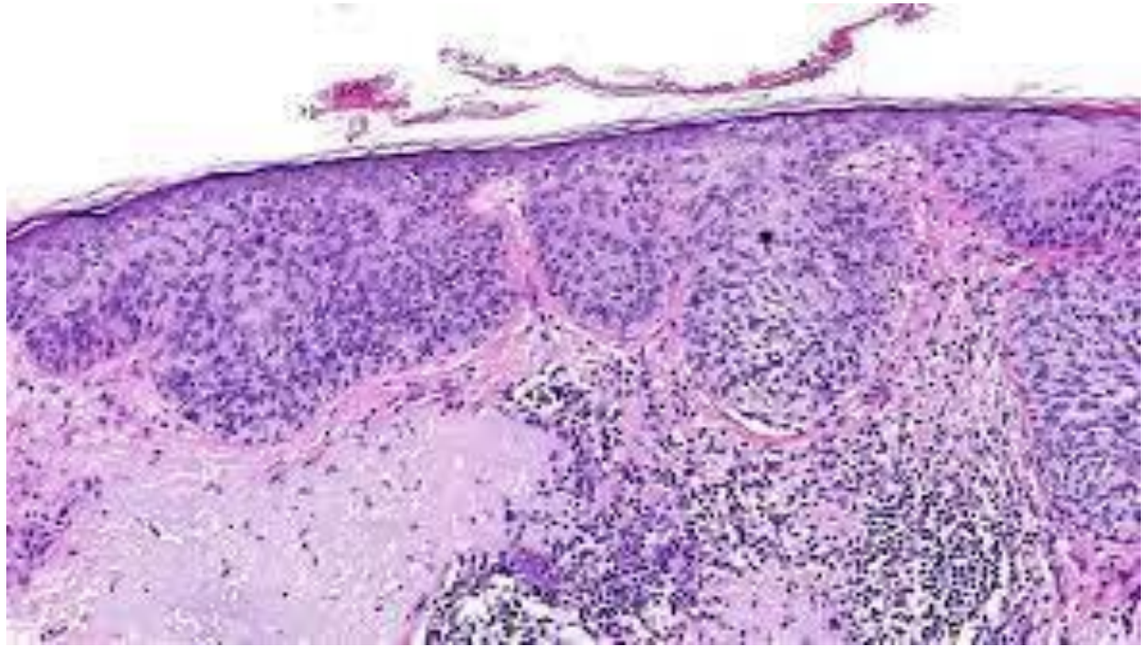




- **UV light damage DNA via mutations in TP53**

- **They progress to squamous cell carcinoma (rate: 1-3%)**

Some consider actinic keratosis a form of **carcinoma in situ**, as the atypical keratinocytes remain confined to the epidermis. To evaluate potential progression to invasive squamous cell carcinoma, special stain for the basement membrane components can be used to assess the integrity of the basement membrane and detect evidence of invasion.



Seborrheic keratosis

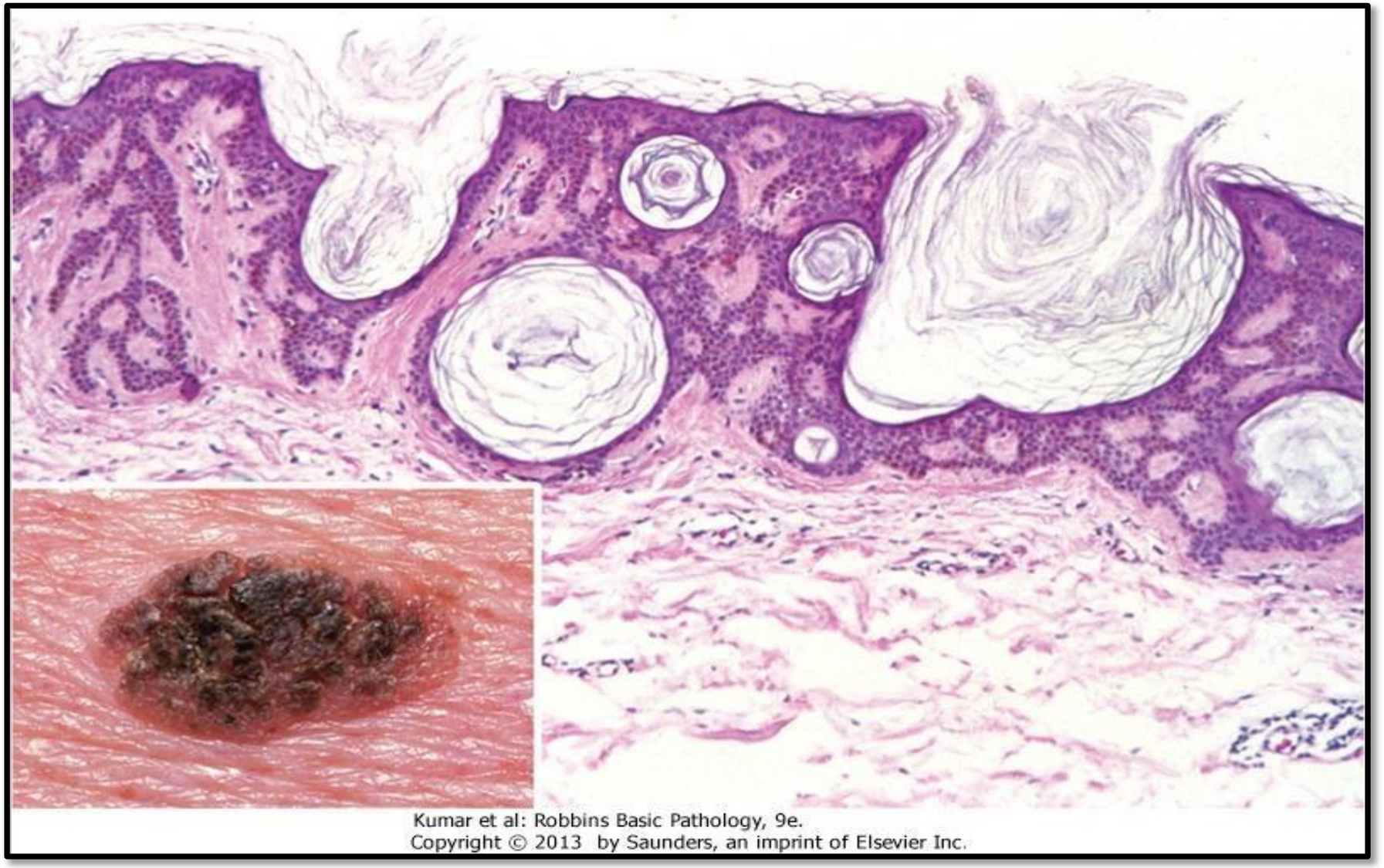
- Very common pigmented neoplasms (although it may lack pigmentation)
- Middle age- older patients; anywhere but mainly trunk
- FGFR3 mutations (different pathogenesis)
- Clinically insignificant (removed to R/O malignancy)

Although SK is a true neoplasm, it is entirely benign and non-invasive. These lesions are often removed to exclude malignancy or for cosmetic reasons

- Coin-like lesions, usually pigmented, elevated "Stuck-on"

Clinically, SK often appears as a well-demarcated, "stuck-on" lesion, usually brown to black in color. Histologically, it consists of proliferating squamous epithelium with features such as keratin-filled cysts (horn cysts) and surface hyperkeratosis (PLEASE SEE NEXT SLIDE)

Seborrheic keratosis



Kumar et al: Robbins Basic Pathology, 9e.

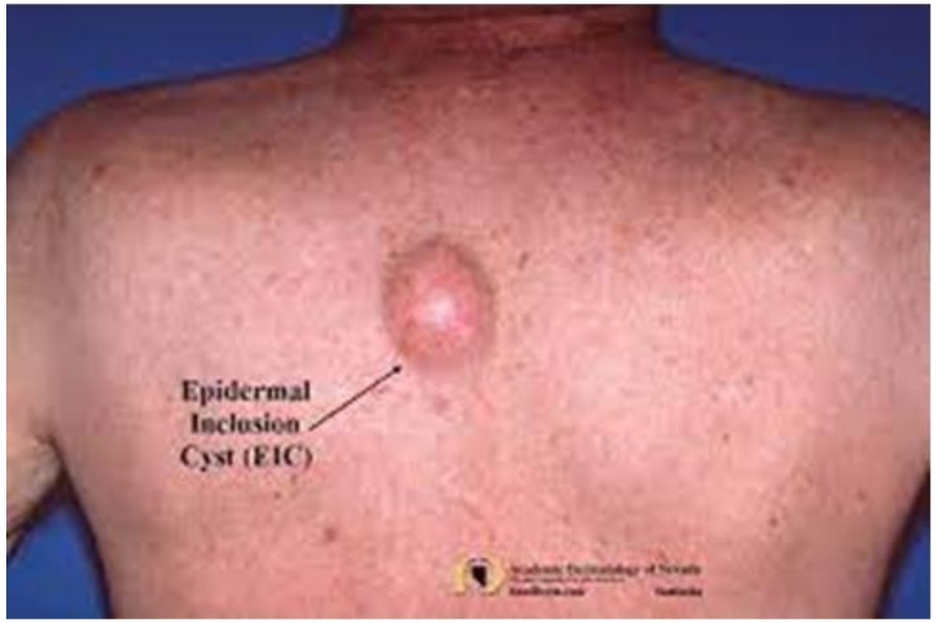
Cysts

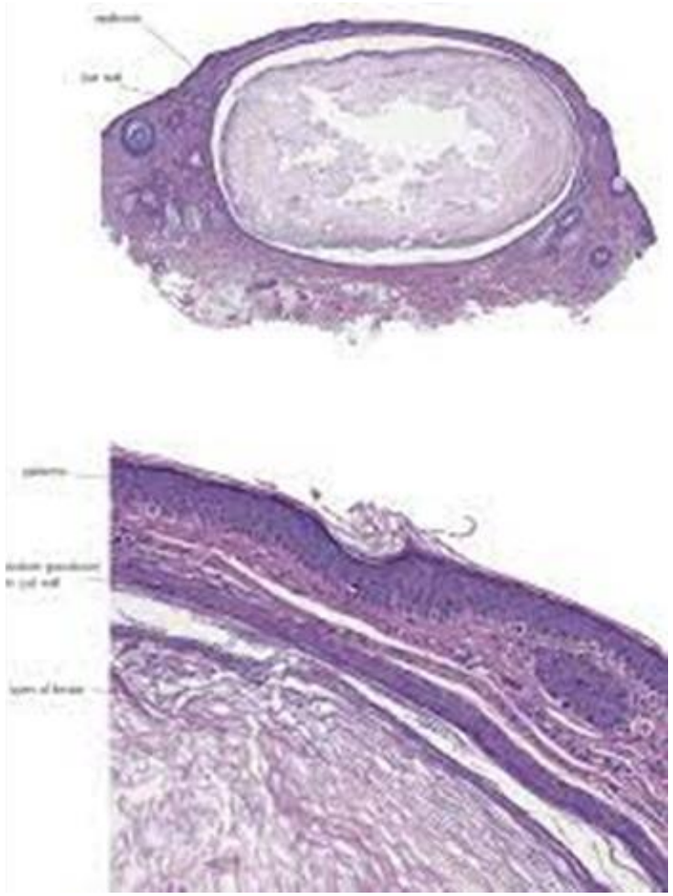
- Very common (one of the most common pathologies of the skin)
- Almost all are benign (Skin bumps)
- Clinically: the surgeon call them "Sebaceous cyst"
- Malignant transformation is extremely rare

These are true cysts, meaning they are lined by stratified squamous epithelium and contain keratinous material. They are generally benign, but can become inflamed or infected, prompting removal.
In cases of rupture, the keratin content is released into the dermis, triggering an inflammatory reaction. Histologically, this is characterized by mixed inflammatory infiltrates, often with multinucleated giant cells responding to the keratin debris.

- Many types:
  - Epidermal inclusion cyst
  - Dermoid cyst
  - Trichilemmal cyst is typically found on the scalp

Epidermal (epithelial) inclusion cyst



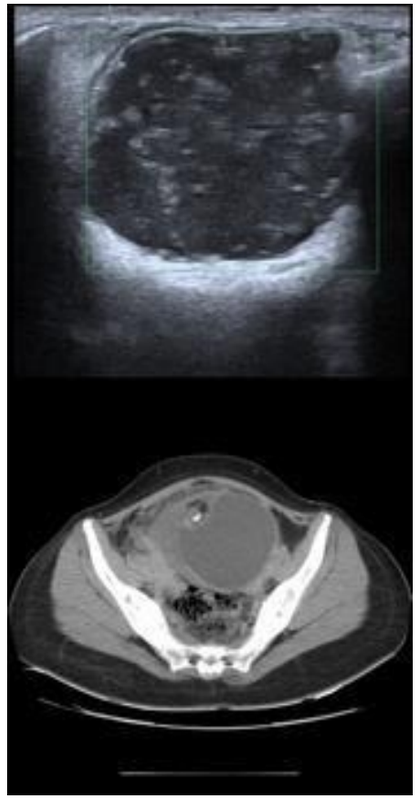


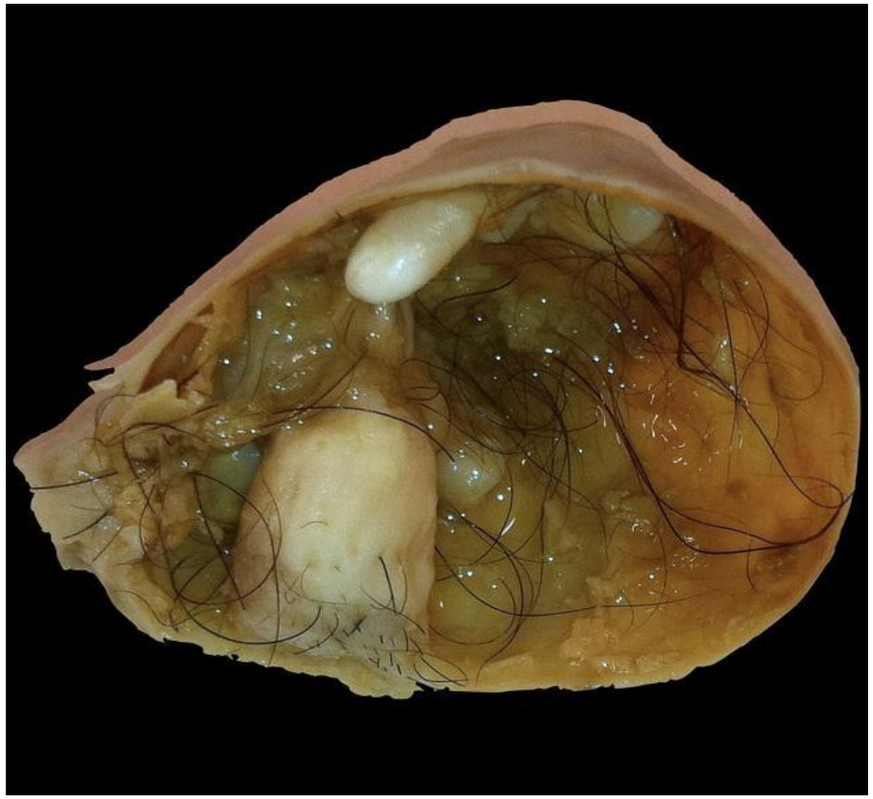
These are cysts in the back, containing keratin flakes and true cysts (cysts lined by epithelium)

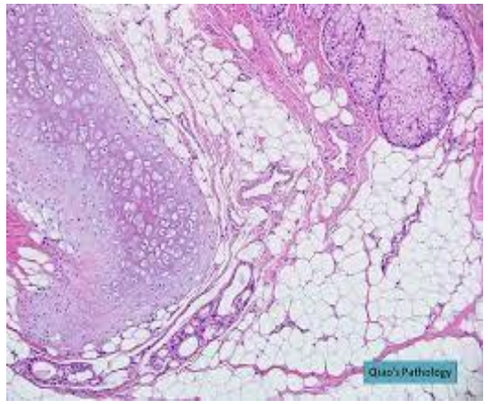
Dermoid cyst

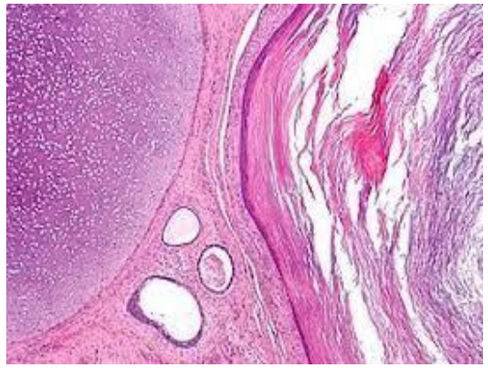
- A dermoid cyst is a growth of normal tissue enclosed in a pocket of cells called a sac. This tissue grows in or under your skin in an unexpected location.
- A cyst is a lump or bump that may contain fluid or other material. Most often, dermoid cysts contain a greasy yellow material, but they may contain: mature tissues (bone, hair, muscle, teeth…etc)
- Dermoid cysts can be anywhere on your body.
- Rarely (5–10)% they can have immature or malignant elements (malignant dermoid cysts or teratoma)
- Peri-orbital, ovarian, spinal…etc

Dermoid cyst







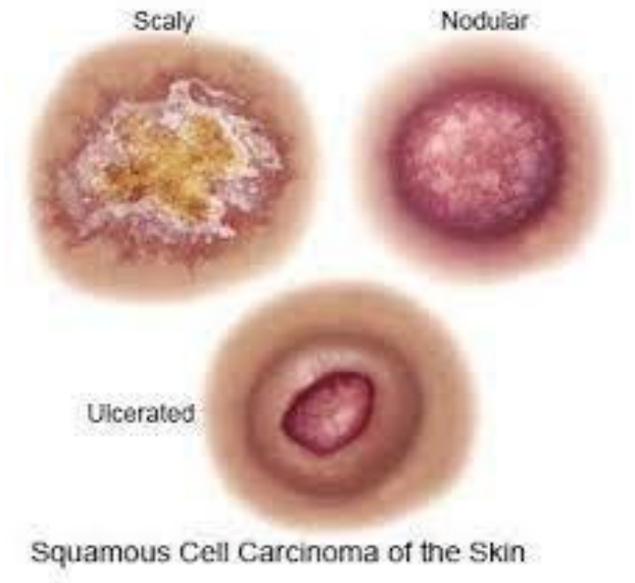


The images show an ovarian dermoid cyst containing mature elements such as teeth and hair, consistent with a mature cystic teratoma. Radiological findings and histological confirmation support the diagnosis.

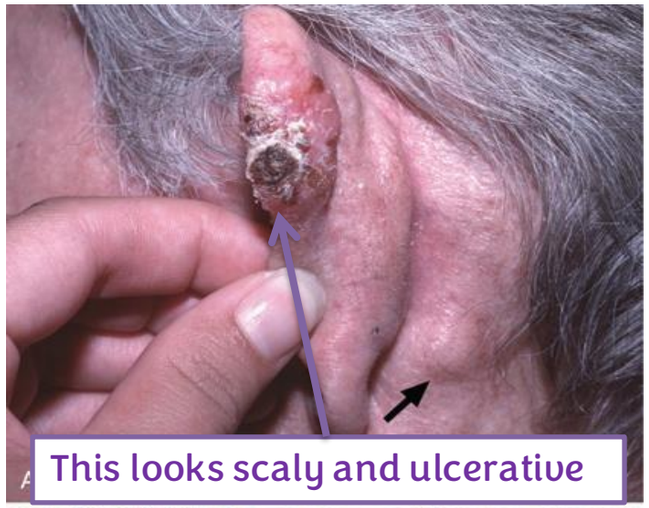
Squamous cell carcinoma

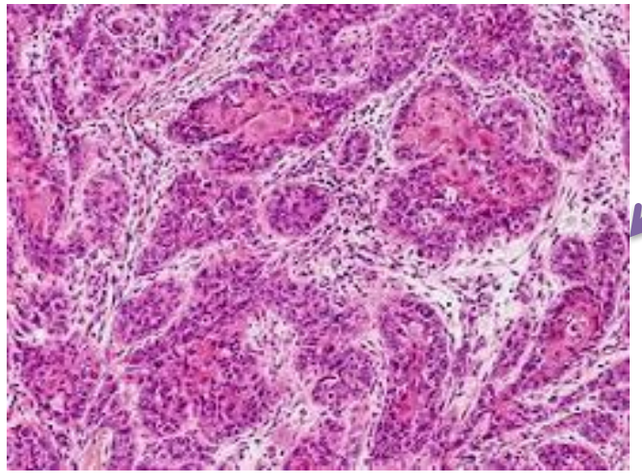
- **Common neoplasms**
- **Sun damage (sun exposed areas)**
- **Most commonly localized with rare deep infiltration or metastasis.**
- **Invasive, usually keratinizing squamous cell carcinoma**
- **Risk increases: immunosuppression (HPV), prolonged sun exposure, tars & oils** (chewing tobacco may leads to chronic irritation of the mucosa = SCC) **, old burns, ionizing radiation,** in addition to the UV light (most common)

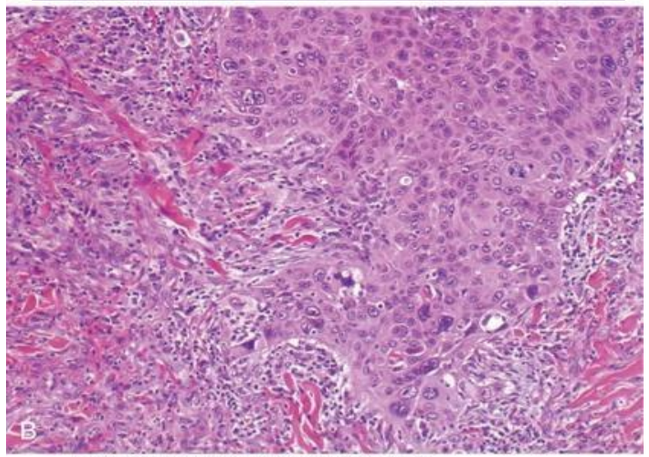
- Squamous cell carcinoma appears variable. It can look scaly, nodular, or even have an ulcer.
- Something that is checked histologically is the tumor connection to squamous to confirm that this lesion is primary in this area.
- Metastases don't mean invasion. Invasion means it reaches the tissue below it while metastases is a tumor spreading to another part of the body.

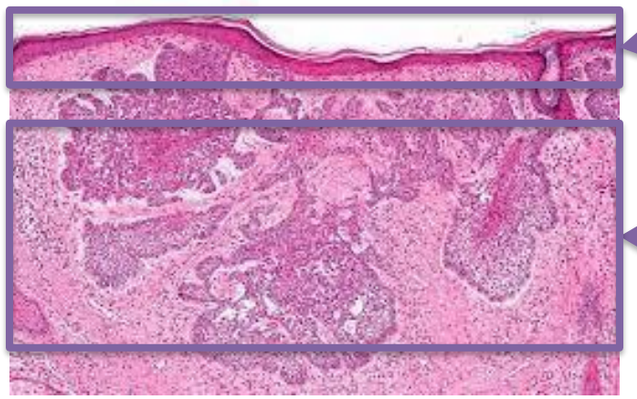


Squamous Cell Carcinoma of the Skin

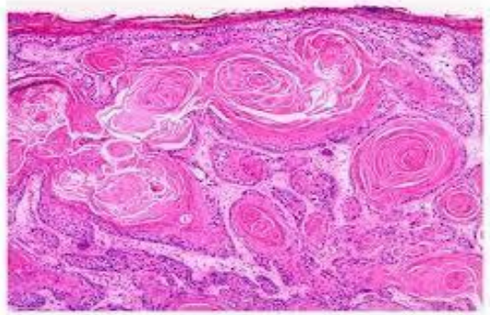

This looks scaly and ulcerative


This is invasive carcinoma


Kumar et al: Robbins Basic Pathology, 9e.


This is the normal squamous epithelium

This is invasive tumor –unlike actinic keratosis that is not invasive.


This squamous cell carcinoma histologically looks like superficial squamous cells and is well-differentiated. The circle structures are called squamous pearls. This is clearly a squamous cell carcinoma and should be surgically removed.

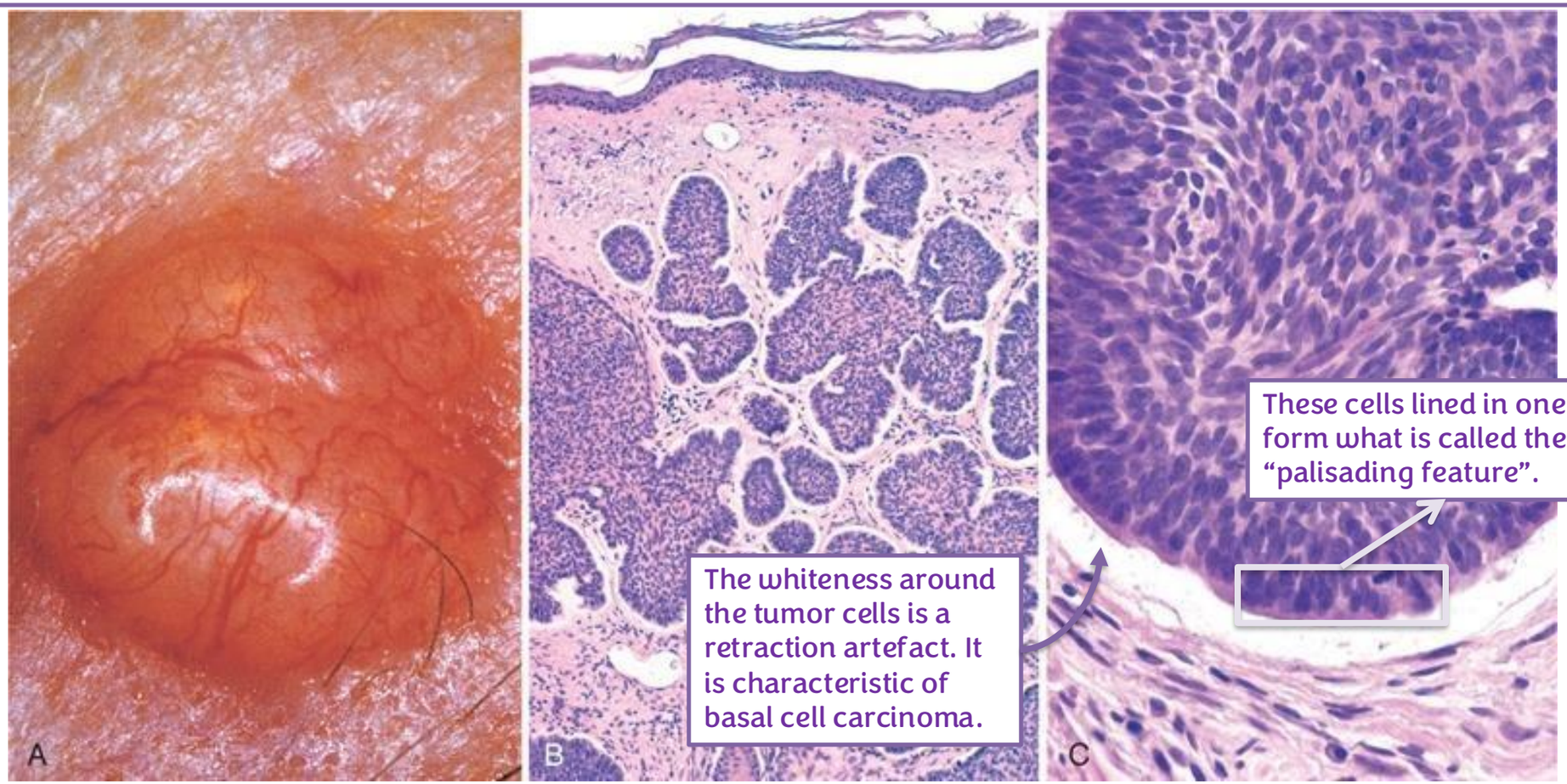
- This is moderately to poorly differentiated, it has high aplastic features.
- Sometimes, you need stains to confirm the cell origin being basal cells of the skin, and sometimes, it can be obvious, and the cure would be complete excision.

Basal cell carcinoma:

- Arise from basal cells of epidermis
- Sun exposure
- Can be multiple → Multifocality is common in skin carcinomas, specifically basal cell carcinomas.
- Papules, slightly pigmented
- Localized, deep infiltration and metastasis are extremely rare
- *PTCH1* mutations and *TP53* mutations
- Gorlin syndrome: multiple basal cell carcinoma (Basal cell nevus syndrome)

Basal cell carcinoma:

○ It is a very common tumor, removed completely to cure the patient, doesn't usually metastasize, and rarely invades -unlike melanoma.



○ Histologically, some redness, elevated, sometimes pigmented. Differ in morphology from squamous cell carcinoma -keratinizing squamous cell. Basal cell carcinomas are smaller with higher N:C ratio, and basaloid.
-Basaloid means small cells with a high N:C ratio-

Most dangerous

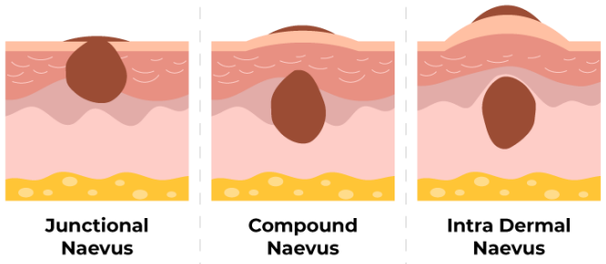
Melanocytic neoplasms:

شامة

- **Nevus: benign congenital melanocytic neoplasm**
- **Melanocytic nevus: any melanocytic neoplasm (congenital or acquired)**

● Sometimes, young patients remove a nevus out of concern that it may become malignant. This type of nevus is called a compound nevus with congenital features. Some nevi are congenital, while most are acquired.

● A nevus is benign, but with factors like irritation or increased UV exposure, it can develop into a dysplastic nevus, which is considered premalignant. If left untreated, it may progress to melanoma. This distinction is important. Although pathologists may occasionally find it challenging, specific features help differentiate a regular nevus from a dysplastic one. It's essential to accurately label them as either intradermal nevus or dysplastic nevus. In contrast, melanoma is generally easier to recognize histologically.



NEVUS

~just for clarification~

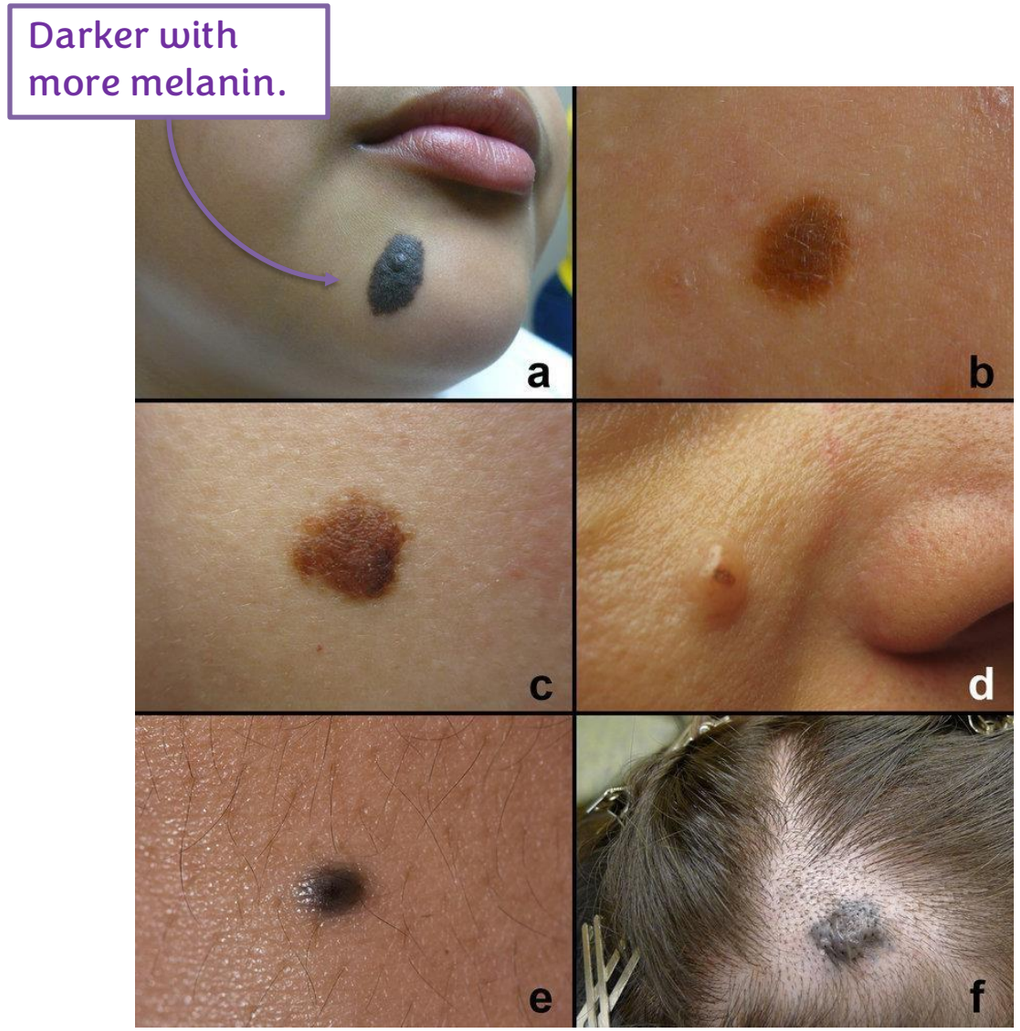
- Benign pigmented melanocytic proliferation
- Caused by somatic gain of function mutation ***BRAF*** or ***RAS*** → BRAF mutation is seen in benign nevus, dysplastic nevus & melanomas too.
- This is followed by inactivity "Senescence"
- Clinically: sharply demarcated, elevated and pigmented. → Clinician would know it's benign mostly.
- Removed surgically for cosmetic reasons, irritation and to rule out dysplasia or melanoma
- Junctional N. ⇨ Compound N. ⇨ Intradermal N

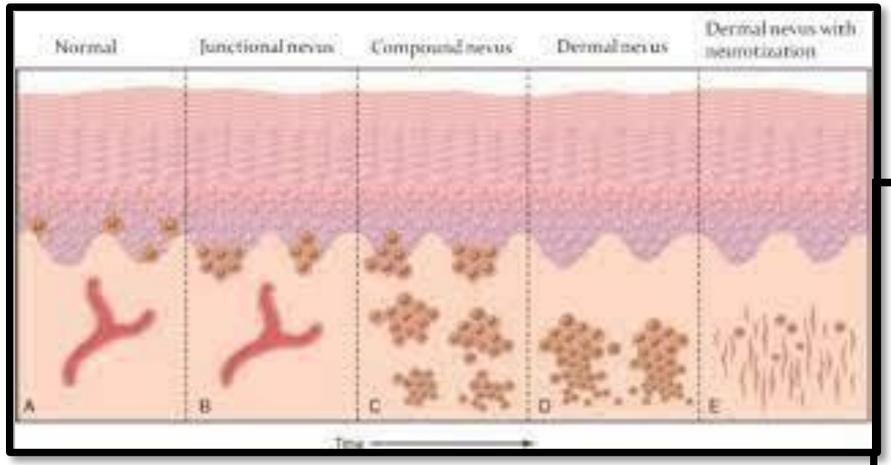
Junctional N.	Compound N.	Intradermal N
On basal cell of the squamous.	On junction and deep.	If only deep without junction.

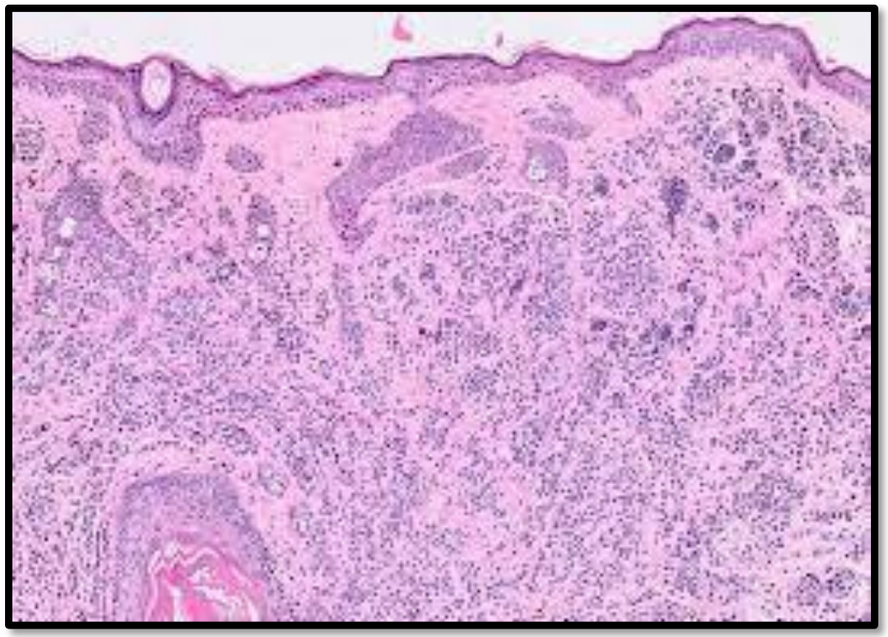
- All are benign

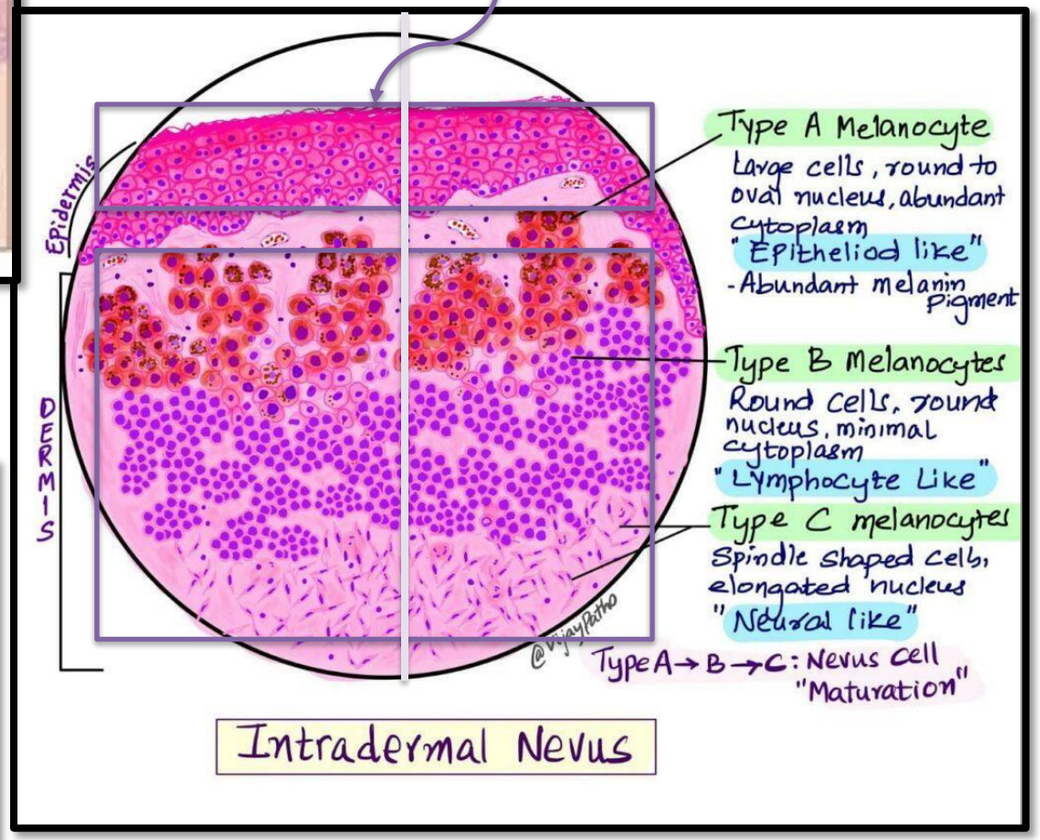
Benign features:

- Well-demarcated
- Sharp borders
- No significant change over time
- Histology: symmetry, absence of atypia (cellular enlargement, nuclear enlargement, nuclear chromatin abnormalities, prominent nucleoli, mitosis, maturation as you move deep into dermis).









Features of benignity:-

- When you examine a nevus, you split it in half like a mirror – the right side is similar to the left ;we call this symmetry. Nevi are symmetric.
- The other feature: as you go deeper, cells get smaller and more spindly –we call this maturation. No mitosis, no necrosis, no atypia –all benign features.

DYSPLASTIC NEVUS:

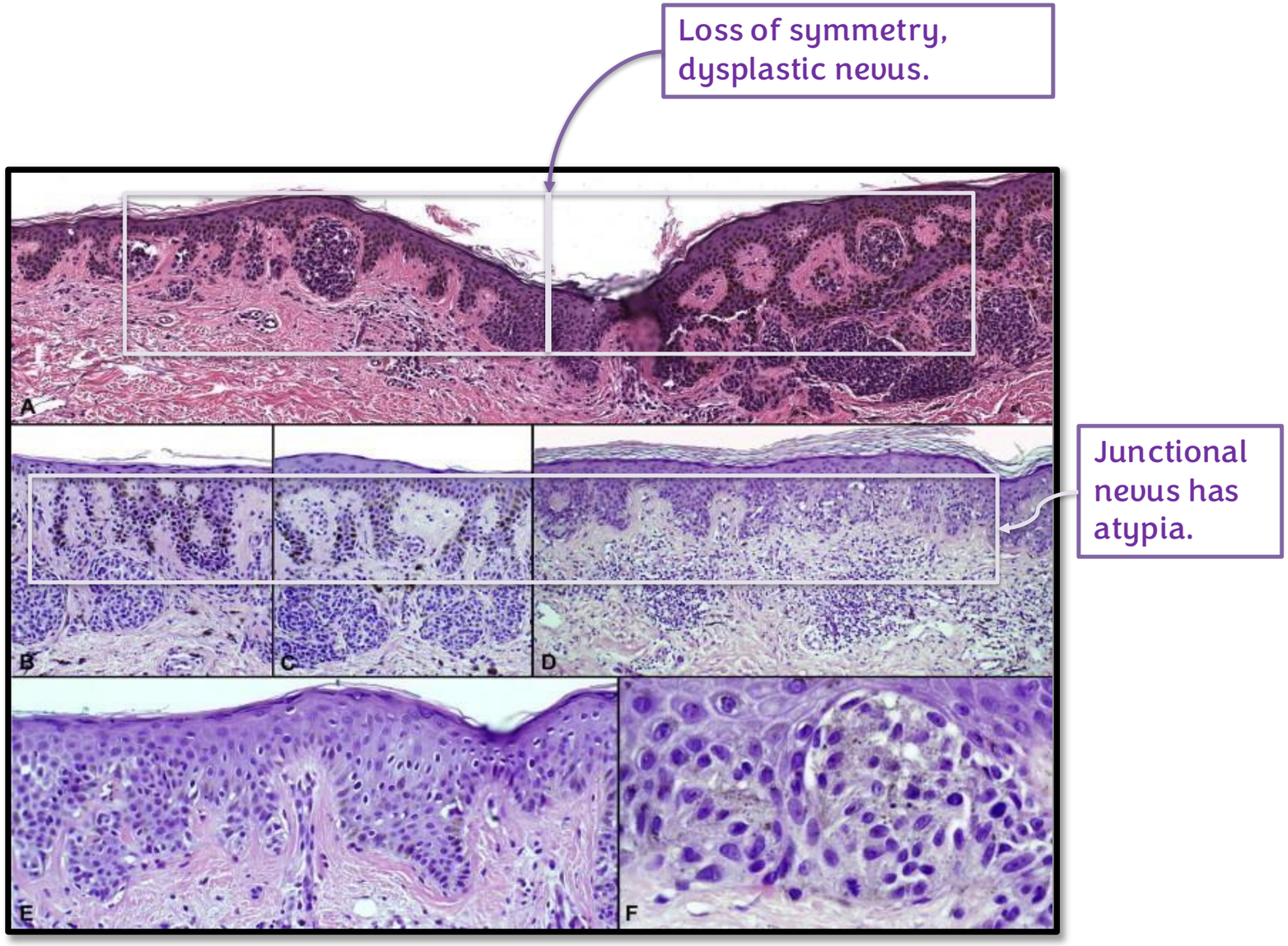
- **Nevi with atypical features, usually larger (>5 mm)**
- **Sporadic or familial**
- **Occur on both sun exposed as well non sun exposed**
- **Can be multiple (specially familial type)**
- **Risk of melanoma is higher than non dysplastic**
- **However: risk is low and most melanomas occur “de novo”**
- ***Familial dysplastic nevus syndrome:*** **high life-time risk**

- Dysplastic nevi show asymmetry, mitoses, and sometimes necrosis. Even one mitosis in a nevus warrants concern for dysplasia or melanoma.
- Familial dysplastic nevus syndrome increases melanoma risk—regular monitoring is essential.
- Chronic irritation and UV exposure can turn a benign nevus into dysplastic, then into melanoma. Suspicious lesions should be removed early.

Histopathological features:

Loss of symmetry

- Fusion of junctional nests
- Cellular and nuclear atypia
- Superficial dermal fibrosis
- Lymphocytic infiltration
- Melanin incontinence



MELANOMA

- Malignant neoplasm of melanocytes and can be fatal
- Less common than Sq. CCa, Basal CCa and nevi
- Currently: most melanomas are cured surgically
- The incidence is on the rise:
  - More sun exposure
  - More surveillance
  - More public awareness

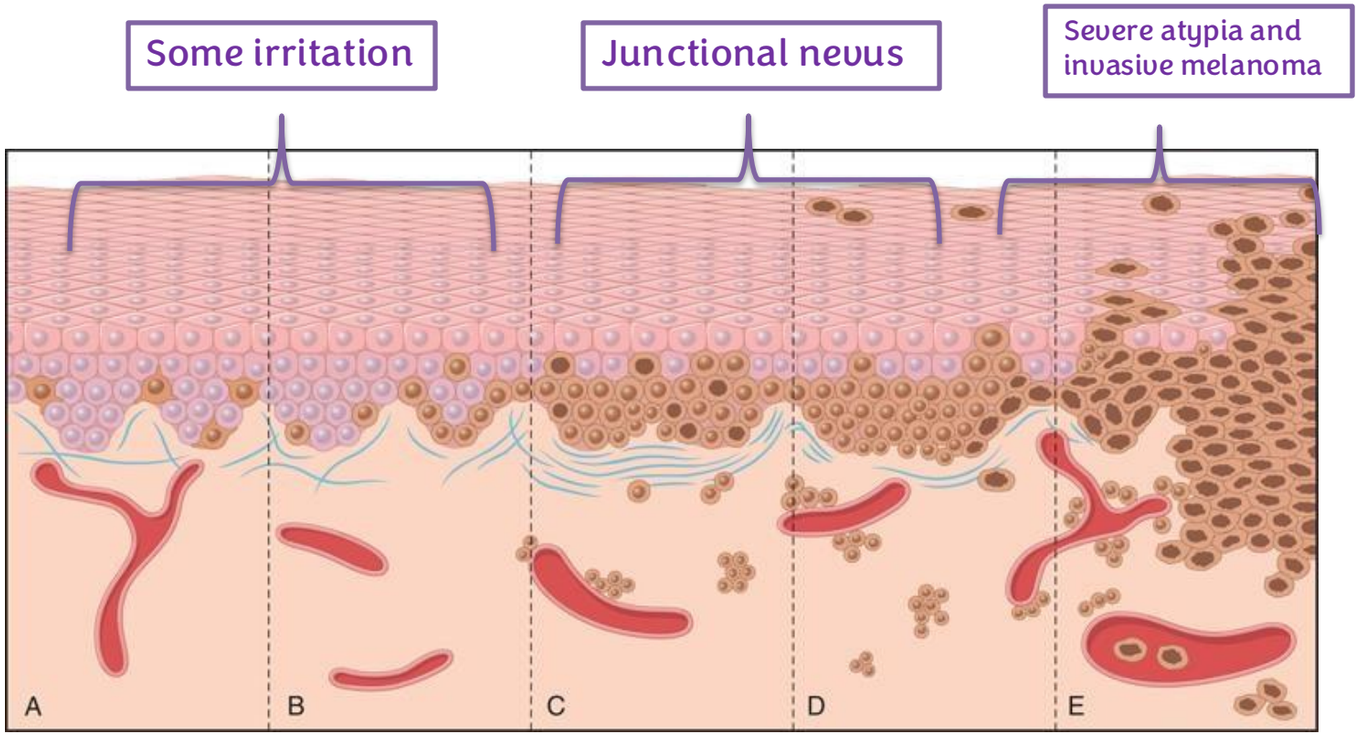
- Due to more awareness among people, most melanomas are caught surgically early as dysplastic before invasion. But there are still late cases.
- In literature, it is stated that the incidence of melanomas is rising. It could be because of more sunbathing or that people are visiting doctors more frequently to check for dysplastic changes –also how they explain more cases of thyroid carcinoma.

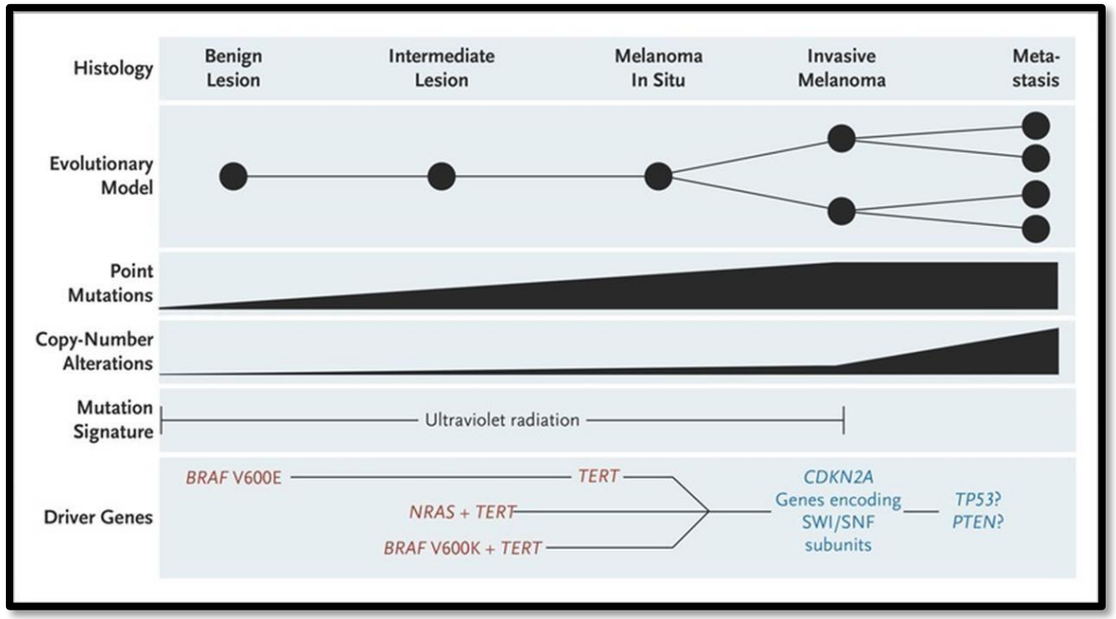
– Lymphoma is malignant, melanoma is malignant, hepatoma –old name of hepatocellular carcinoma– is malignant, these are misnomers.

سبحان الله وبحمده، سبحان الله العظيم

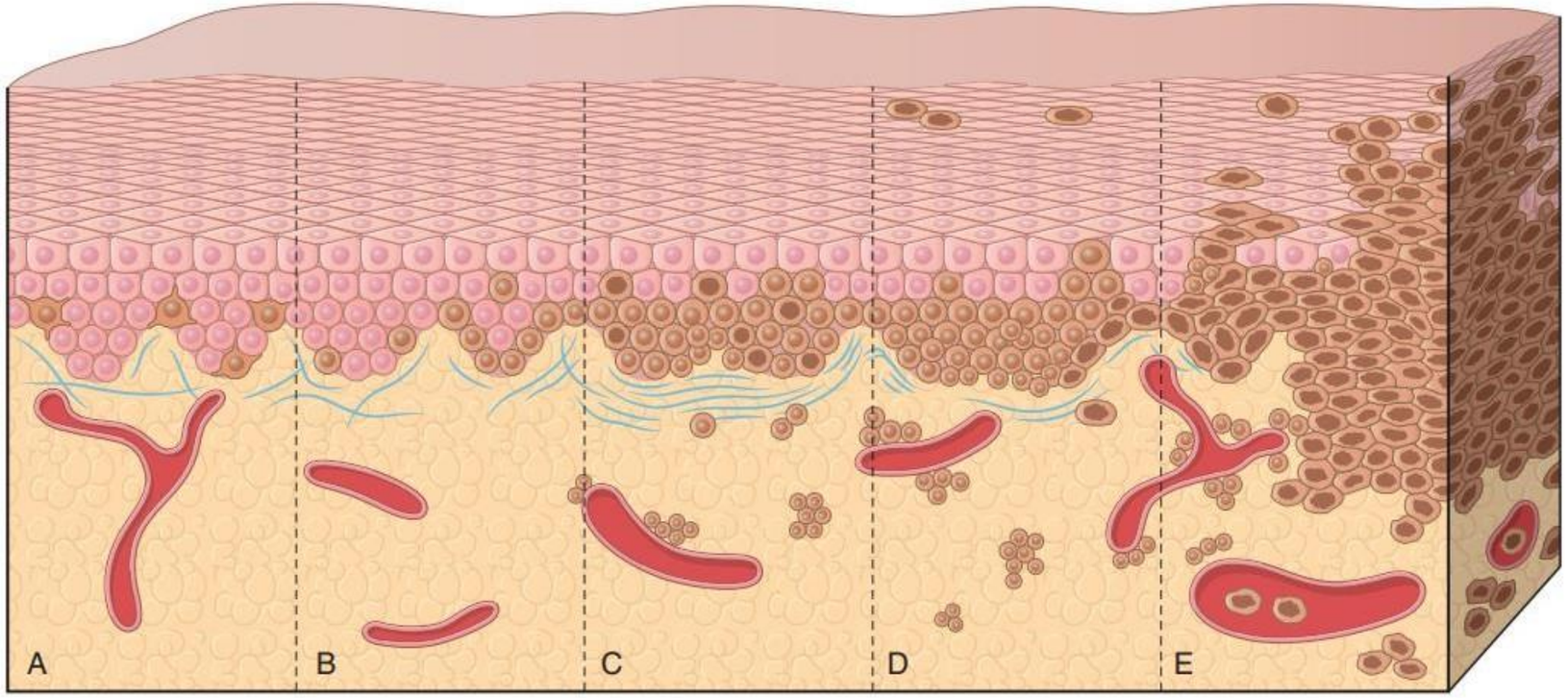
MELANOMA EVOLUTION

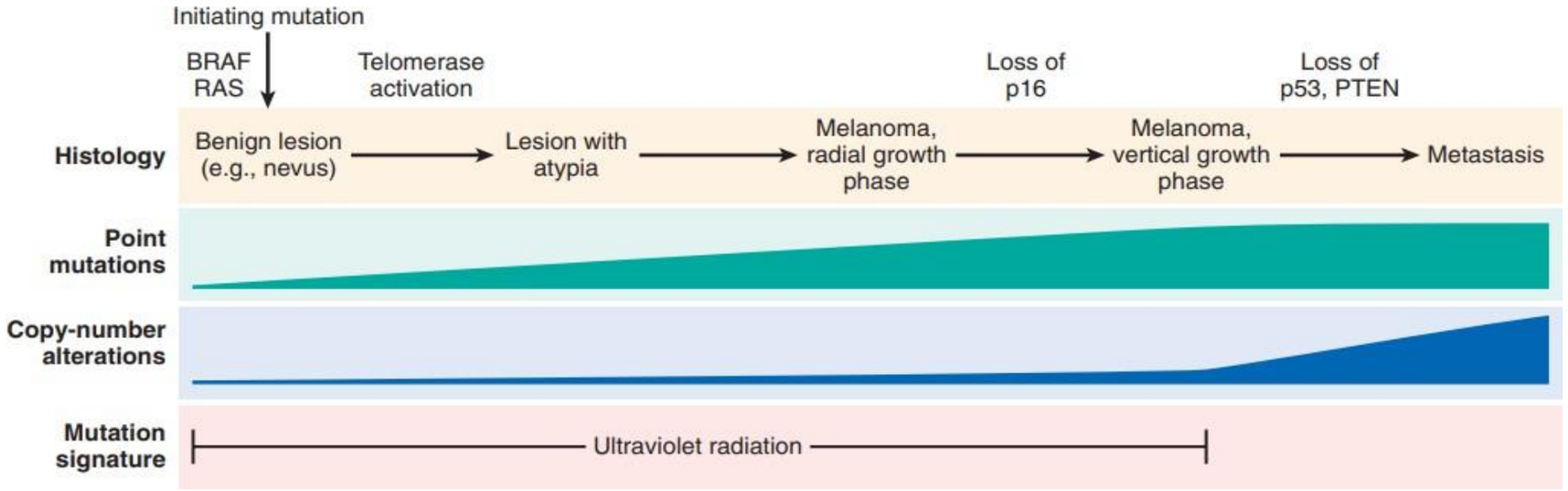
- Melanoma is like cervical carcinoma in which they both evolve.
- Nevus→ dysplastic nevus → melanoma in situ → invasive melanoma
- This process has both early and late changes –**important to know them**.





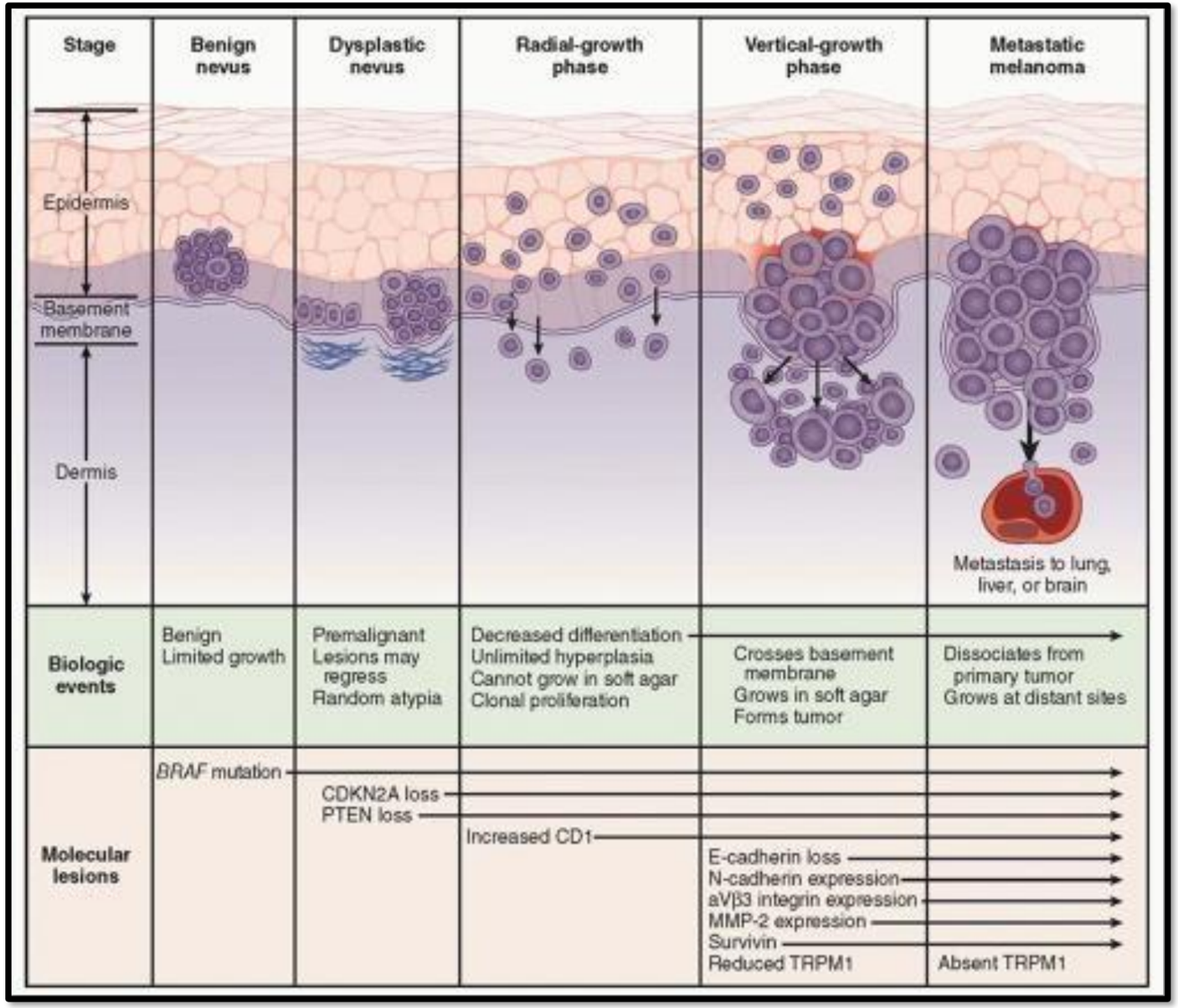
BRAF and BRAS are early, while TP53, PTEN & TERT are late



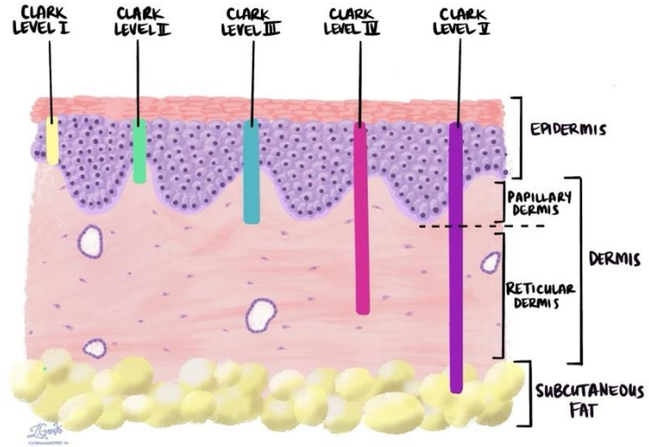


- **Loss of p53 & PTEN is a late change, P16 is before, - BRAF & RAS change very early**, it's important to know the early and late changes in the evolution of melanocytic neoplasms.

See the next slide..



- The most important prognostic factor in melanoma is early diagnosis followed by pathological staging.
- Staging primarily depends on the depth of vertical invasion.



~this picture is just for clarification~

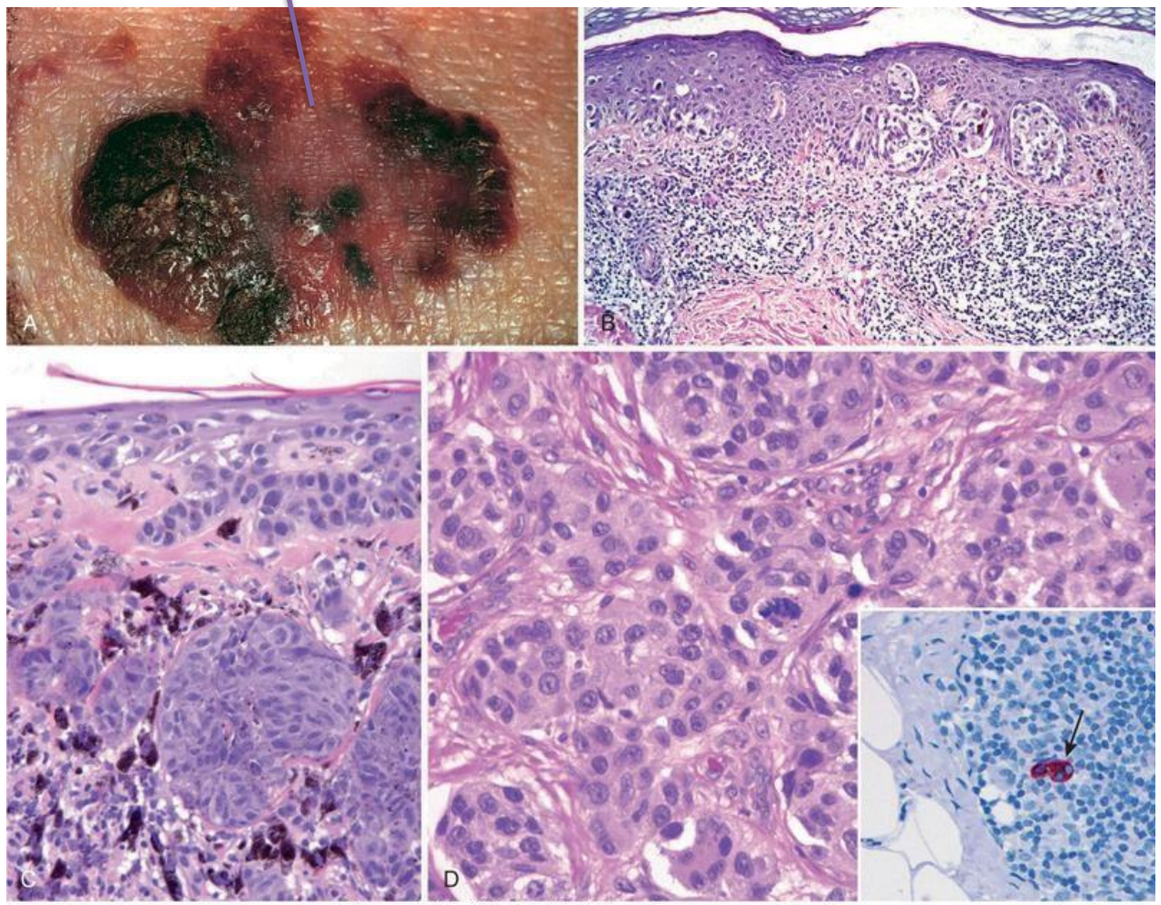
□ **The vertical growth phase** of melanoma is when the tumor begins to grow **deeply into the dermis** and possibly the subcutaneous tissue, indicating invasion.
□ Melanoma is **already malignant** at diagnosis; its depth of invasion determines the **pathological stage,** which is the **most important prognostic factor**.

- This depth was previously described using **Clark levels (I–V),** with level V indicating invasion into **subcutaneous tissue.**
- Currently, **Breslow thickness**, measured in **millimetres**, is used instead.
- Overall, prognosis in melanoma depends heavily on the depth of invasion and whether it is in the early or advanced stage.

Pathological features:

- Irregular borders and pigmentation
- Irregular nesting with increased numbers of single cells
- Radial and vertical growth → Radial & vertical growth only appear after biopsy histologically.
- Increased thickness (Breslow thickness)
- Deeper invasion
- Larger atypical cells
- Atypical larger nuclei with prominent cherry-red nucleoli

clinically, worrisome signs: asymmetric borders, variable pigmentation.



Kumar et al: Robbins Basic Pathology, 9e.

- Sometimes when we are not sure if it is basal cell, squamous cell, melanoma, or even poorly differentiated metastatic breast carcinoma. Especially if it is a poorly differentiated tumor, we use stains to find origin of cells.

A Pathologist gives the diagnosis after you get a shave biopsy, which gets checked under the microscope.

WARNING SIGNS OF MELANOMA:

- **Rapid enlargement of a preexisting nevus**
- **Itching or pain**
- **New pigmented lesions development**
- **Irregular borders of a pigmented lesion**
- **Variegation of color within a pigmented lesion** → Areas are dark, and areas are less dark.

CLINICAL FEATURES AND PROGNOSIS:

- Most can be cured surgically
- Stage is critical (depth of invasion)
- Metastatic disease exhibits poor prognosis
- "Sentinel node" evaluation may help in stage determination
- Recent evolution in treatment options (targeted therapy):
  - Anti *BRAF* and *KIT* agents
  - Immune check point inhibitors (T-cell mediated immunotherapy)

→ A patient can stay 5-10 years with stage IV melanoma and still is able to live normally with such new treatments.

- Melanoma is a very bad tumor that can metastasize to pancreas, brain, bone.
- Most are still to these days treated by surgical excision.
- Sentinel means الحارسة
- Breast cancer goes to one lymph node at first -sentinel- then returns to the axillary lymph nodes, (same happens with melanoma).
- They add pigment to the tumor then follow it to find which lymph node the pigment has reached; they remove it and present it to the pathologist mid-surgery to do a frozen section. If the lymph node is positive they will have to proceed with a dissection of regional lymph nodes like what happens in breast cancer.

~more explanation
The sentinel nodes are the first few lymph nodes to which cancer spreads. In sentinel node biopsy, a tracer material is used to help the surgeon find the sentinel nodes during surgery. The sentinel nodes are removed and tested in a lab. If the sentinel nodes are free of cancer, then cancer probably hasn't spread.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

Videos chosen by Dr. Mousa about skin tumours:

- **Skin Cancer: Different Types, Causes, Prevention & Treatments | Dr. Sam Ellis**
- **Diagnosing Melanoma**

رسالة من الفريق العلمي:

﴿ يا يَحيى خُذِ الكِتابَ بِقُوَّةٍ ﴾ ليس قـوة يـد وبـدن وإنما قوة قلب وعقيدة، وأنت أيضاً :خُذ الكتاب بقوة !كن راسخاً في إيمانك ثابتاً في عقيـدتـك .لومال الناس كلهـم، فاثبت !ولو انتكس الناس كلهـم، فلا تترك صلاحك !إن هـذا الدين منتصر بـك، أو بـدونـك !وحدك الذي ستخسر إن مضت القافلة ولم تكن فيها !

لَا تَحْسَبَنَّ الَّذِينَ كَفَرُوا مُعْجِزِينَ فِي الْأَرْضِ ۚ وَمَأْوَاهُمُ النَّارُ ۖ وَلَبِئْسَ الْمَصِيرُ]النور[57 :

لا تنسوا اخوانا المسلمين من دعائكم