

Metaplasia, Dysplasia, and Carcinoma In Situ

Epithelial adaptation, precancer, and the invasion boundary

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Learning objectives

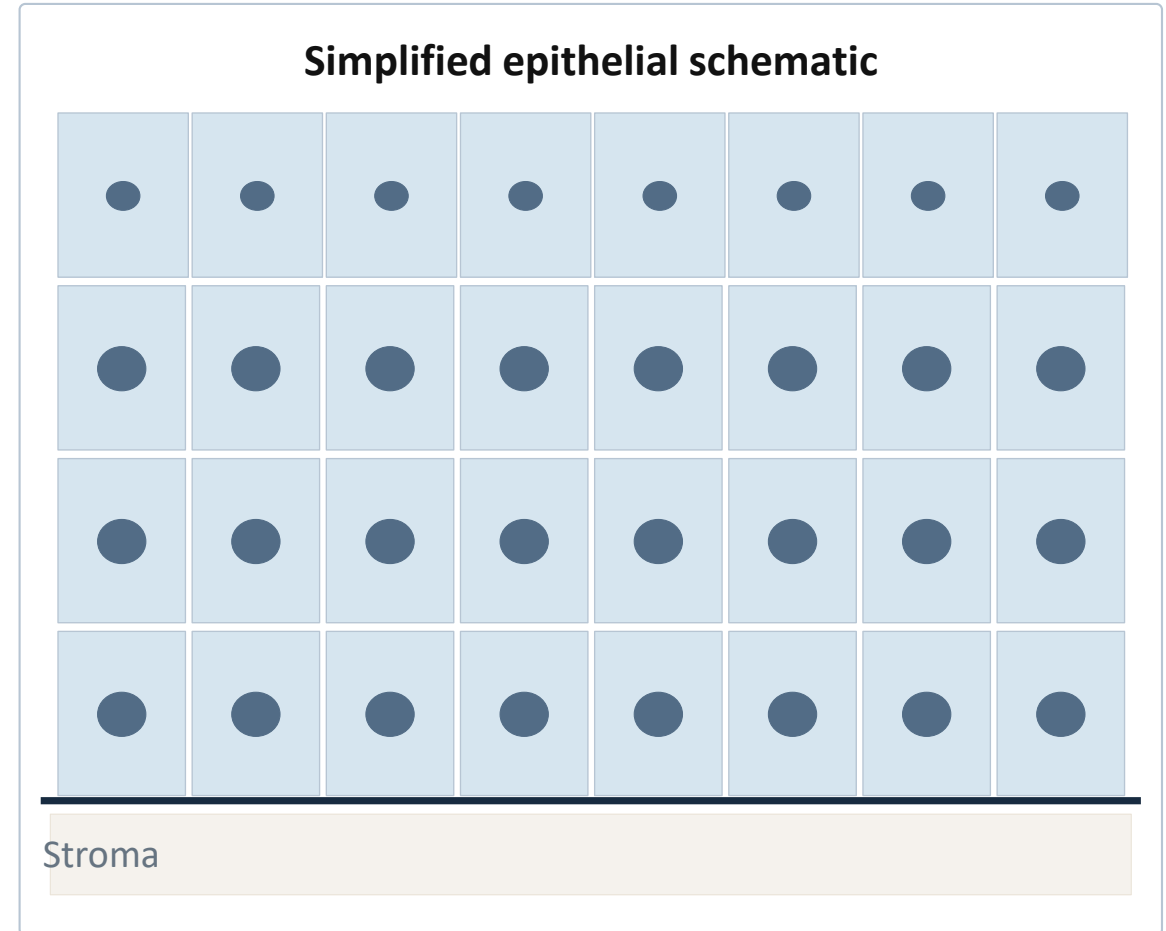
- Explain why chronic injury may replace an epithelial phenotype.
- Identify cytologic and architectural criteria for dysplasia.
- Diagnose the in situ–invasive boundary from epithelial architecture.
- Interpret progression, regression, and precursor risk without assuming inevitability.

Three related terms, three different meanings

Metaplasia	Replacement by another mature cell phenotype	Adaptation
Dysplasia	Disordered epithelial growth and maturation	Premalignant change
Carcinoma in situ	Full-thickness malignant cytology; No stromal invasion	Intraepithelial cancer

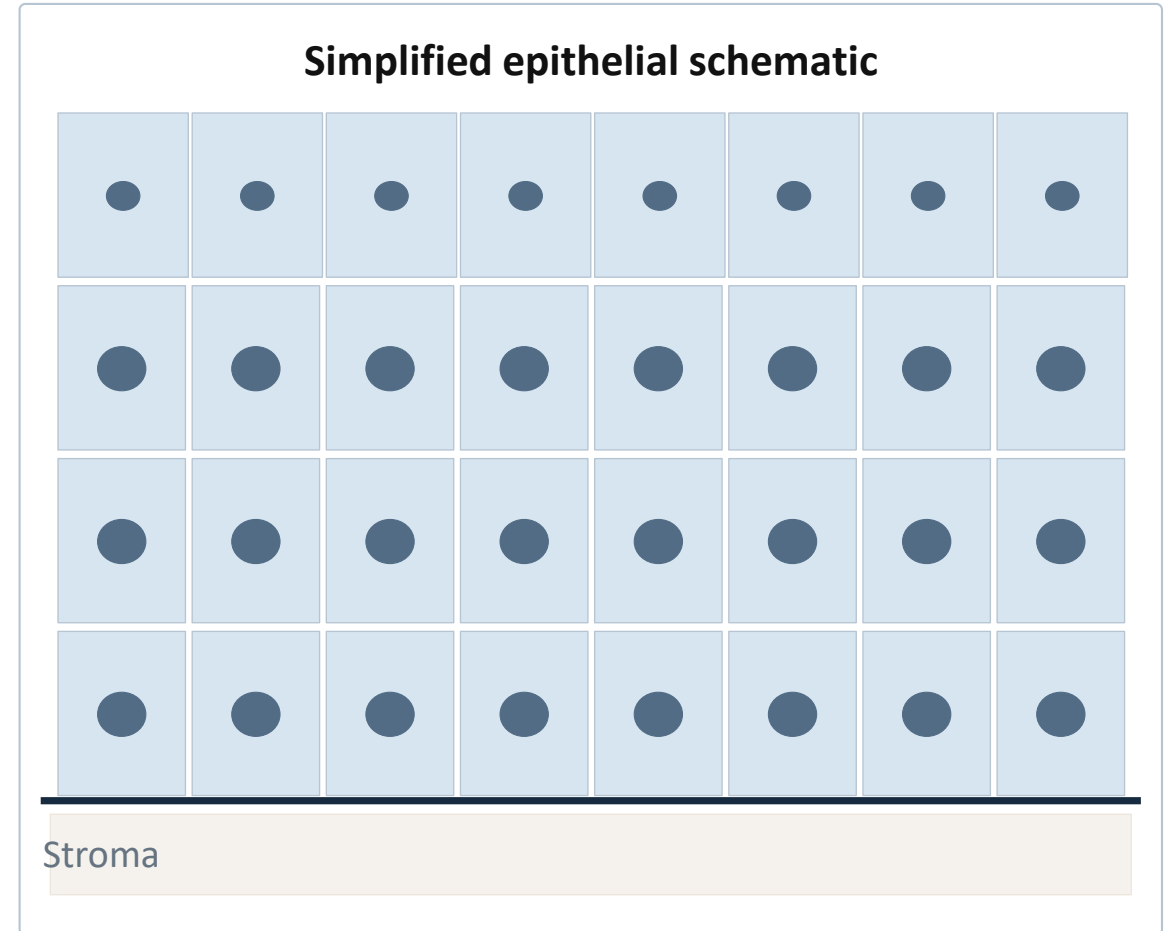
Epithelial topography controls interpretation

- Surface epithelium is separated from supporting stroma by a basement membrane.
- Cytologic atypia describes the cells; Invasion describes their location.
- The basement membrane is the critical boundary when distinguishing in situ from invasive carcinoma.



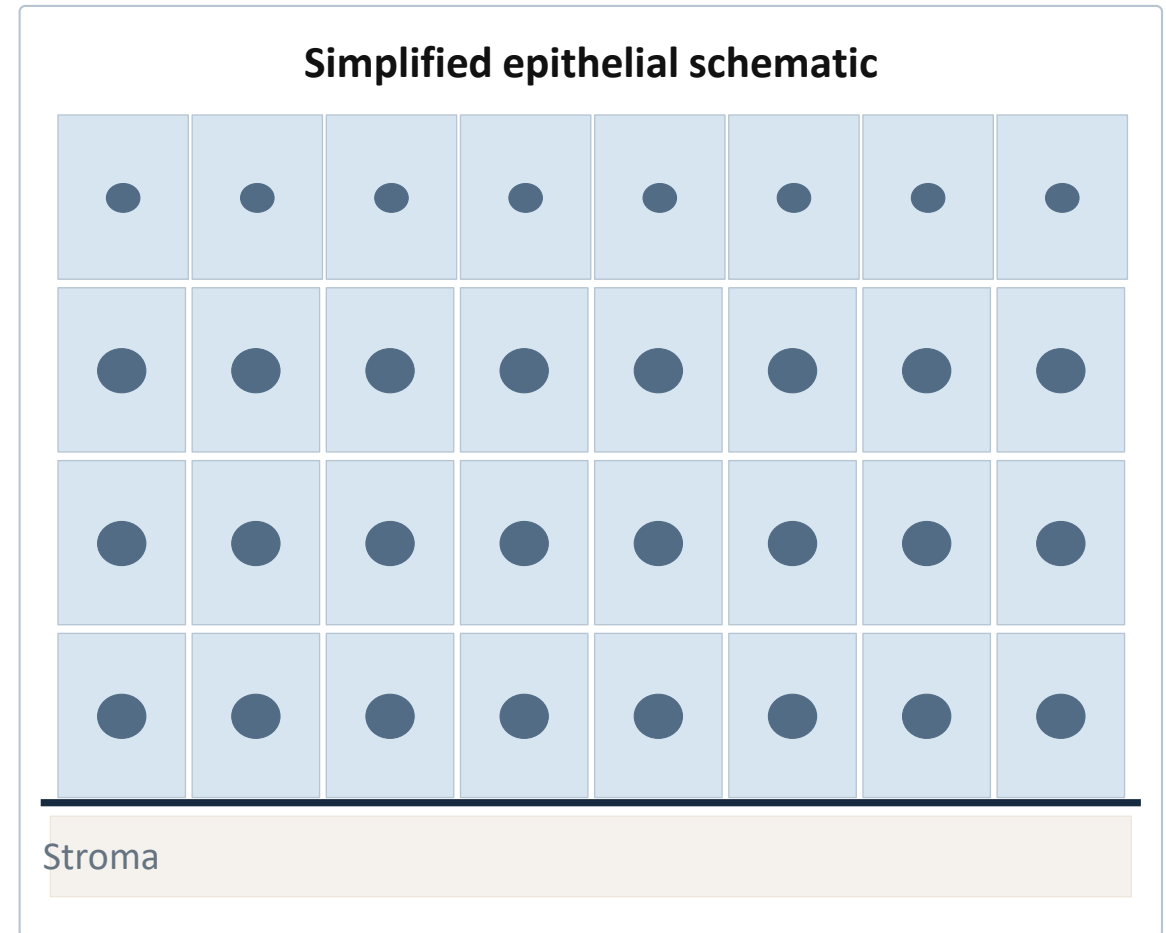
Normal stratified squamous epithelium matures upward

- Proliferative basal cells are relatively tall and immature.
- Progressive maturation produces flattened superficial squamous cells.
- Orderly stratification provides the reference against which dysplasia is recognized.



Normal squamous mitoses are basally restricted

- Normal mitotic activity is concentrated in the basal compartment.
- Cells acquire differentiated morphology toward the epithelial surface.
- Mitotic figures well above the basal region suggest disrupted maturation when accompanied by atypia.



Differentiation means resemblance to normal tissue

Differentiated phenotype

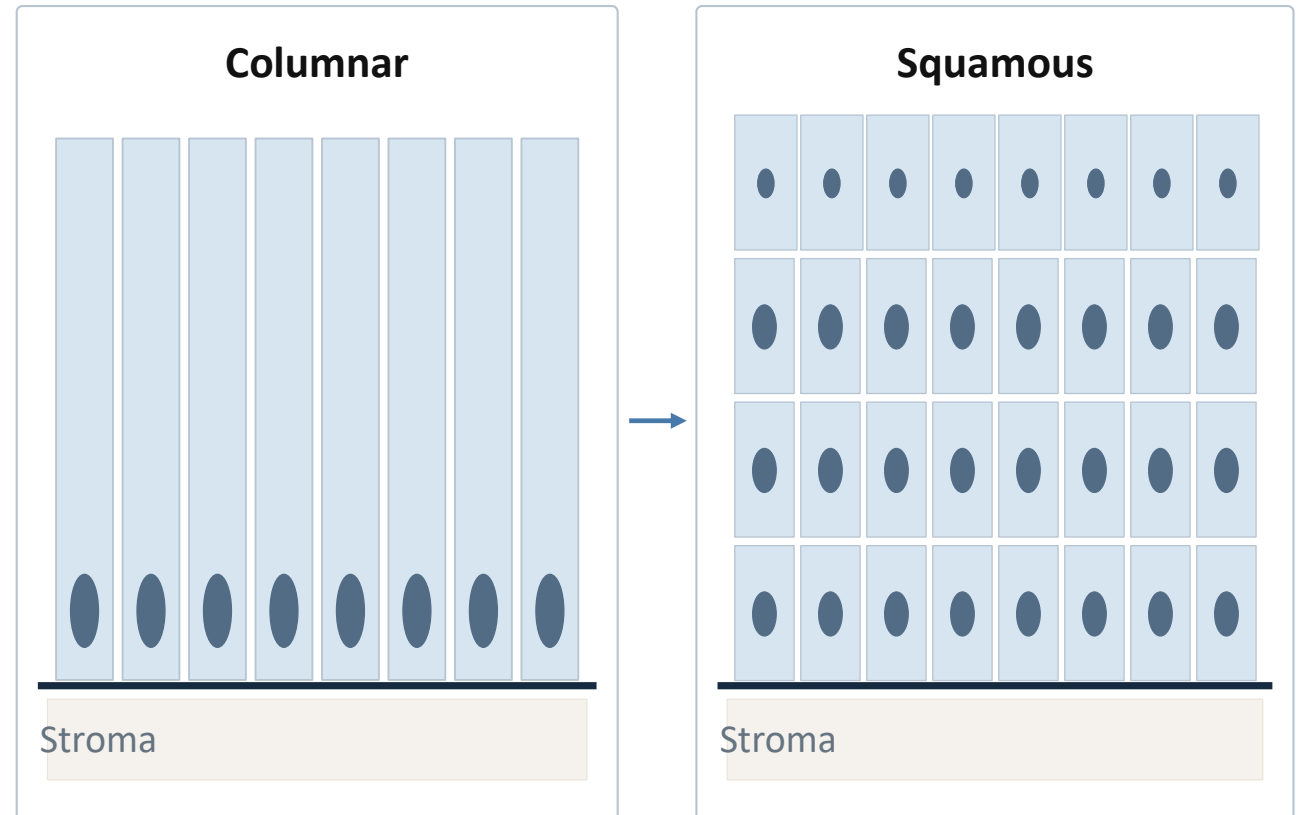
- Recognizable cell form
- Specialized epithelial function
- Orderly architectural organization

Loss of differentiation

- Failure of normal maturation
- Architectural disarray
- Potentially increasing atypia

Metaplasia is replacement, not simply proliferation

- One differentiated epithelial cell type is replaced by another.
- Metaplasia usually occurs during tissue damage, repair, and regeneration.
- It is generally an adaptive response to persistent adverse exposure.



Metaplastic epithelium may tolerate the stress better

Chronic environmental stress



Repair / regeneration



**Alternative, better-tolerated
cell type**

- A more durable epithelial phenotype can survive a hostile local environment.
- An adaptive advantage under stress does not imply normal physiologic function.

Metaplasia is potentially reversible

Inciting exposure



Metaplastic differentiation

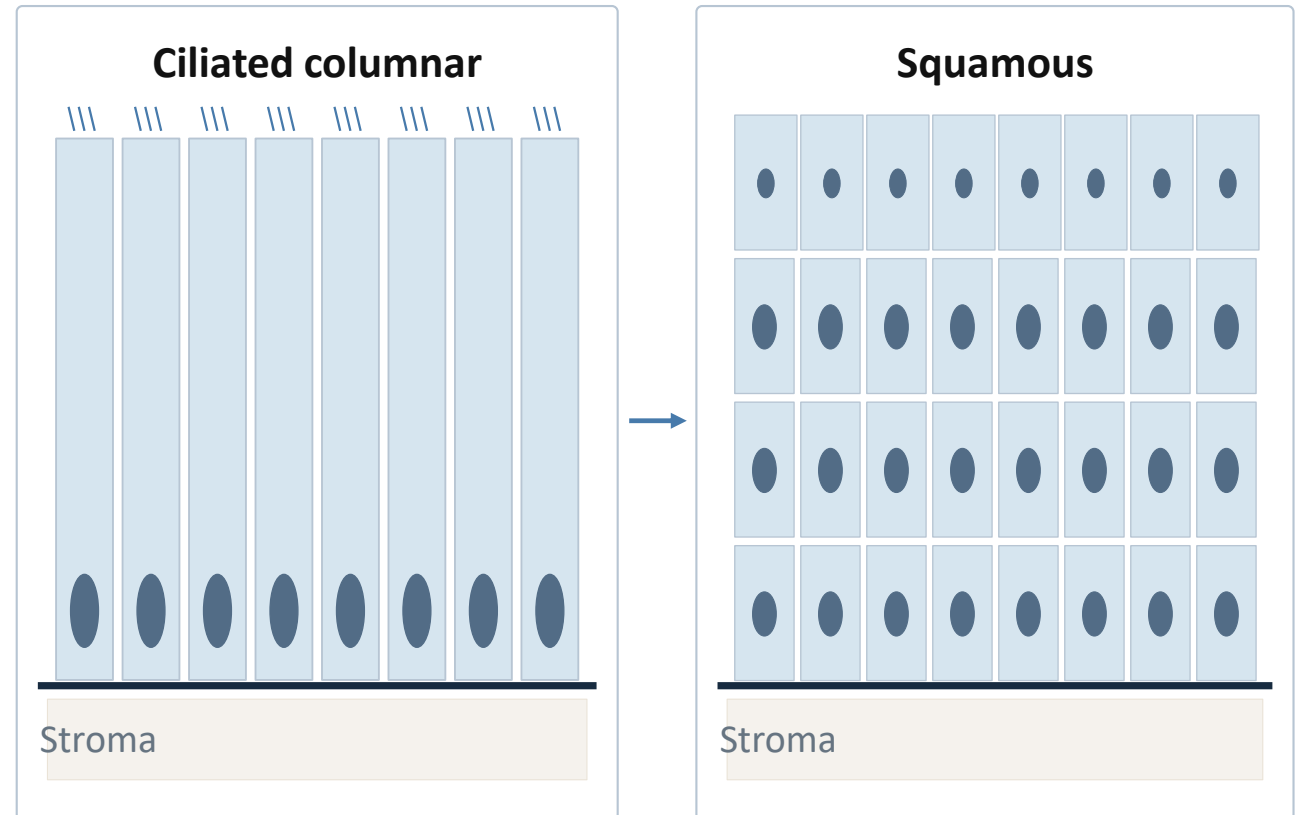


**Exposure removed →
potential reversal**

- Metaplasia as a reversible differentiation change.
- Persistence and duration of the underlying injury influence the tissue context.
- Reversibility should not be confused with absence of cancer risk.

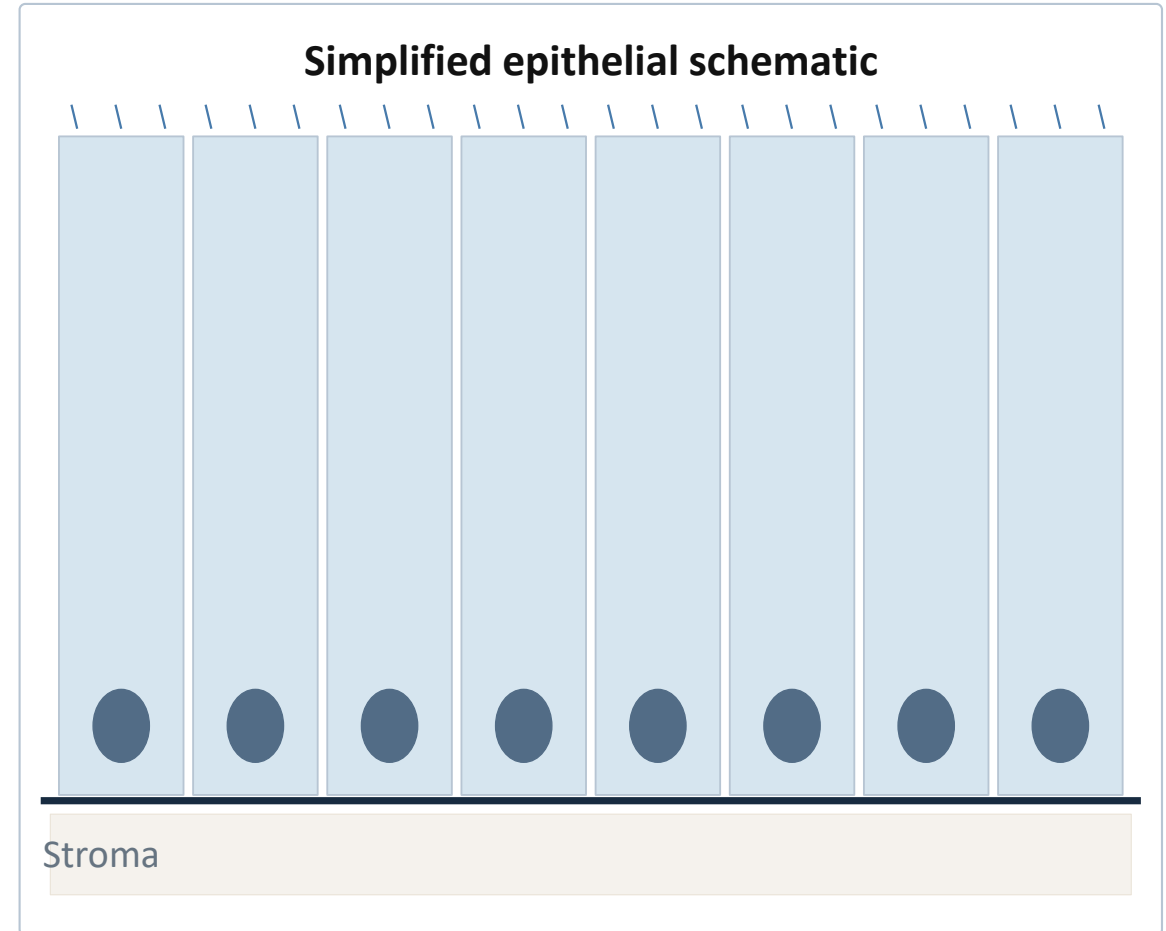
Bronchial epithelium: Columnar-to-squamous replacement

- Chronic tobacco smoke exposure damages glandular/ciliated bronchial epithelium.
- Stratified squamous cells may replace the normal columnar lining.
- This is a classic epithelial example of metaplasia.



Ciliated bronchial cells are functionally specialized

- The normal airway lining contributes mucus secretion and ciliary transport.
- These mechanisms help protect the respiratory tract against infection.
- Loss of a differentiated function is important even if metaplastic cells survive better.



Squamous metaplasia trades function for resistance

Adaptation gained

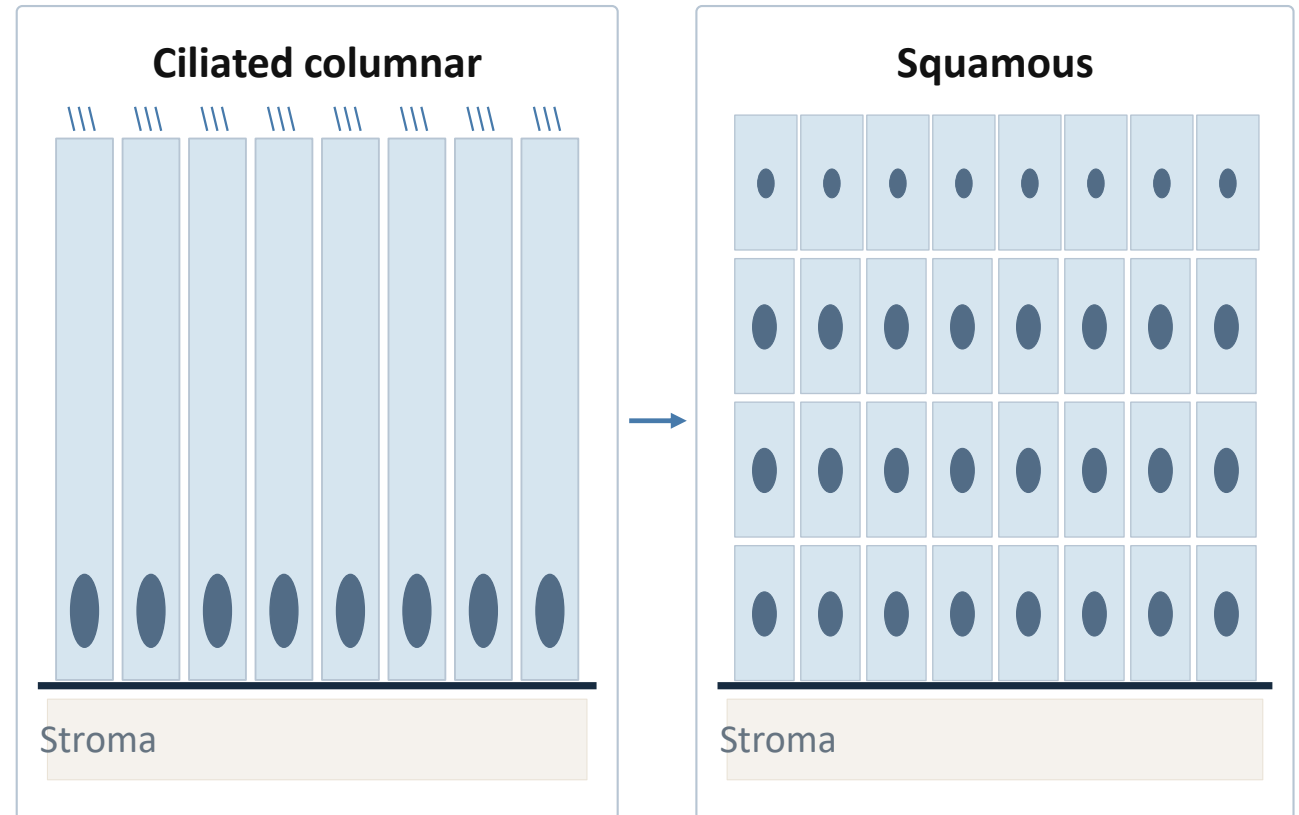
- Rugged stratified squamous lining
- Better tolerance of chronic irritation
- Continued epithelial coverage

Function lost

- Normal mucus secretion
- Ciliary clearance
- Part of airway defense against infection

The smoking-associated epithelial response is not cancer

- Squamous metaplasia describes a change in cell type, not autonomous invasion.
- It is not equivalent to dysplasia or carcinoma.
- Persistent carcinogenic influences may also create a setting for later malignant transformation.



Vitamin A deficiency can induce squamous metaplasia

Altered retinoic-acid signaling



Altered differentiation
program



Squamous metaplasia

- Squamous metaplasia in respiratory epithelium and cornea with vitamin A deficiency.
- The corneal consequence is particularly detrimental to vision.

Duct obstruction is another setting for squamous change

Stone / pressure / irritation



Ductal epithelial injury

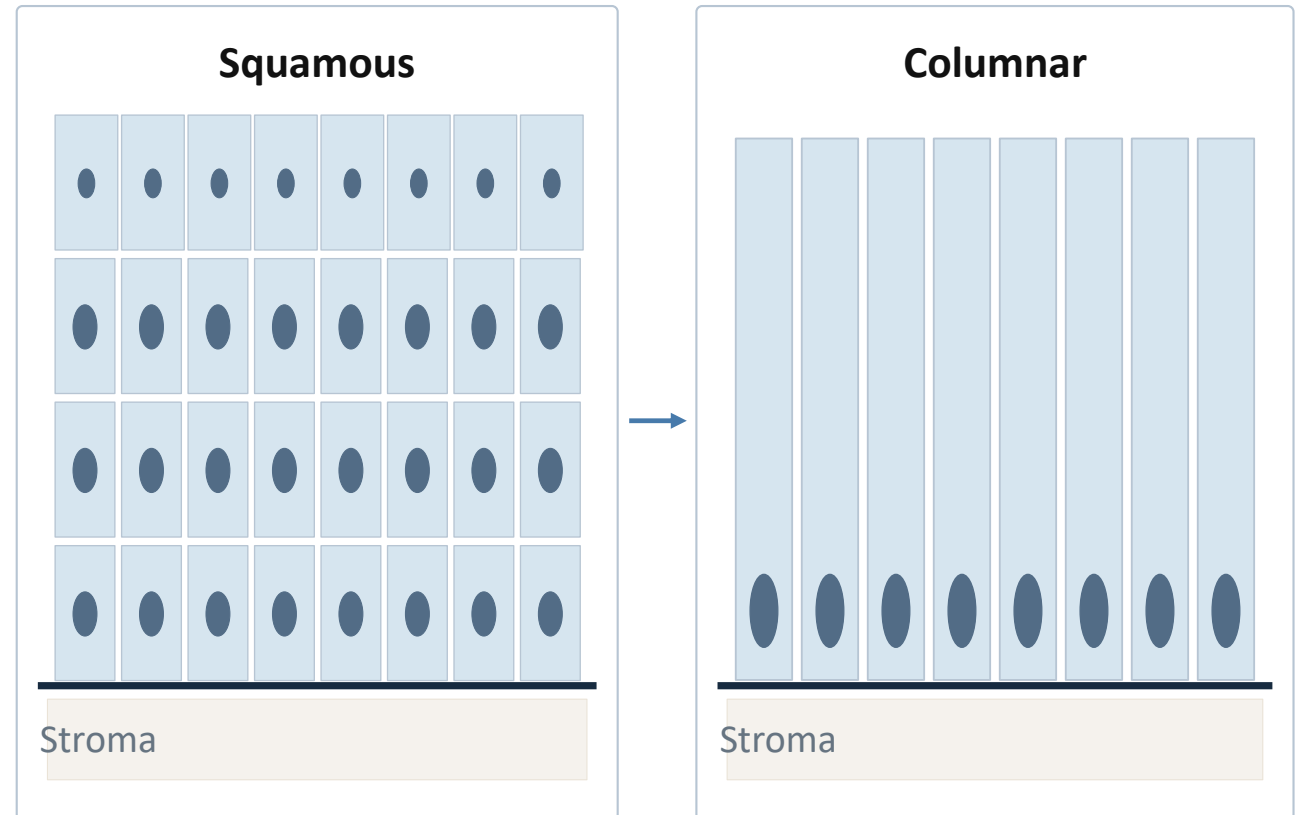


Squamous metaplasia

- Excretory ducts of salivary glands, pancreas, and bile ducts are cited examples.
- The usual secretory columnar epithelium may be replaced by squamous lining.

Metaplasia can also convert squamous to columnar

- Direction is not restricted to columnar → squamous.
- The best-known reverse example is Barrett esophagus.
- The final phenotype depends on the local injury and differentiation context.



Barrett esophagus develops under reflux injury

Gastroesophageal reflux



Damage to esophageal
squamous lining



**Glandular/intestinal-type
replacement**

- Gastric secretions injure the native squamous esophageal epithelium.
- Glandular epithelium is better able to withstand the acid-exposed environment.

Barrett: Adaptive phenotype but clinically relevant risk

Immediate response

- Replacement of injured squamous epithelium
- Acid-tolerant glandular/intestinal-type phenotype

Long-term concern

- Metaplastic epithelium is not inherently dysplastic
- Cancers in Barrett-associated fields are typically gland-forming adenocarcinomas

Different epithelia give rise to different carcinomas

Bronchial squamous metaplasia	Squamous phenotype	Associated with squamous cell carcinoma development
Barrett esophagus	Glandular/intestinal phenotype	Typically associated with adenocarcinoma

Epithelial and mesenchymal metaplasia are distinct

Epithelial	One epithelial phenotype replaces another	May occur in a carcinogenic injury field
Mesenchymal	Bone, cartilage, or adipose differentiation at an unusual site	Robbins does not link this category to increased cancer risk

Myositis ossificans illustrates mesenchymal metaplasia

Intramuscular injury /
hemorrhage



Ectopic osseous
differentiation



Bone within muscle

- Bone formation in muscle after intramuscular hemorrhage.
- The change may reflect injury rather than an obvious protective adaptation.
- It must not be presented as epithelial dysplasia.

Not every metaplasia increases cancer risk

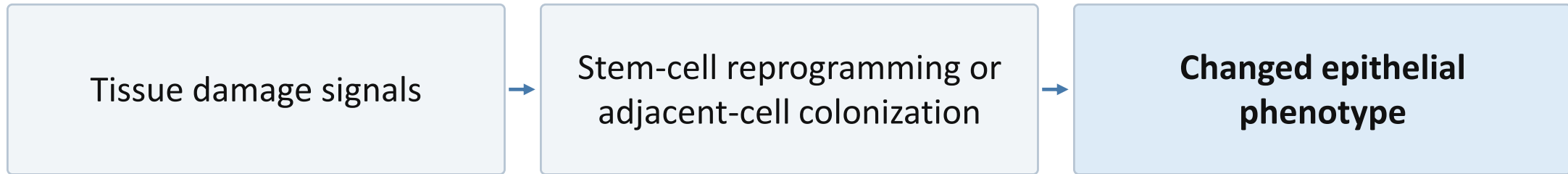
Epithelial metaplasia

- Frequently linked with persistent epithelial injury
- Certain metaplastic fields may precede carcinoma
- Cancer is not an inevitable outcome

Connective-tissue metaplasia

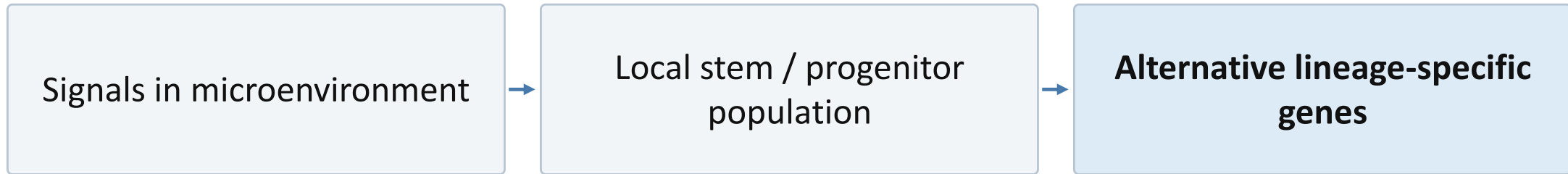
- Cartilage, bone, or fat in unexpected tissue
- May follow local tissue injury
- Not associated with elevated cancer risk

Metaplasia does not require mature-cell conversion



- Robbins explicitly rejects direct phenotypic conversion of an already differentiated cell as the usual explanation.
- Alternative cell-population sources can create the new epithelium.

Local stem cells can adopt a new differentiation program



- Stem-cell reprogramming changes the differentiation output of renewing tissue.
- New epithelial cells acquire a phenotype suited to the exposed site.

Adjacent differentiated populations can colonize tissue

Injured epithelial
compartment



Colonization by cells from
adjacent site



**Alternative mature cell
population**

- Colonization from a neighboring epithelial population as another mechanism.
- This is distinct from reprogramming of local tissue stem cells.

The microenvironment directs metaplastic differentiation

Cytokines / growth factors /
extracellular matrix



Differentiation signaling



New tissue phenotype

- Regenerative signals arise in the cells' local environment.
- They influence expression of genes driving a particular differentiation pathway.

Retinoic acid links signaling to lineage identity

Retinoic acid



Nuclear retinoid receptors



**Transcriptional differentiation
program**

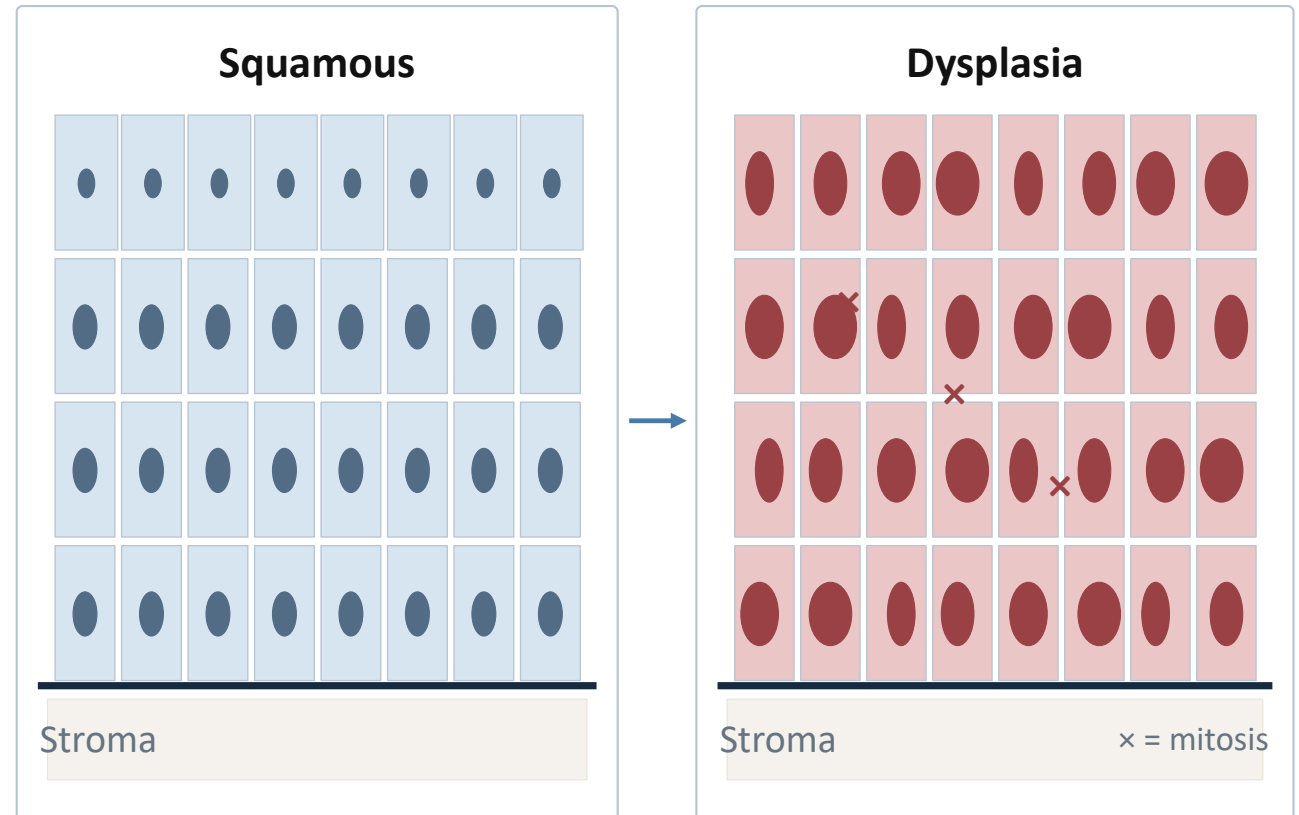
- Retinoic acid directly regulates transcription through nuclear retinoid receptors.
- Deficiency or excess can disturb normal epithelial differentiation.

Metaplasia differs fundamentally from hyperplasia

Hyperplasia	More cells from proliferation/renewal	Cell number changes
Metaplasia	Replacement with a different differentiated cell type	Cell phenotype changes
Dysplasia	Atypical growth and disordered maturation	Cell/architecture abnormality

Metaplasia alone does not diagnose dysplasia

- Metaplasia changes the epithelial phenotype.
- Dysplasia requires atypical cytology and disturbed organization.
- Dysplasia may arise within metaplastic epithelium, but the two changes are not synonymous.



Chronic injury creates a setting for precursor lesions

Chronic epithelial injury



Compensatory regeneration



At-risk epithelial field

- Chronic inflammatory and precursor conditions can increase epithelial replication.
- The presence of a precursor field raises cancer concern; It does not establish that invasive cancer is present.

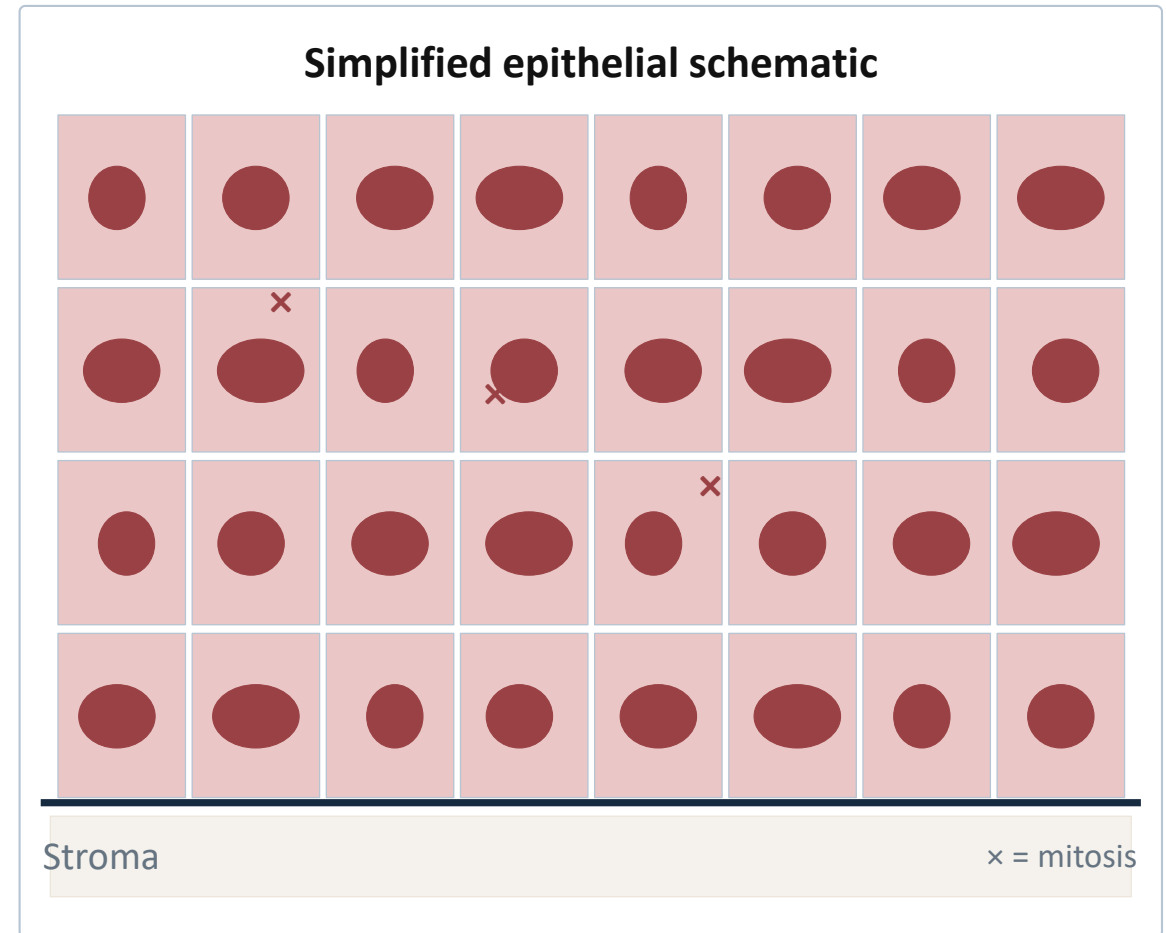
Precursor lesions are localized fields of risk

Hyperplasia	Increased epithelial proliferation
Metaplasia	Altered epithelial phenotype
Dysplasia	Cytologic atypia and architectural disarray

Robbins groups these morphologic changes among epithelial precursor lesions.

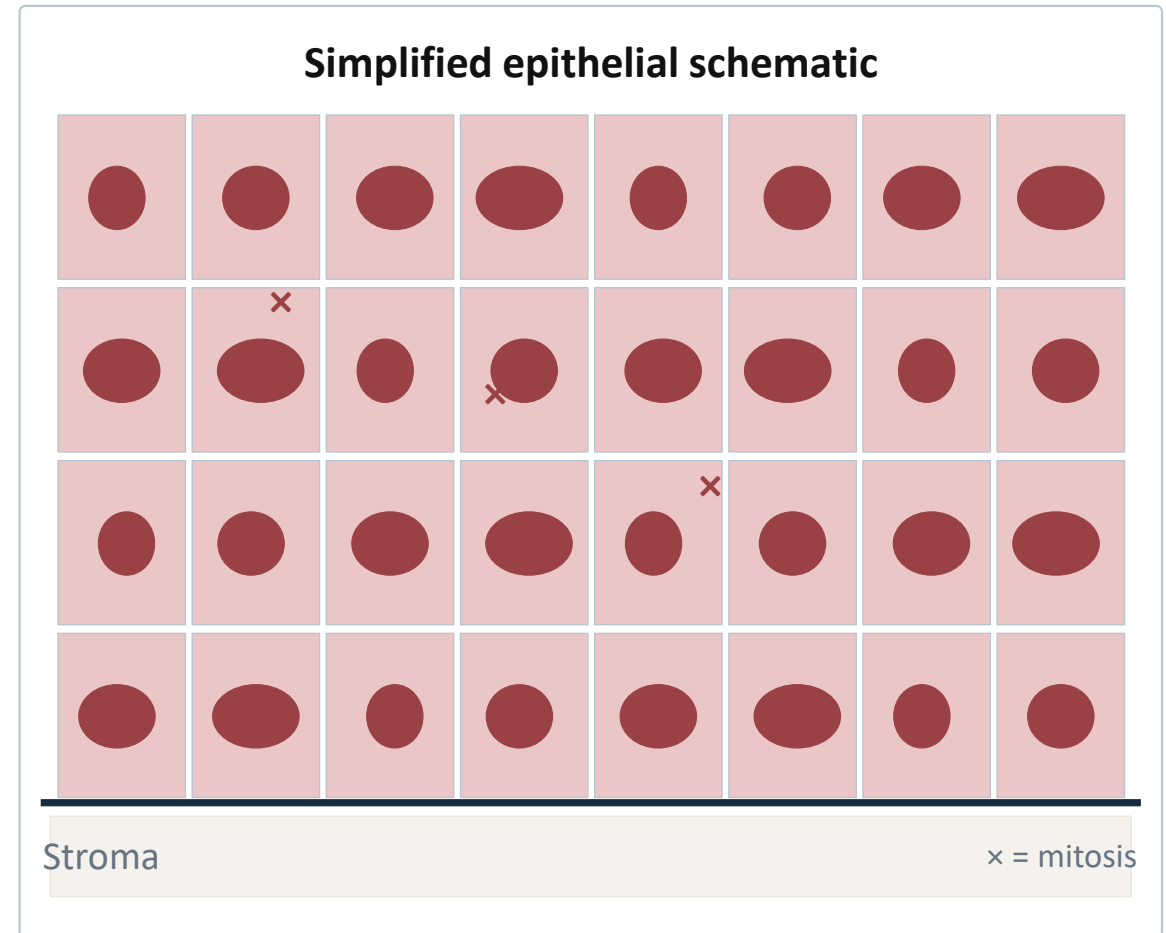
Dysplasia literally means disordered growth

- This premalignant morphologic change is encountered principally in epithelia.
- Diagnosis relies on a combination of cellular and architectural abnormalities.
- Unlike metaplasia, dysplasia denotes loss of growth and maturation order.



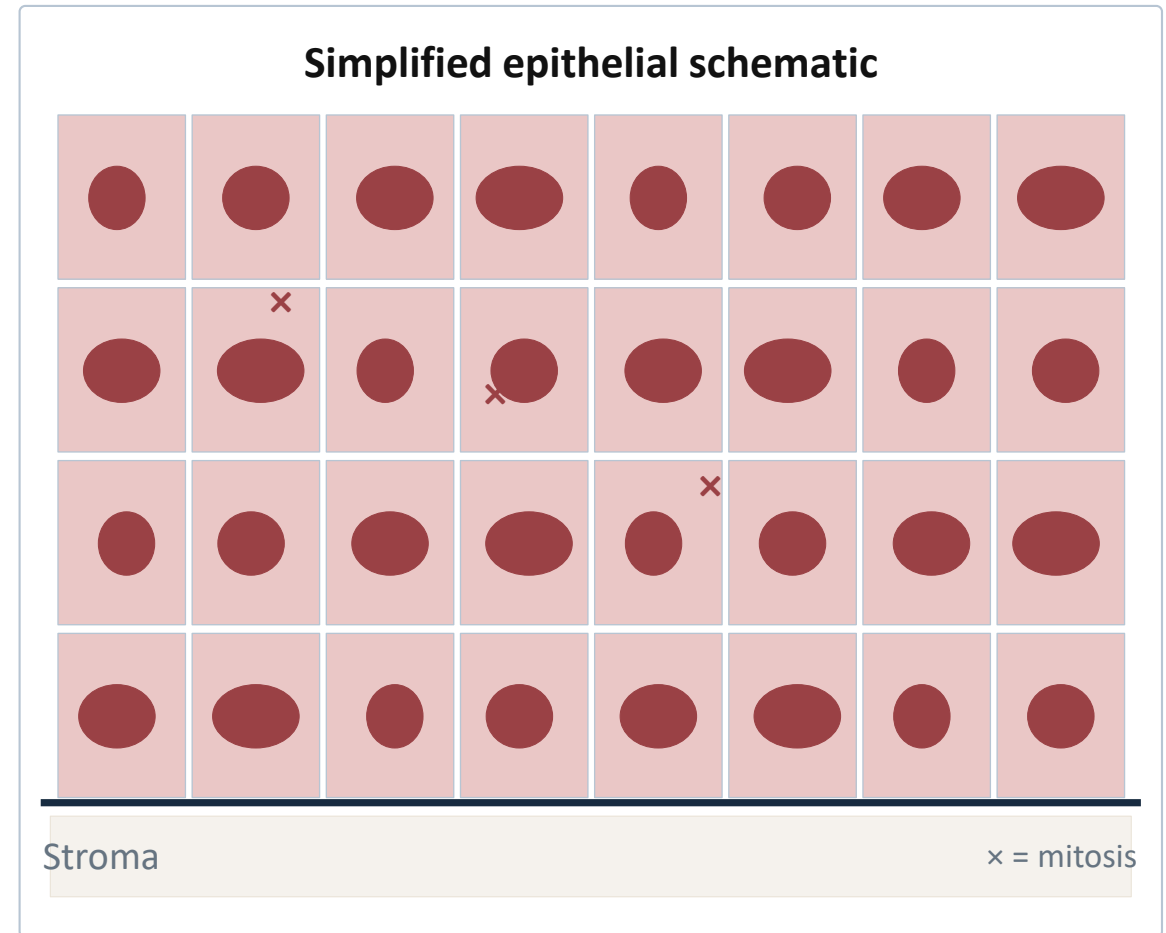
Pleomorphism: Dysplastic cells vary in shape and size

- Cell-to-cell uniformity is reduced.
- Variation includes both cytoplasmic outlines and nuclear appearance.
- Pleomorphism contributes to a dysplastic pattern but should be interpreted with architecture.



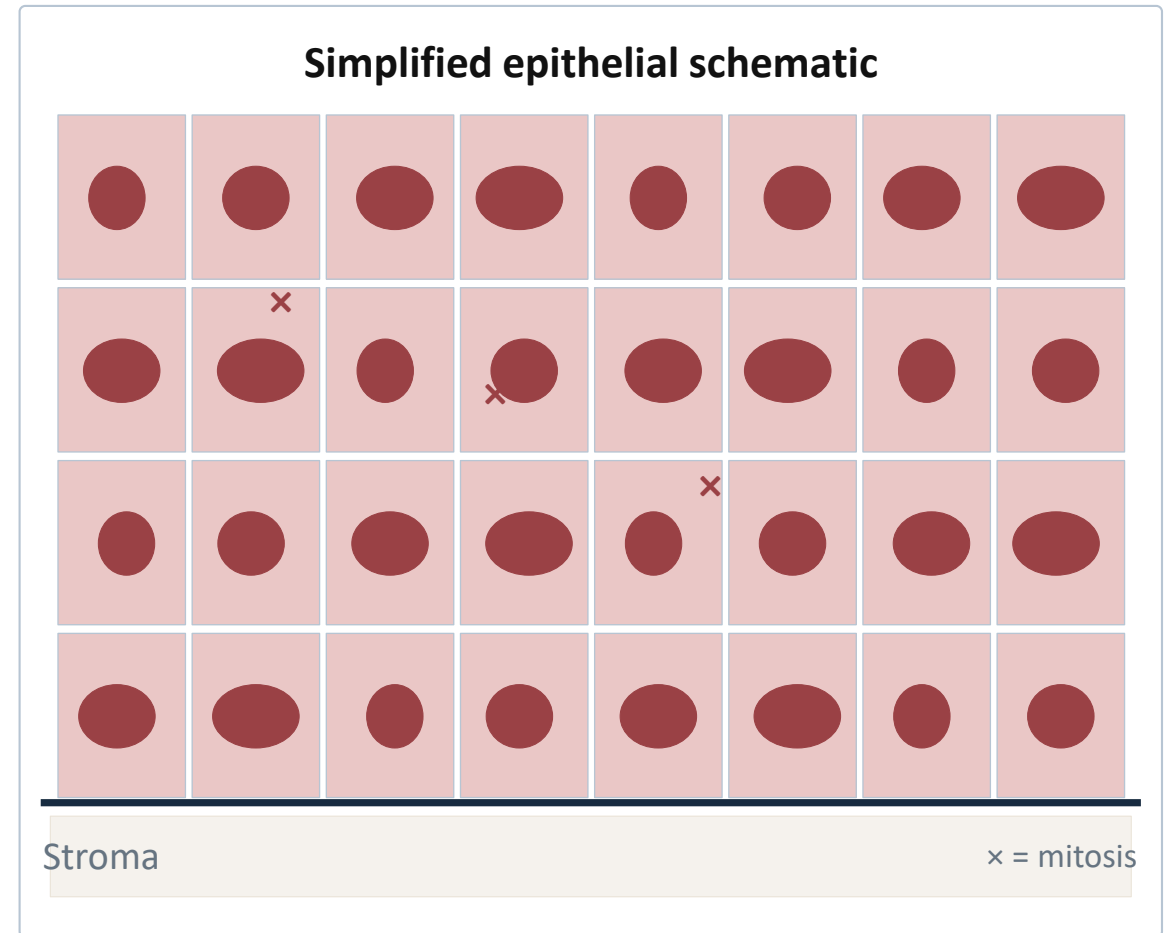
Nuclear hyperchromasia is a dysplastic clue

- Dysplastic cells often have large, deeply staining nuclei.
- Hyperchromasia is assessed with other atypical cellular features.
- Large dark nuclei alone do not establish basement-membrane invasion.



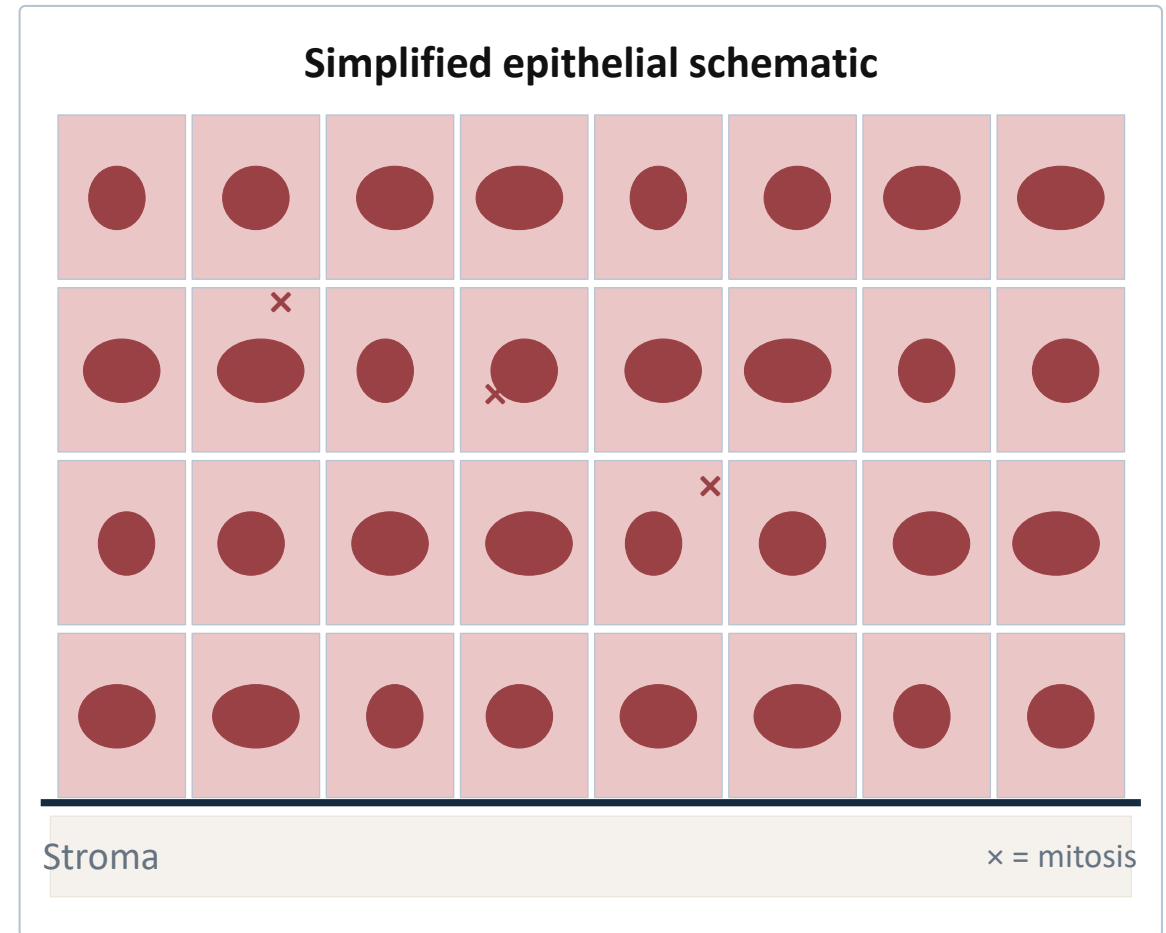
A high nuclear-to-cytoplasmic ratio signals atypia

- The nucleus occupies an increased share of the cell.
- Elevated nuclear-to-cytoplasmic ratio among dysplastic features.
- This finding complements nuclear pleomorphism and loss of maturation.



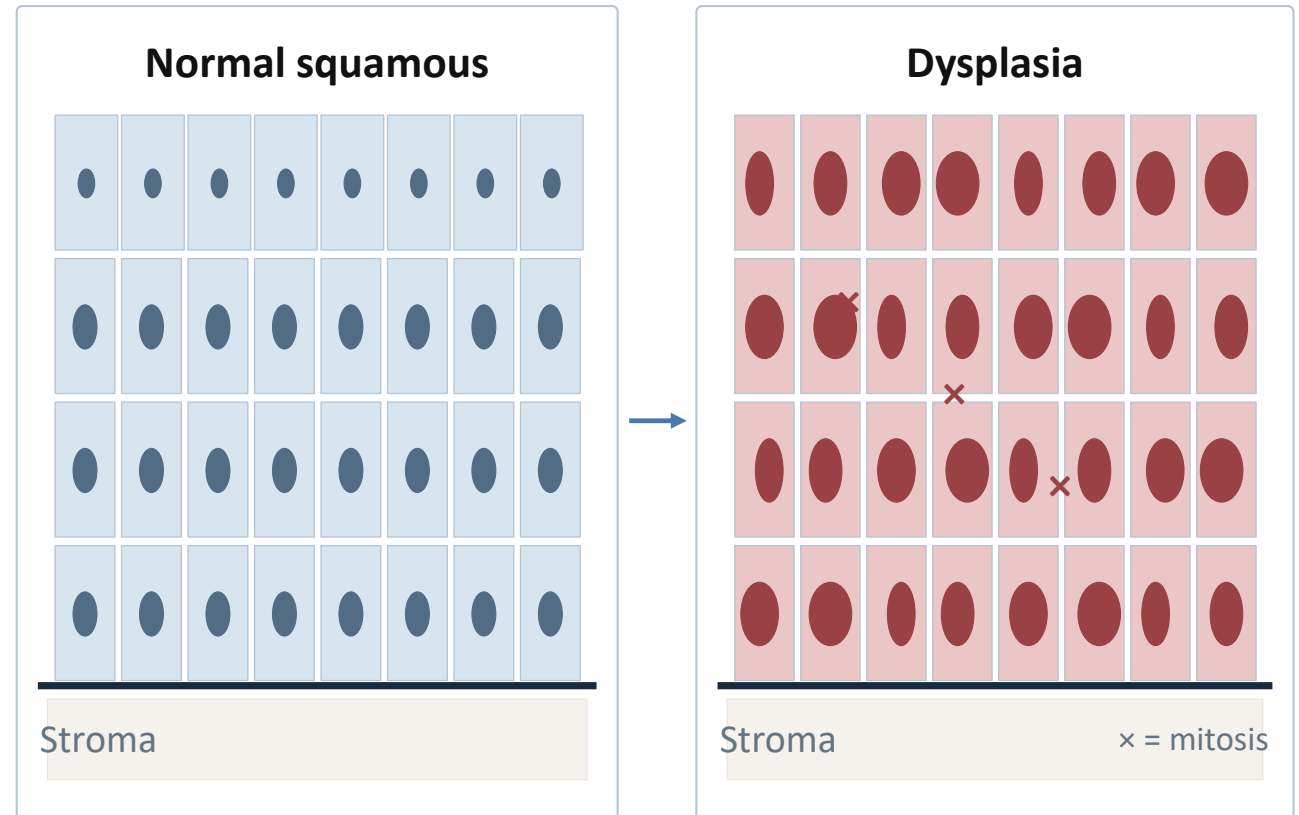
Architectural disarray disrupts epithelial polarity

- Normal relative cell positions and alignment are disturbed.
- Epithelium loses the organized progression from basal cells to mature surface cells.
- Architecture should be judged across a tissue section, not only in isolated cells.



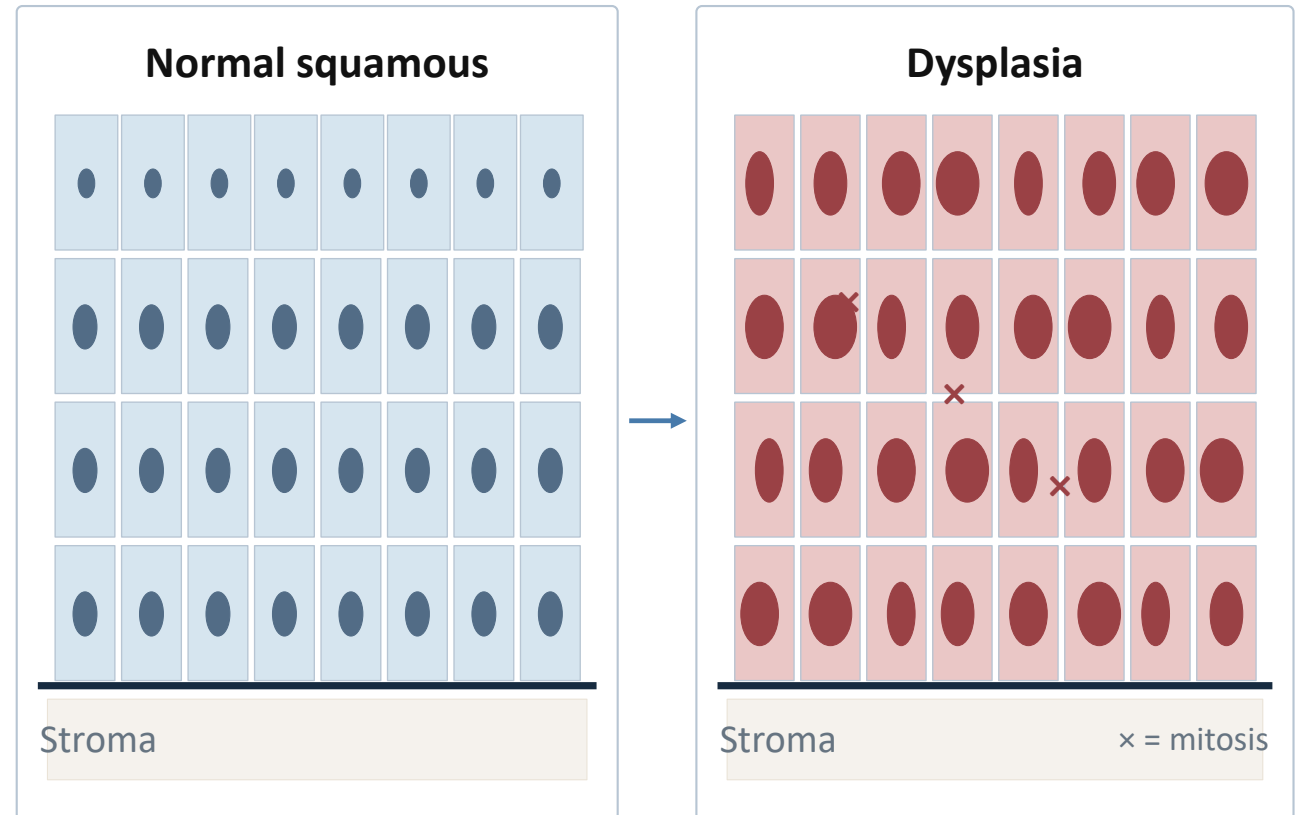
Failure of maturation is central to squamous dysplasia

- Normal basal cells progressively become flatter toward the surface.
- In dysplasia, immature basal-like cells may extend toward superficial levels.
- The maturation defect may be partial or nearly complete.



Mitoses extend beyond the basal compartment

- Normal squamous mitoses generally remain basal.
- Dysplasia shows increased mitoses, sometimes throughout the epithelial thickness.
- Distribution adds diagnostic information beyond the absolute number of mitotic figures.



Normal and dysplastic epithelium differ in two dimensions

Cytology

- Pleomorphism
- Large hyperchromatic nuclei
- High nuclear-to-cytoplasmic ratio

Architecture

- Loss of stratified maturation
- Epithelial polarity disorder
- Mitoses above basal layer

Recognize dysplasia from a pattern of features

Cytologic atypia



Disordered maturation and
mitoses

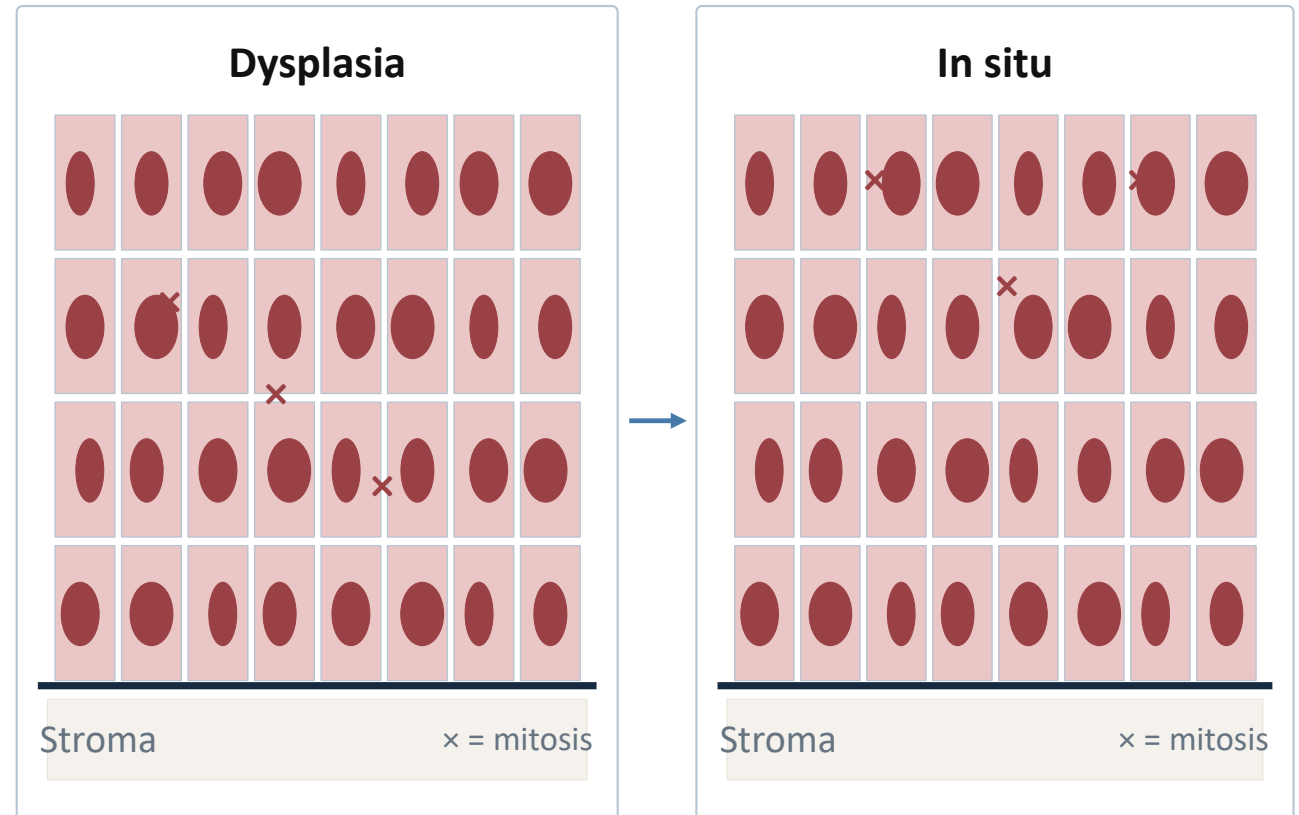


Dysplastic epithelial pattern

- Do not equate atypical nuclear appearance with tissue invasion.
- The histologic pattern includes both cell morphology and tissue architecture.

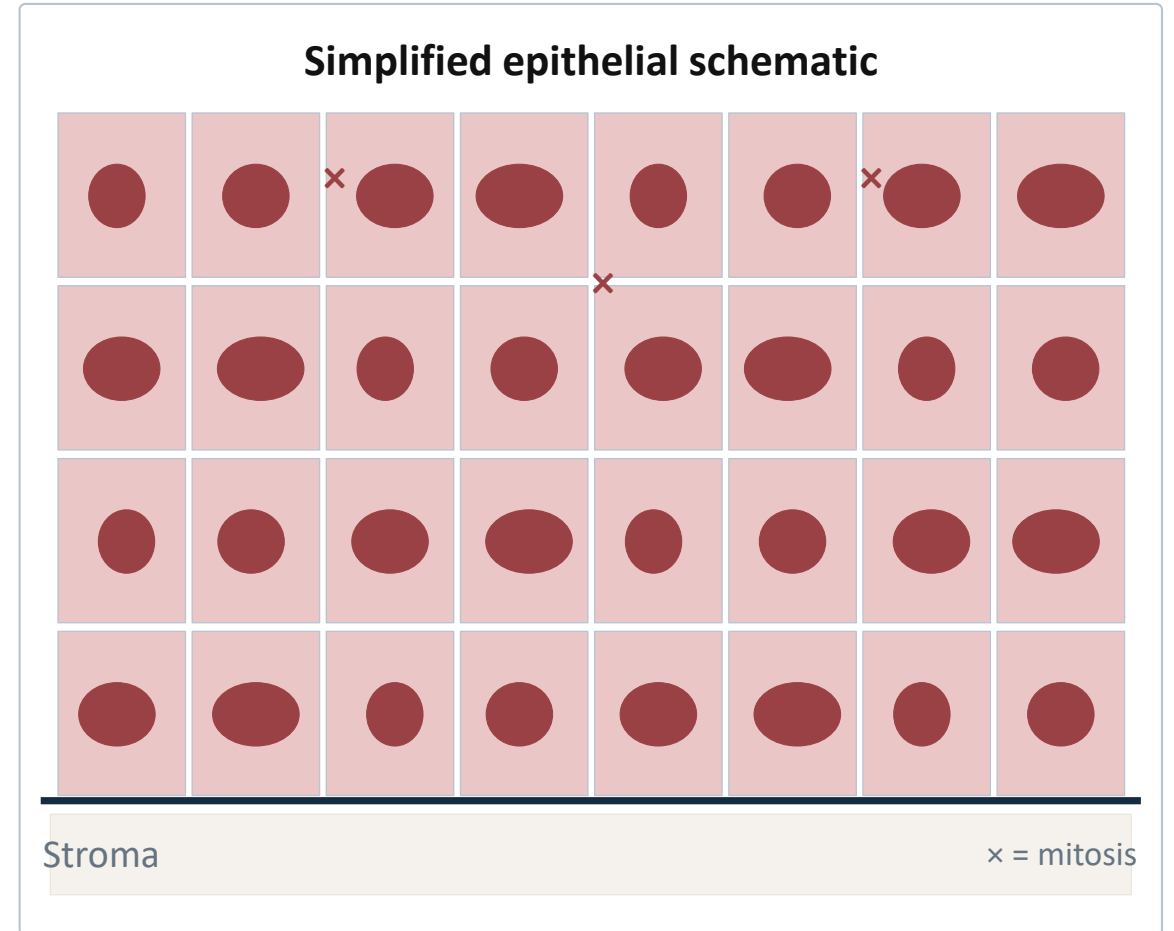
Dysplasia spans a range of morphologic severity

- Some dysplasias retain part of the normal epithelial maturation pattern.
- The most extensive atypical transformation may involve the entire epithelial thickness.
- The full-thickness noninvasive extreme as carcinoma in situ.



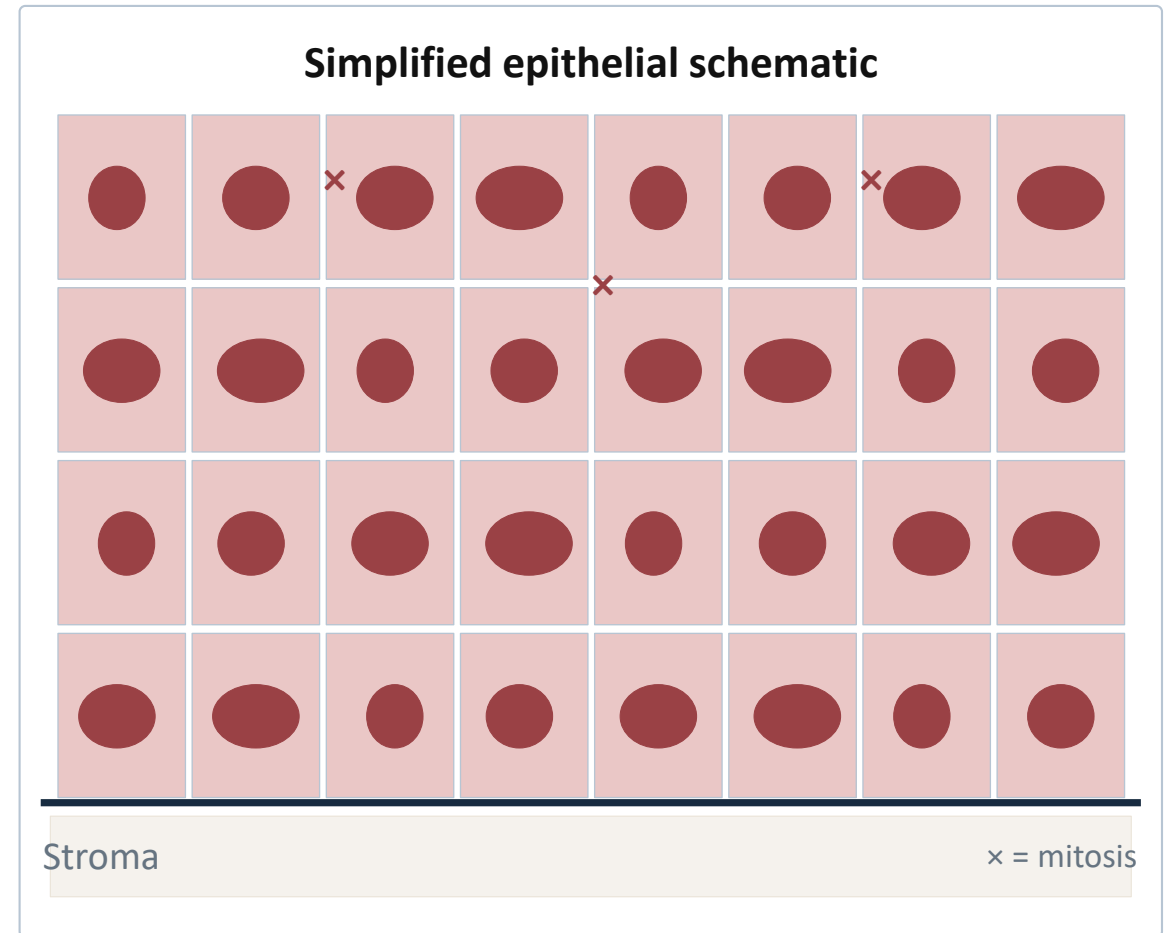
Carcinoma in situ involves full epithelial thickness

- The entire epithelium is replaced by markedly atypical cells.
- Normal squamous surface maturation is absent.
- The basement membrane remains intact and no tumor lies in underlying stroma.



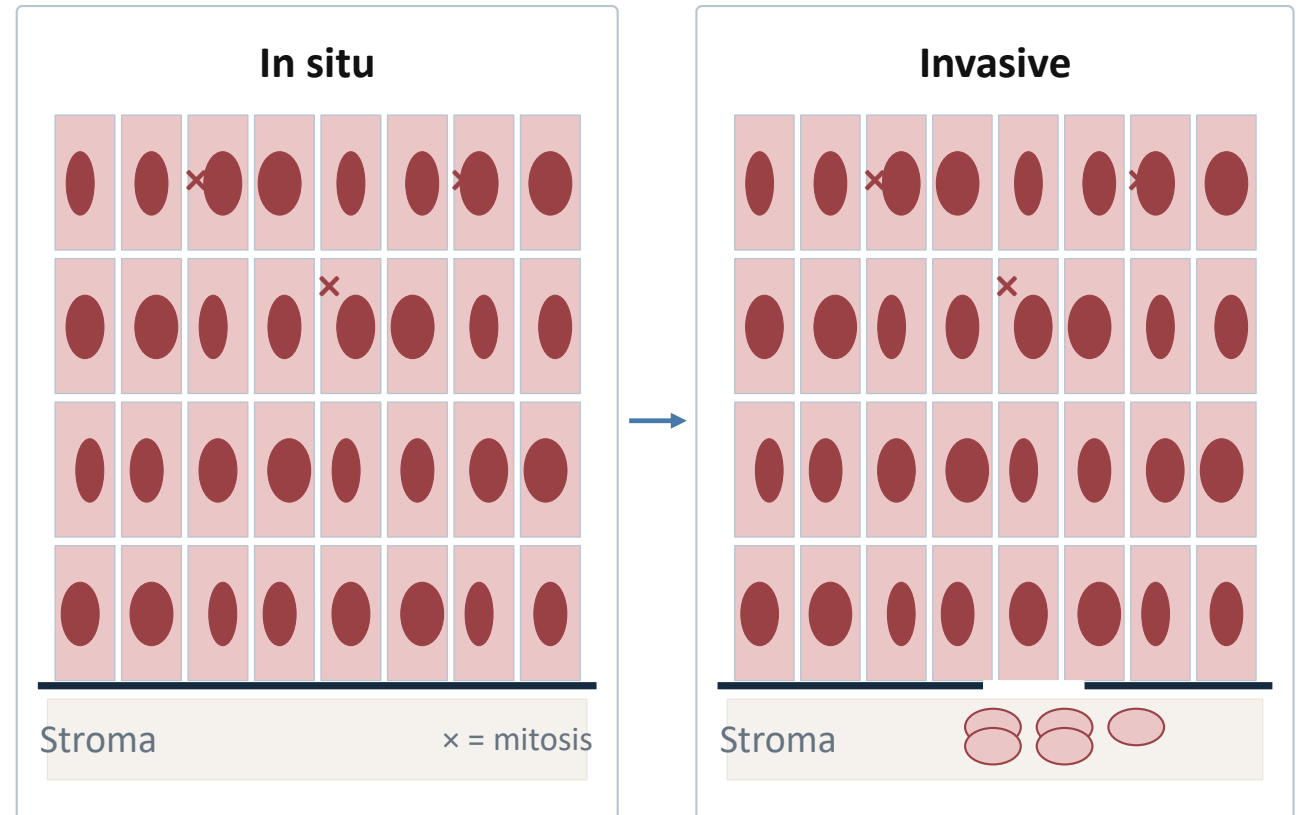
“In situ” is an anatomic statement

- Malignant cytologic features can exist while the lesion remains within epithelium.
- Cytologic malignancy does not automatically mean stromal invasion.
- The decisive boundary is basement-membrane penetration.



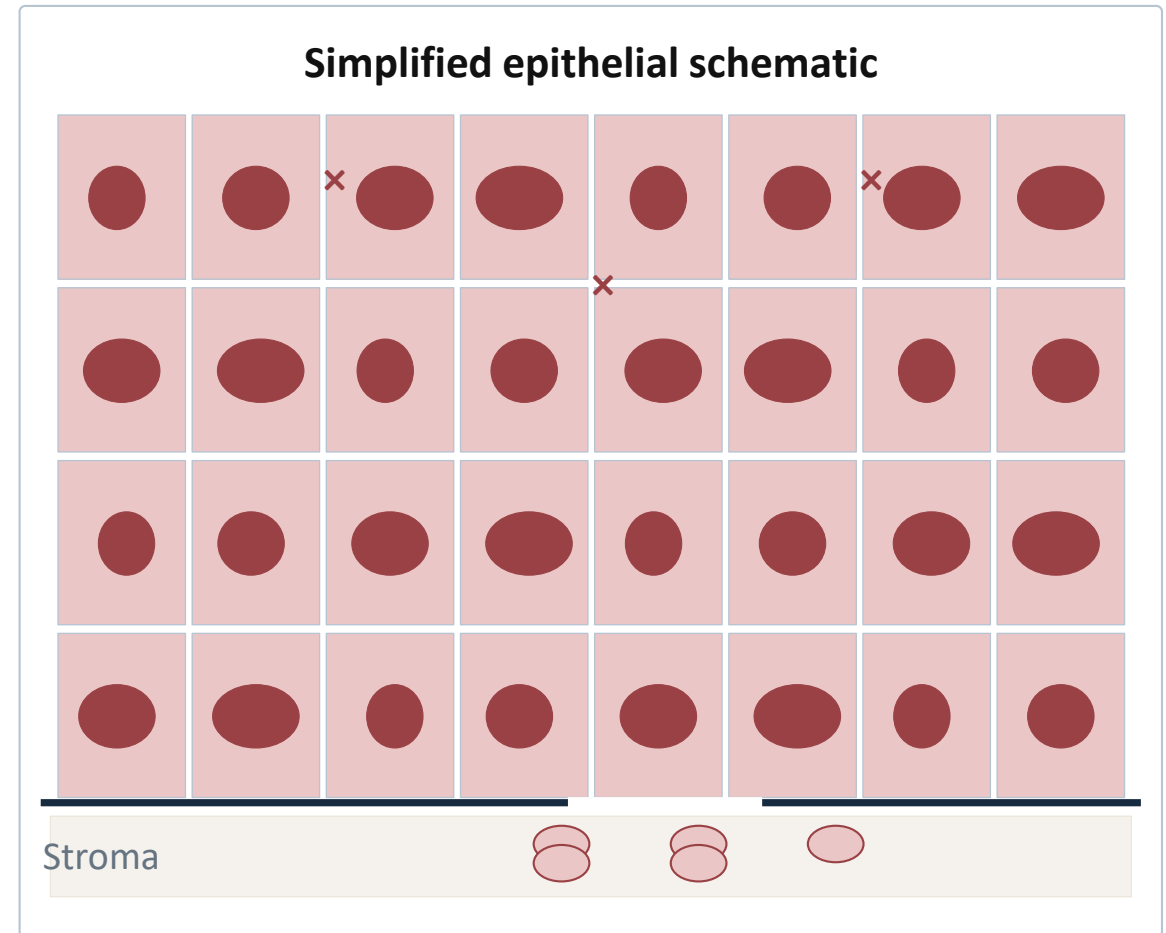
Intact basement membrane separates in situ from invasion

- Carcinoma in situ: Atypical cells are restricted to the epithelial compartment.
- Invasive carcinoma: Neoplastic cells extend into the subjacent stromal compartment.
- Recognition of invasion changes the pathologic category.



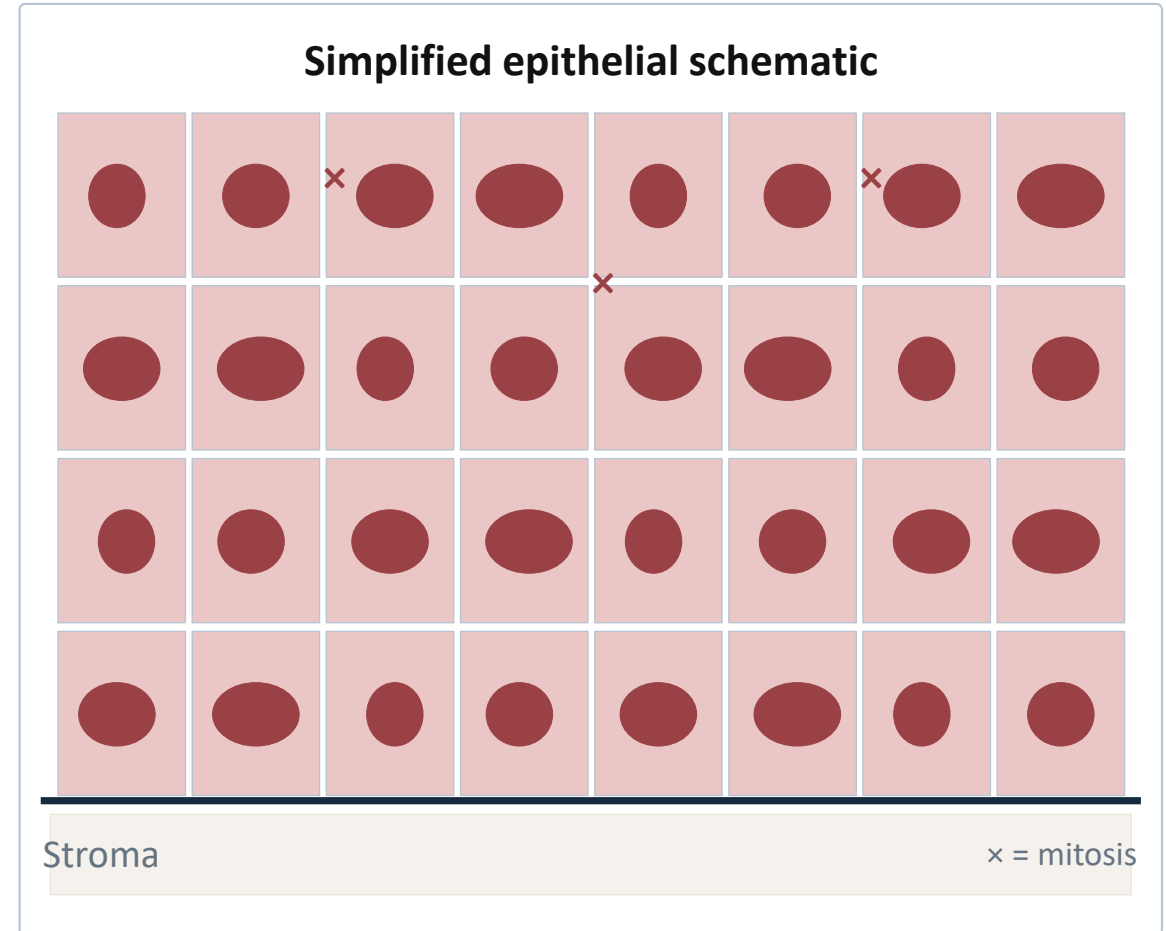
Invasion means extension into surrounding tissue

- Malignant cells infiltrate adjacent structures rather than remaining intraepithelial.
- Invasiveness as a major discriminator of malignancy.
- This is separate from the mere appearance of severe nuclear atypia.



The classic in situ morphology has no stromal tumor

- Robbins Figure 7.9 describes epithelium entirely replaced by atypical dysplastic cells.
- Normal squamous differentiation is lost and mitoses reach superficial levels.
- The described basement membrane is intact and the subepithelial stroma is free of tumor.



Carcinoma in situ is recognized across several organs

Skin	In situ epithelial carcinoma can occur
Uterine cervix	Severe dysplasia/in situ change may precede invasion
Urinary bladder	In situ epithelial carcinoma can occur
Breast	In situ carcinoma can occur

The cervix exemplifies a recognized precursor sequence

Severe epithelial dysplasia



Carcinoma in situ

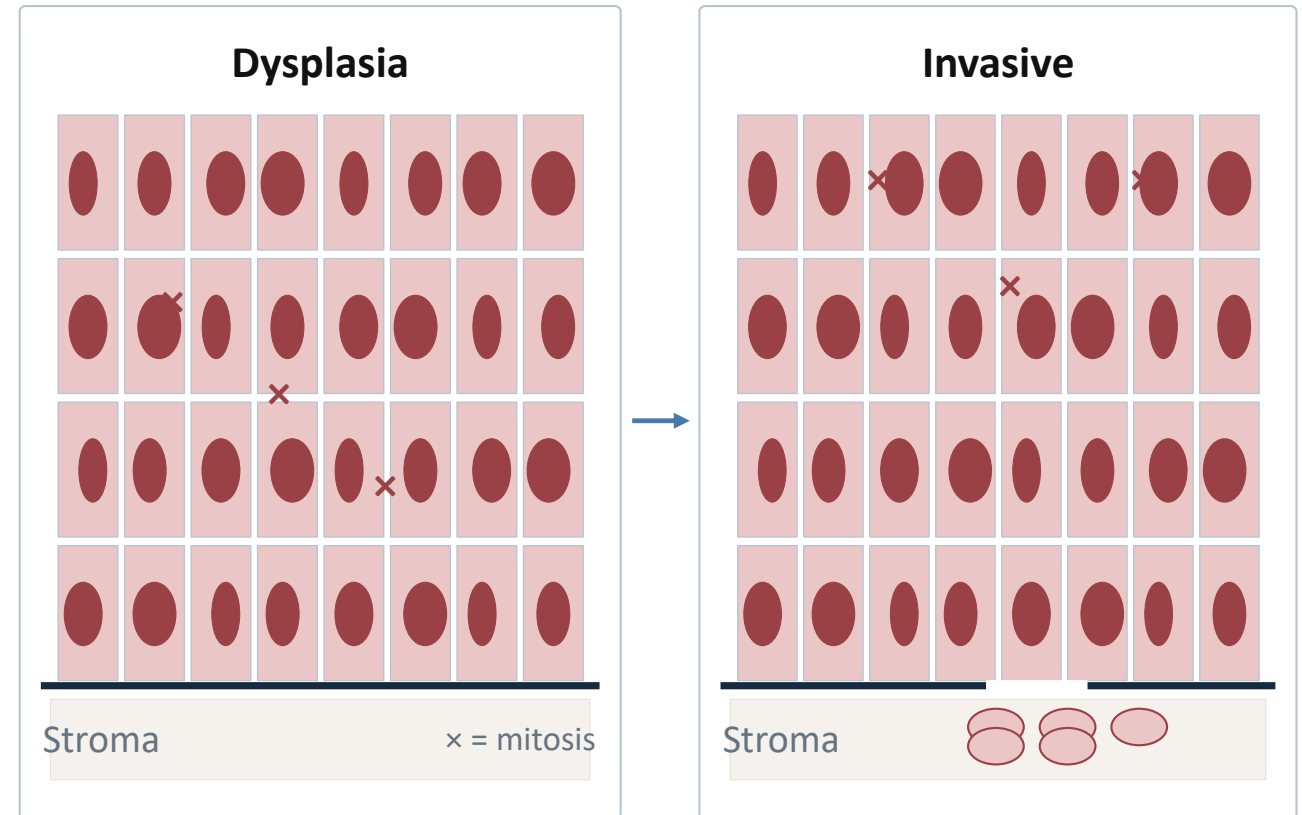


**Possible subsequent invasive
cancer**

- Severe dysplasia or carcinoma in situ frequently antedates invasive cervical cancer.
- This relationship supports precursor recognition but is not a guarantee of progression in every lesion.

Dysplasia can abut invasive carcinoma

- Dysplastic epithelium is often found adjacent to invasive tumor foci.
- The proximity supports a histologic precursor relationship.
- The boundary of invasive growth must still be established separately.



Molecular abnormalities may precede severe morphology

Early dysplastic lesion



Cancer-associated genetic
changes may already be
present



**Morphologic progression
remains variable**

- Mutations associated with cancer can be present even in mild dysplasia.
- A molecular alteration alone does not establish invasion or inevitable progression.

Invasive cancer reflects cumulative genomic change

Accumulating mutations



Additional epigenetic changes



Fully malignant phenotype

- The time required for progression likely reflects acquisition of a sufficient set of changes.
- The textbook does not prescribe a fixed number or universal order of changes for these lesions.

Dysplasia is a precursor, not a guaranteed cancer

Possible regression

- Removal of an inciting cause
- Reversal of some moderately severe dysplasia
- Return toward more orderly epithelium

Possible progression

- Persistent precancerous field
- Further molecular evolution
- Development of invasive cancer in a subset

Some in situ lesions may persist for years

Carcinoma in situ



Prolonged noninvasive
persistence is possible



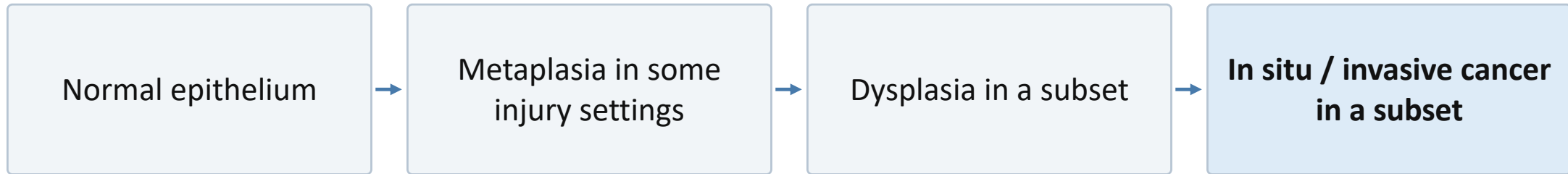
Invasion may occur later

- Latency does not make carcinoma in situ biologically trivial.
- Substantial untreated progression risk while emphasizing variability in timing.

Cancer risk and cancer diagnosis are different claims

Metaplasia	Adaptation; May occur in an at-risk field	Not automatically dysplasia
Dysplasia	Premalignant epithelial alteration	Not automatically carcinoma
Carcinoma in situ	Malignant cytology without stromal invasion	Not invasive carcinoma
Invasive carcinoma	Tumor enters adjacent stroma	Requires demonstration of invasion

Anatomic progression is not a required linear sequence



- Metaplasia can occur without dysplasia.
- Dysplasia may arise in, but need not always follow, metaplastic epithelium.
- Both regression and long-term noninvasive persistence are recognized possibilities.

Diagnostic reasoning begins with the epithelial phenotype

Different mature epithelial phenotype?



If yes: Consider metaplasia



**Assess separately for
cytologic/architectural
dysplasia**

- Metaplastic differentiation and dysplastic atypia answer different questions.
- A single biopsy can contain both changes.

Diagnostic reasoning next tests the stromal boundary

Severe full-thickness atypia



Inspect basement membrane
/ underlying stroma



**Intact: In situ | breach:
Invasive**

- Do not infer stromal invasion from nuclear atypia alone.
- Interpret the epithelial compartment and underlying tissue together.

Case: Smoker with bronchial squamous lining

Clinical–pathologic vignette

A bronchial sample from a person with prolonged tobacco exposure shows stratified squamous epithelium replacing a previously ciliated columnar lining; There is no described atypia.

Question

What morphologic term best describes the epithelial replacement?

Interpretation: Squamous metaplasia; Replacement of phenotype does not by itself diagnose dysplasia.

Case: Chronic reflux with columnar-lined esophagus

Clinical–pathologic vignette

A patient with long-standing reflux has columnar/intestinal-type epithelium replacing the usual esophageal squamous lining.

Question

Is the fundamental morphologic change dysplasia or metaplasia?

Interpretation: Metaplasia. Dysplasia requires additional cytologic and architectural abnormalities.

Case: Disordered squamous maturation

Clinical–pathologic vignette

A squamous epithelial biopsy shows large hyperchromatic nuclei, pleomorphism, disturbed stratification, and mitotic figures well above the basal region.

Question

Which constellation supports a premalignant diagnosis?

Interpretation: Epithelial dysplasia, based on combined cytologic and architectural abnormalities.

Case: Atypia reaches the surface but stroma is free

Clinical–pathologic vignette

Squamous epithelium is replaced throughout its thickness by atypical cells. The basement membrane is intact and the underlying stroma contains no tumor.

Question

What distinguishes this lesion from invasive carcinoma?

Interpretation: The lesion meets Robbins' description of carcinoma in situ; No stromal invasion is present.

Case: A microscopic focus lies beneath the epithelium

Clinical–pathologic vignette

An epithelial malignancy with full-thickness atypia has an additional focus of tumor cells infiltrating beneath a breached epithelial–stromal boundary.

Question

Which finding changes the interpretation?

Interpretation: Stromal infiltration establishes invasion, rather than an exclusively in situ process.

Common error: Equating metaplasia with malignant change

Incorrect inference

- New epithelial phenotype automatically means dysplasia
- All metaplasia inevitably progresses to cancer

Source-consistent interpretation

- Metaplasia is an adaptive replacement
- Dysplasia requires disordered cytology/architecture
- Outcomes depend on tissue and exposure

Common error: Using nuclear atypia as proof of invasion

What cytology can show

- Pleomorphism
- Hyperchromasia
- Elevated nuclear-to-cytoplasmic ratio

What invasion requires

- Tumor beyond the epithelial compartment
- Evidence of stromal infiltration
- Assessment of basement-membrane boundary

Compare the four epithelial states

Normal	Orderly maturation	Basement membrane intact
Metaplastic	Different mature cell phenotype	Basement membrane intact
Dysplastic	Atypia and disordered growth	No invasion implied
Carcinoma in situ	Full-thickness cytologic malignancy	Basement membrane intact
Invasive carcinoma	Neoplastic infiltration	Beyond basement membrane

Integrative interpretation: Appearance, site, boundary

Identify epithelial
phenotype



Evaluate cytologic +
architectural atypia



Examine stromal
interface



**State morphology
precisely**

- Use “metaplasia” for mature phenotype replacement.
- Use “dysplasia” for disordered epithelial growth.
- Use “in situ” or “invasive” only after evaluating the anatomic boundary.

Five statements that should remain distinct

- Metaplasia is generally reversible and may sacrifice specialized function.
- Dysplasia is a morphologic premalignant change, not certain future cancer.
- Carcinoma in situ has severe full-thickness epithelial atypia without stromal invasion.
- Accumulating genetic/epigenetic alterations may explain progression over time.
- The basement membrane is central to the in situ–invasive distinction.

Primary source and section context

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Chapter 7, “Neoplasia”: Metaplasia, Dysplasia, and Carcinoma In Situ, p. 241.
- Related context: Chapter 2 “Metaplasia,” p. 55; Chapter 7 “Local Invasion,” pp. 241–242.
- Figures discussed from the supplied textual descriptions; original diagnostic images not reproduced.