

Vulvar intraepithelial neoplasia and vulvar carcinoma

Two pathogenetic pathways, distinct precursors, and clinicopathologic
consequences

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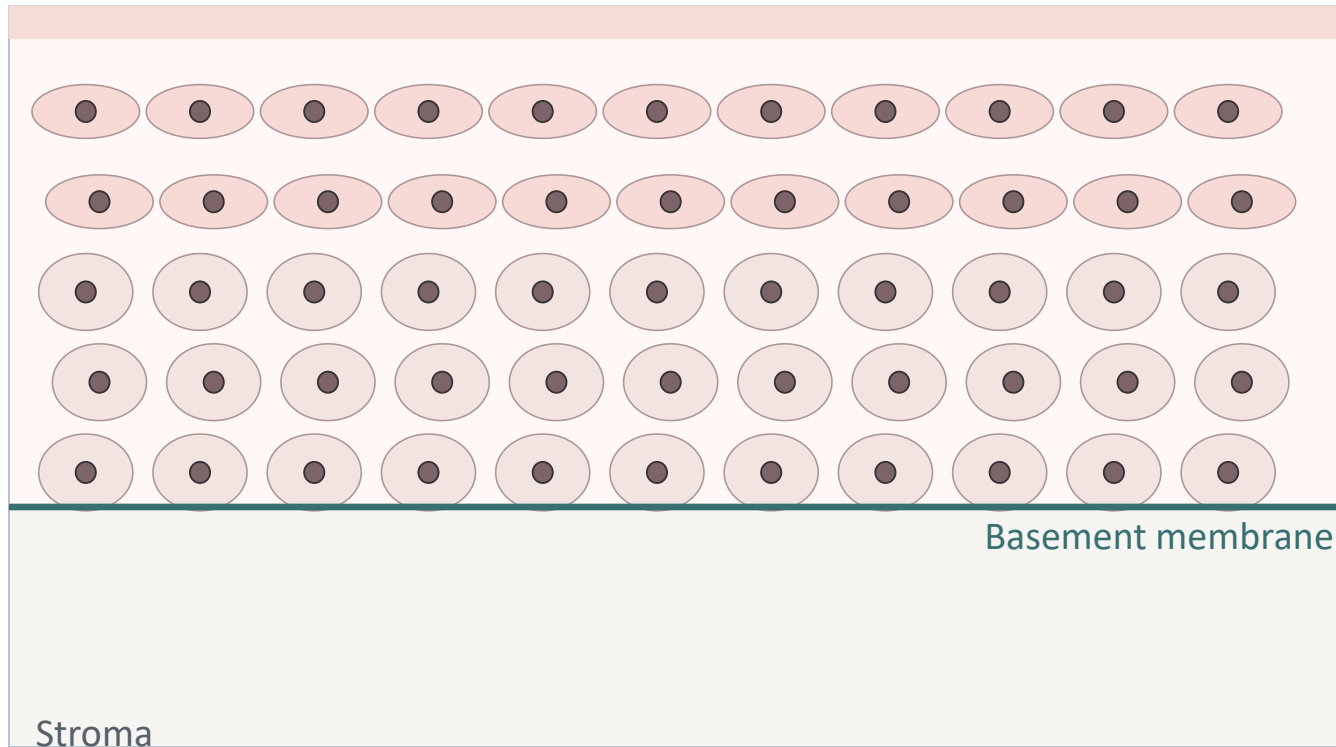
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Learning outcomes

- Differentiate HPV-associated from HPV-independent vulvar squamous carcinoma.
- Recognize the precursor patterns: Classic VIN and differentiated VIN.
- Link the gross and microscopic findings to tumor pathogenesis.
- Explain the principal determinants of invasion, spread, and prognosis.

The vulvar squamous epithelial compartment

Epithelium



Basement membrane

Stroma

Schematic — not a histologic specimen

Squamous epithelial maturation normally proceeds from basal to superficial layers.

The basement membrane separates intraepithelial disease from stromal invasion.

Normal architecture is the reference for recognizing both VIN patterns.

A visible white plaque is not a diagnosis

- “Leukoplakia” describes opaque, white, plaquelike thickening, often with pruritus or scaling.
- Its causes include inflammatory dermatoses, lichen disorders, VIN, Paget disease, and carcinoma.
- The same clinical label can therefore denote benign or malignant pathology.

Vulvar carcinoma: Clinical scale

$\sim 3\%$

Of female genital cancers

$\sim 1/8$

As frequent as cervical
carcinoma

$\sim 2/3$

In patients older than 60
years

Squamous cell carcinoma predominates

- Squamous cell carcinoma is the commonest histologic type of vulvar cancer.
- The clinically important division is pathogenetic, not simply architectural.
- Two groups differ in precursor disease, typical age, and microscopic appearance.

The two major pathogenetic groups

HPV-associated

High-risk HPV, commonly type 16

Approximately 30%

Typical average age ~60 years



HPV-independent

Not attributed to HPV

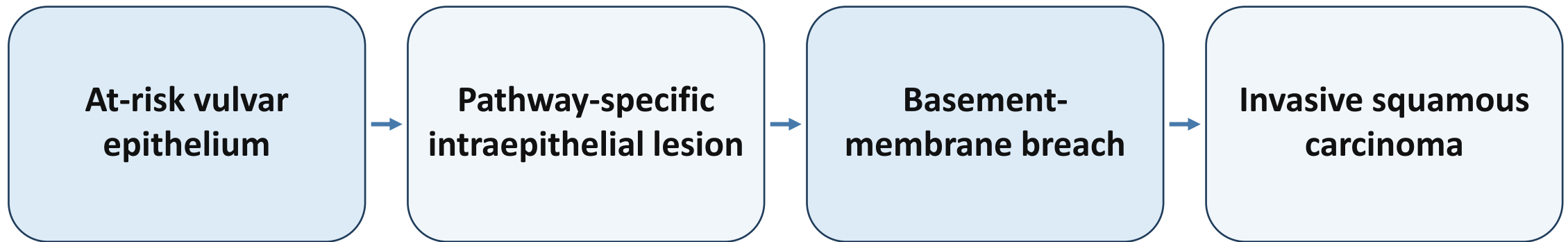
Approximately 70%

Typical average age ~75 years

Etiologic pathways: At a glance

Feature	HPV-associated	HPV-independent
Relative frequency	~30%	~70%
Typical average age	~60 years	~75 years
Precursor	Classic VIN / squamous intraepithelial lesion	Differentiated VIN; Other described forms
Frequent background	High-risk HPV infection	Chronic lichen disorders
Invasive pattern	Basaloid or warty	Keratinizing

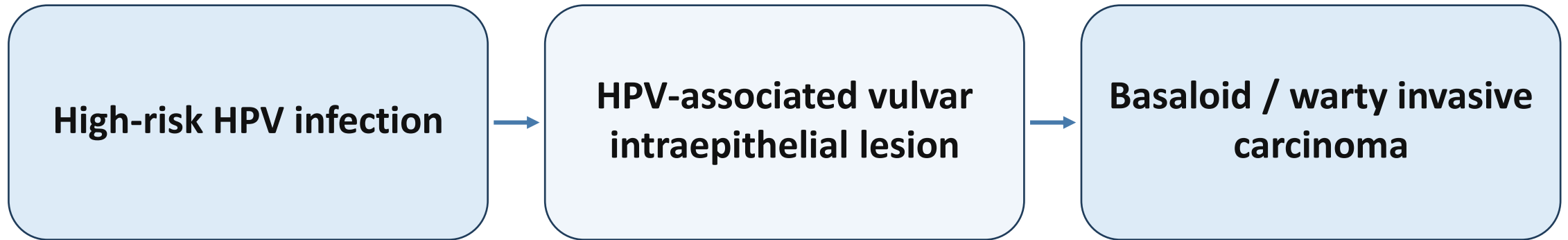
Precursor → invasion: Disease framework



High-risk HPV drives one carcinogenic pathway

- HPV-associated tumors are linked to infection with high-risk HPV types.
- HPV-16 is the most commonly implicated type in the Robbins account.
- A vulvar squamous intraepithelial lesion is the established precursor.

HPV-related pathway: Structural sequence



Classic VIN occurs in younger patients

- HPV-associated VIN tends to occur during reproductive years.
- This differs from the older population typical of HPV-independent disease.
- Clinical age distribution supports, but does not establish, etiologic assignment.

Epidemiologic exposures parallel cervical SIL

- Young age at first intercourse.
- Multiple sexual partners.
- Male partner with multiple sexual partners.
- These epidemiologic associations are linked to HPV acquisition.

HPV infection can affect multiple epithelial sites

Vulvar VIN

Often multicentric

May coexist with other genital tract lesions

Vagina / cervix

HPV-related squamous lesions may coexist

10%–30% of VIN patients affected

Concurrent lower-genital-tract lesions

10%–30%

Of patients with VIN have HPV-related vaginal or cervical lesions

Multicentric

Is a characteristic tendency of HPV-related VIN

Regression is possible—but variable

- Spontaneous regression of classic VIN has been reported.
- Regression is described most often in younger patients.
- Possible regression does not remove the need to recognize the lesion as a precursor.

Risk factors for VIN progression

- Progression risk is greater in patients older than 45 years.
- Immunosuppression also increases the risk of invasive transformation.
- Patient context changes the expected biologic behavior of a precursor lesion.

Gross presentation of HPV-associated VIN

White / hyperkeratotic

Discrete lesion

Keratin-associated opacity

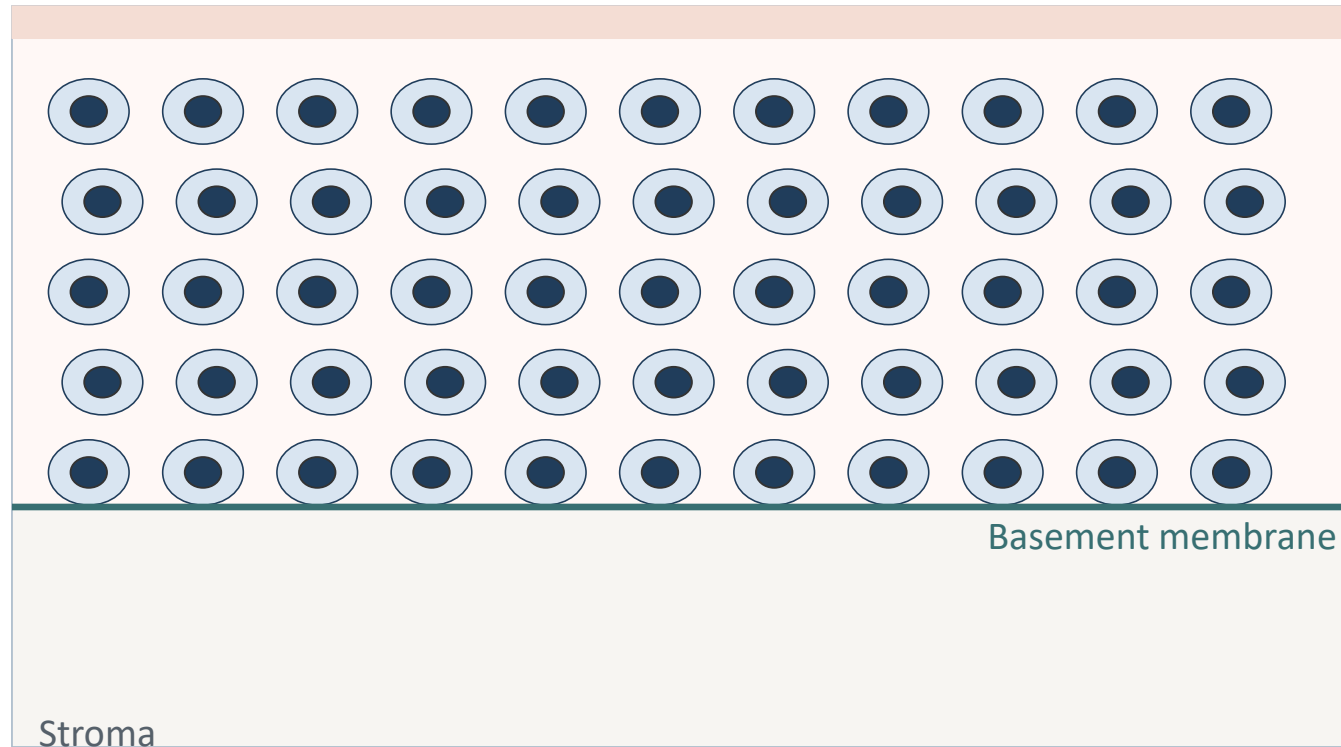
Raised / pigmented

May be only slightly elevated

Color alone does not establish invasiveness

Classic HPV-associated VIN: Loss of maturation

Epithelium



Epidermal thickening accompanies intraepithelial atypia.

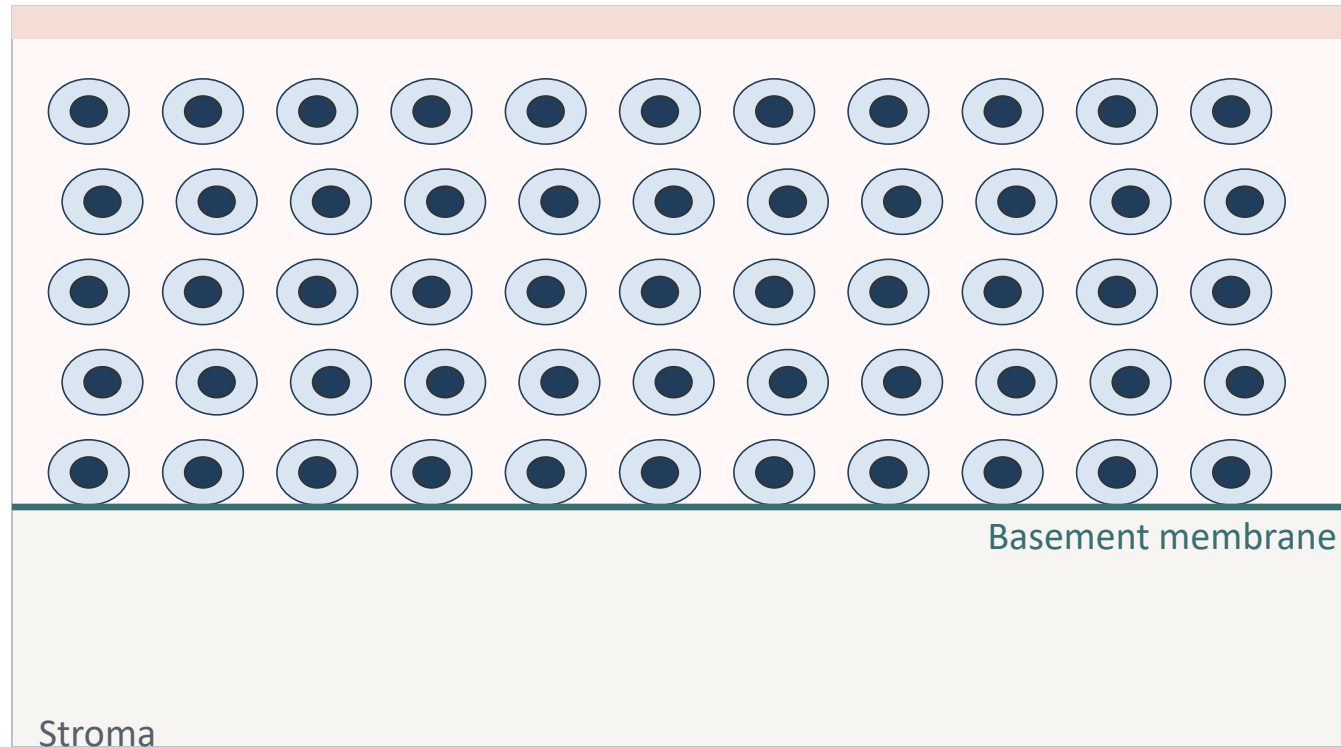
Atypical small, immature cells may span epithelial thickness.

Nuclear atypia and increased mitotic activity accompany disordered maturation.

Schematic — not a histologic specimen

Classic VIN remains intraepithelial

Epithelium



The abnormal squamous epithelium extends to the basement membrane.

The defining distinction from invasive carcinoma is the absence of stromal invasion.

Atypia across epithelial thickness is not itself evidence of invasion.

Schematic — not a histologic specimen

The key microscopic criteria in classic VIN

Feature	Observed pattern
Epithelial thickness	Epidermal thickening
Nuclear appearance	Atypia; Immature basaloid cells
Cell kinetics	Increased mitotic activity
Maturation	Reduced or absent orderly maturation
Invasion	Not present in the intraepithelial lesion

Why the basaloid appearance matters

- “Basaloid” describes resemblance to small cells of the basal squamous layer.
- In HPV-associated neoplasia, maturation can be lost throughout the epithelial thickness.
- The pattern helps connect intraepithelial VIN with basaloid invasive carcinoma.

Invasive HPV-related carcinoma: Gross morphology

Exophytic growth

Tumor may project outward

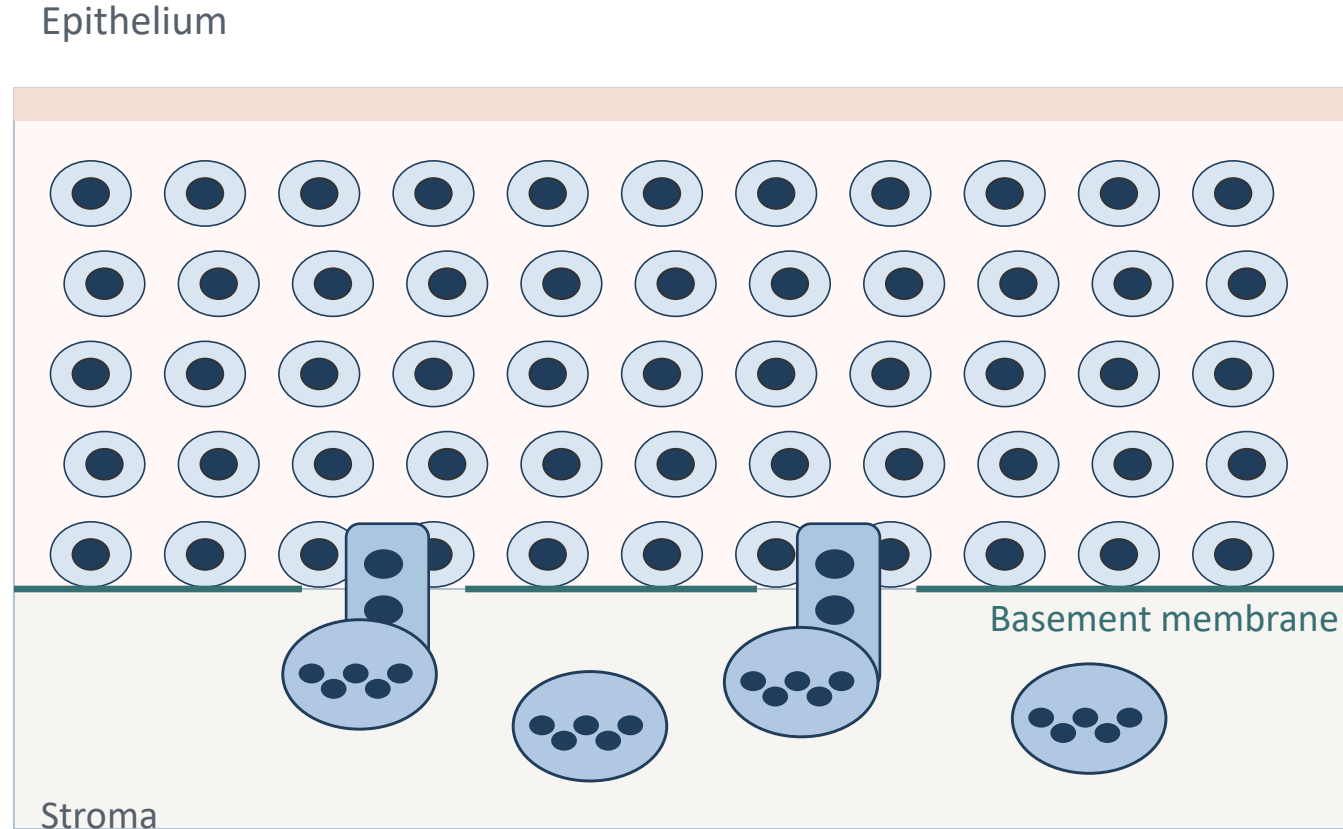
A visible mass may be present

Indurated / ulcerated

Firm lesion

Central ulceration may occur

Basaloid carcinoma: Invasion of the stroma



Schematic — not a histologic specimen

Nests and cords of tightly packed malignant squamous cells extend into stroma.

Cells are small and show limited maturation.

Tumor architecture is invasive rather than confined to surface epithelium.

Necrosis may occur within basaloid carcinoma

- HPV-related basaloid carcinoma may contain foci of central necrosis.
- Necrosis occurs within a neoplastic population of immature tightly packed cells.
- It is an associated finding, not a defining sign of HPV causation by itself.

Warty carcinoma: A different architecture



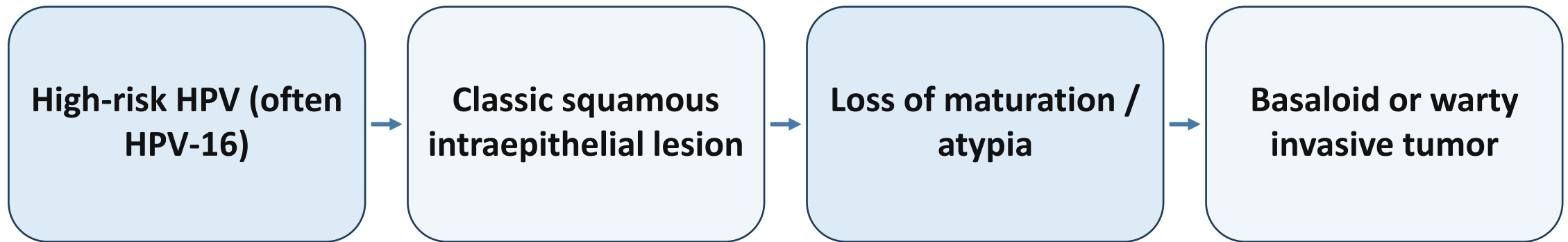
Basaloid versus warty invasive patterns

Feature	Basaloid	Warty
Overall growth	Nests / cords of small cells	Exophytic papillary pattern
Cell morphology	Immature, basal-like cells	Koilocytic atypia prominent
Additional features	Central necrosis may occur	Wartlike architecture
Shared group	HPV-associated squamous carcinoma	HPV-associated squamous carcinoma

Koilocytic atypia signals viral cytopathic effect

- Koilocytes have nuclear enlargement and hyperchromasia.
- A perinuclear cytoplasmic halo is a characteristic feature.
- Koilocytic change is a cellular pattern; Invasive behavior requires separate assessment.

Integrating the HPV-related pathway



HPV-independent carcinoma is more common

- Approximately 70% of vulvar squamous carcinomas are HPV-independent.
- This group is predominantly encountered in older patients.
- The stated average age is approximately 75 years.

Chronic epithelial disease is an important context

Lichen sclerosis

Long-standing inflammatory / sclerosing disorder

Often thin, white epithelium

Lichen simplex chronicus

Repeated rubbing or scratching

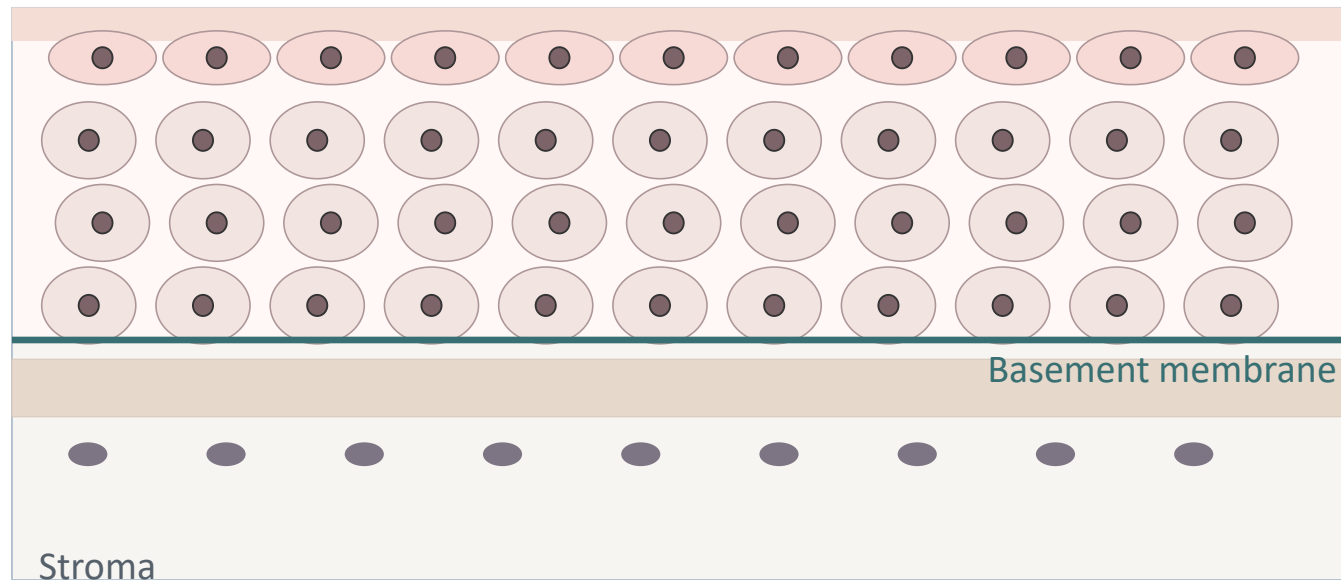
Thickened hyperkeratotic epithelium

Lichen sclerosis: Distinctive gross appearance

- Smooth white plaques or macules may enlarge and coalesce.
- The surface can appear porcelain-like or parchment-like.
- Extensive disease may produce labial atrophy, adhesions, and introital narrowing.

Lichen sclerosis: Thinning and sclerosis

Epithelium



Epidermal thinning and basal-cell degeneration.

Hyperkeratosis at the epithelial surface.

Sclerosis of superficial dermis with deeper bandlike lymphocytic inflammation.

Schematic — not a histologic specimen

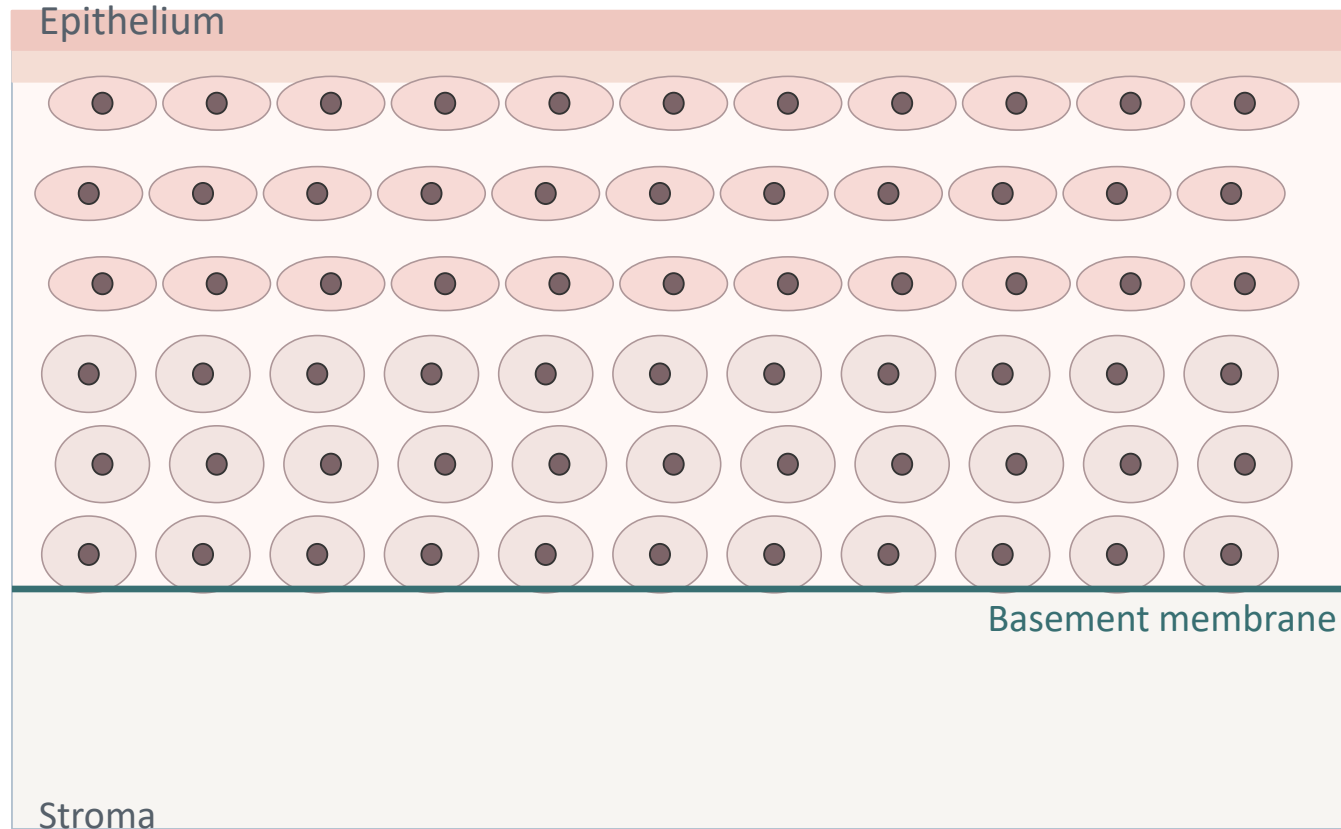
Lichen sclerosis is not itself dVIN

- Robbins explicitly does not classify lichen sclerosis as a premalignant lesion.
- Affected patients nevertheless have a slightly increased risk of HPV-independent carcinoma.
- Background risk and morphologically defined neoplasia must not be conflated.

Lichen simplex chronicus follows scratching

- Pruritus may initiate repetitive rubbing or scratching.
- The epithelial reaction produces acanthosis and hyperkeratosis.
- The lesion may present clinically as leukoplakia.

Lichen simplex: Reactive epithelial thickening



Schematic — not a histologic specimen

Epidermis is thickened (acanthosis).

Hyperkeratosis is present.

Mitotic activity may occur without cellular atypia.

Nonneoplastic background disorders

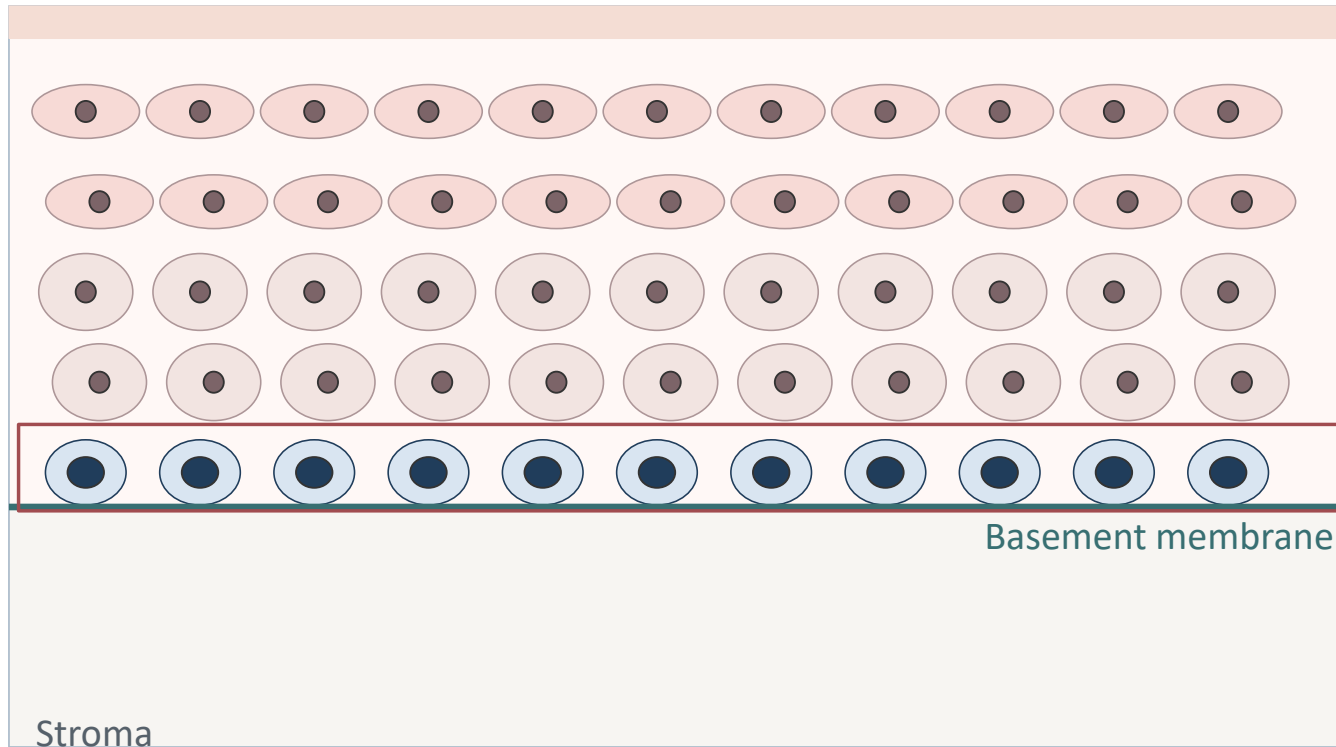
Feature	Lichen sclerosis	Lichen simplex chronicus
Epidermis	Thinned	Thickened (acanthotic)
Surface	Hyperkeratosis	Hyperkeratosis
Dermis	Superficial sclerosis; Lymphocytes	Sometimes lymphocytes
Cytologic atypia	Not a defining feature	Absent
Relationship	Associated increased cancer risk	Can be present at carcinoma margins

Differentiated VIN is the major named precursor

- DVIN is a precursor to HPV-independent vulvar squamous cell carcinoma.
- It is often encountered in a background of long-standing lichen disorders.
- Its intraepithelial atypia has a different distribution from classic HPV-related VIN.

DVIN: Atypia concentrated at the basal layer

Epithelium



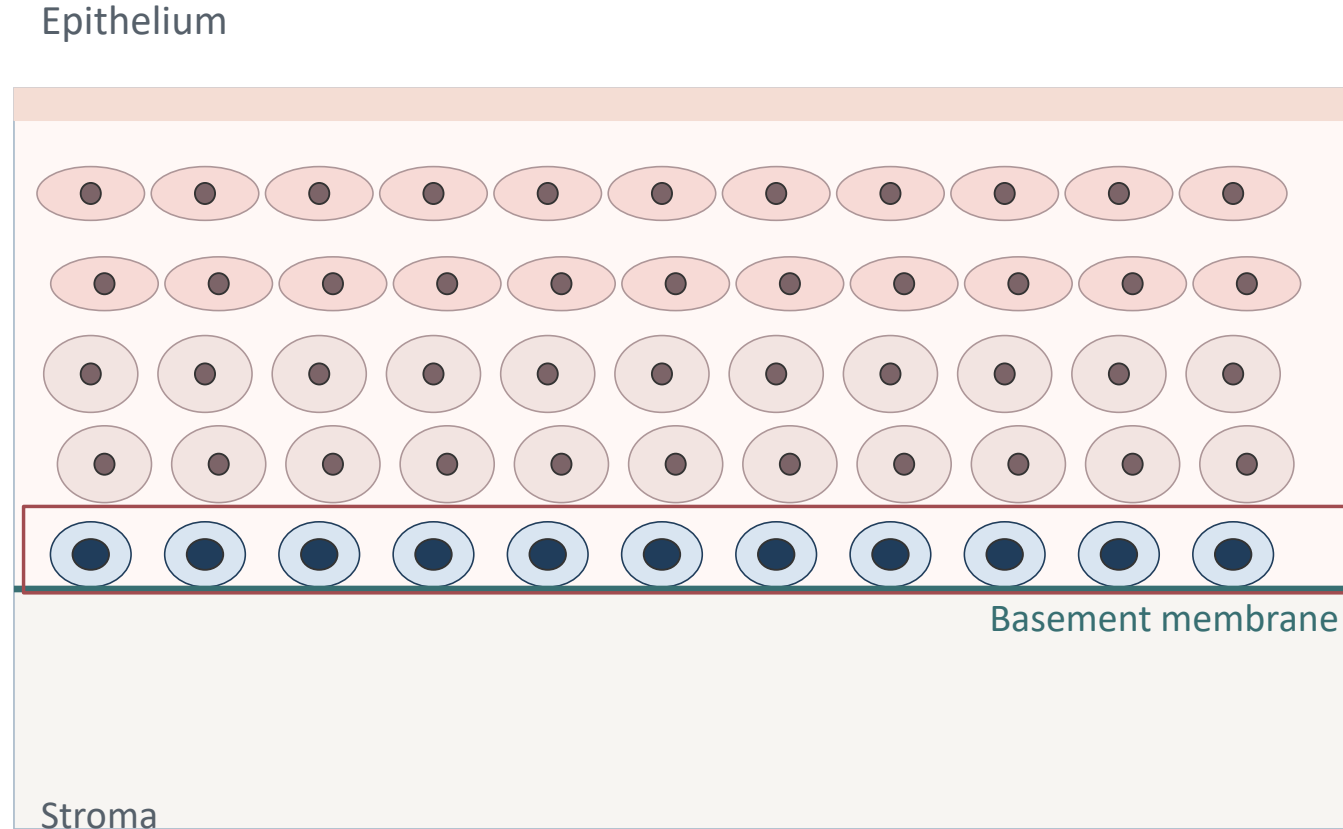
Pronounced cytologic atypia affects basal epithelial cells.

More superficial layers display relatively normal-appearing differentiation.

The contrast between abnormal basal and mature superficial epithelium is central.

Schematic — not a histologic specimen

DVIN: Superficial maturation is preserved



Maturation in upper layers may resemble normal squamous differentiation.

Therefore, full-thickness immaturity is not required for this precursor.

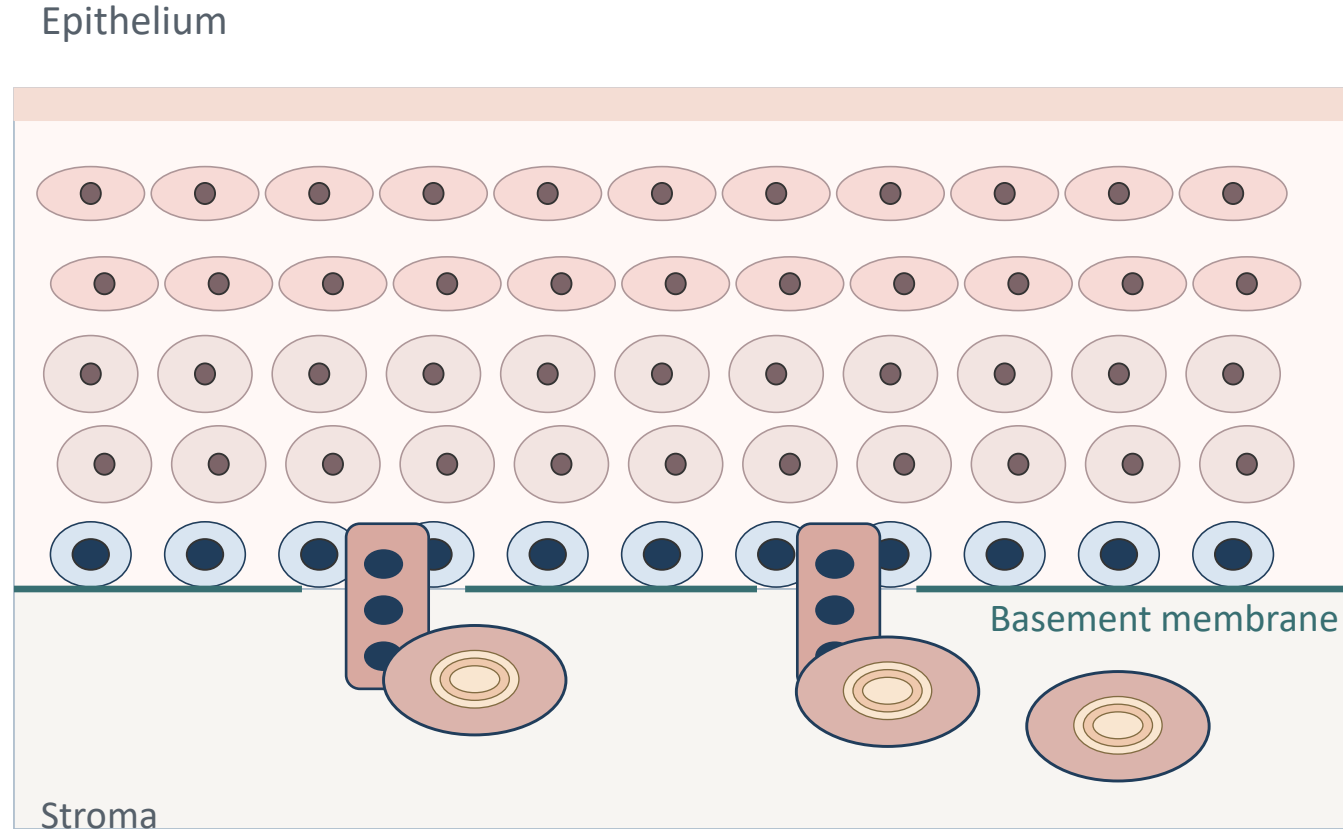
Recognition requires attention to the basal compartment.

Schematic — not a histologic specimen

Classic VIN versus differentiated VIN

Feature	HPV-associated / classic VIN	HPV-independent / dVIN
Usual setting	Younger; HPV exposure	Older; Lichen disorder background
Atypia distribution	Broad / full thickness	Predominantly basal
Maturation	Absent or disordered	Relatively preserved superficially
Typical carcinoma	Basaloid or warty	Keratinizing
Molecular theme	High-risk HPV association	Somatic TP53 often present

HPV-independent carcinoma: Invasive keratinization



Malignant nests and tongues invade the stromal compartment.

Squamous differentiation produces prominent central keratin pearls.

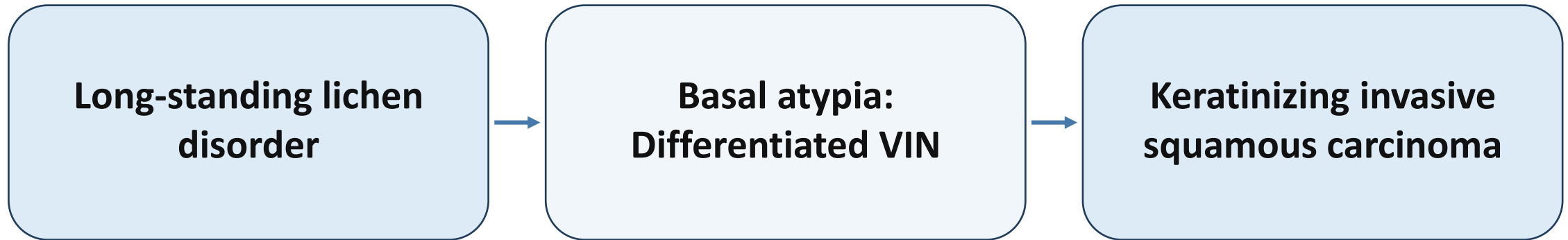
Keratinizing morphology is characteristic in the described dVIN-associated pathway.

Schematic — not a histologic specimen

What a keratin pearl represents

- A keratin pearl is concentrically layered squamous keratinization within a tumor nest.
- It highlights squamous differentiation despite invasive malignant growth.
- Interpret it with infiltrative tumor architecture—not in isolation.

The dVIN-associated sequence



Chronic irritation: Proposed mechanism

- Robbins postulates that longstanding epithelial irritation may promote malignant evolution.
- The proposed process involves acquisition of oncogenic and tumor-suppressor driver alterations.
- The mechanism is postulated, not proven as a complete causal pathway in the supplied excerpt.

TP53 mutations are common, not universal

- Somatic TP53 alterations are frequently found in dVIN.
- They are also common in HPV-independent vulvar squamous carcinoma.
- A mutation association alone does not prove how an individual lesion arose.

Additional HPV-independent molecular pathways

TP53-altered subset

Somatic TP53 mutation commonly found

Classically linked to differentiated VIN

Other reported subsets

TP53 mutation may be absent

Reported genes: PIK3CA, NOTCH1, HRAS

HPV-independent lesions are heterogeneous

- Other morphologic forms of HPV-independent VIN have been described.
- Some lack TP53 mutations and instead harbor alterations in other genes.
- The textbook anticipates classification and terminology changes as studies mature.

Molecular information: Appropriate interpretation

Textbook observation	What can be concluded	What cannot be concluded
High-risk HPV association	One defined etiologic group	HPV positivity proves invasion
Common TP53 mutation	A frequent HPV-independent feature	Every independent tumor is TP53-mutant
Other pathway genes	Molecular heterogeneity exists	A single universal alternate pathway

Differentiation and invasion are separate axes



Invasive vulvar carcinoma: Two gross patterns

Exophytic tumor

Outwardly projecting mass

May be HPV-associated

Indurated or ulcerated

Firm / centrally ulcerated focus

Requires histologic assessment

HPV-independent disease can be clinically deceptive

- Cancer may develop insidiously with long-standing lichen disease.
- Lesions can be mistaken for dermatitis or leukoplakia over prolonged intervals.
- Persistent epithelial symptoms are not sufficient to establish a benign diagnosis.
- These cancers may behave more aggressively than HPV-associated tumors.

Distinguishing reactive change from dVIN

Question	Reactive lichen simplex	Differentiated VIN
What is thickened?	Squamous epithelium	May show surface differentiation
Are cells atypical?	No significant cellular atypia	Marked basal atypia
Where is the warning sign?	Acanthosis / keratin	Basal squamous cells
What is the category?	Nonneoplastic	Precursor neoplasia

Condyloma is not the same as high-risk VIN

Feature	Condyloma acuminatum	HPV-associated VIN
HPV relationship	Low-risk types 6 and 11	High-risk, often type 16
Behavior	Benign wart; Not precancerous	Intraepithelial precursor
Morphology	Papillary fronds; Koilocytes	Atypia, mitoses, loss of maturation
Teaching pitfall	Koilocytosis $\neq$ carcinoma	Invasion needs separate evidence

The clinical risk of VIN is not fixed

- Duration of the lesion influences subsequent cancer risk.
- Extent of disease also contributes.
- Immune status is an important patient-level modifier.
- Age and phenotype add context but do not replace histology.

What marks the transition to invasion?



Prognosis reflects invasive tumor burden

Tumor size

Determines metastatic risk

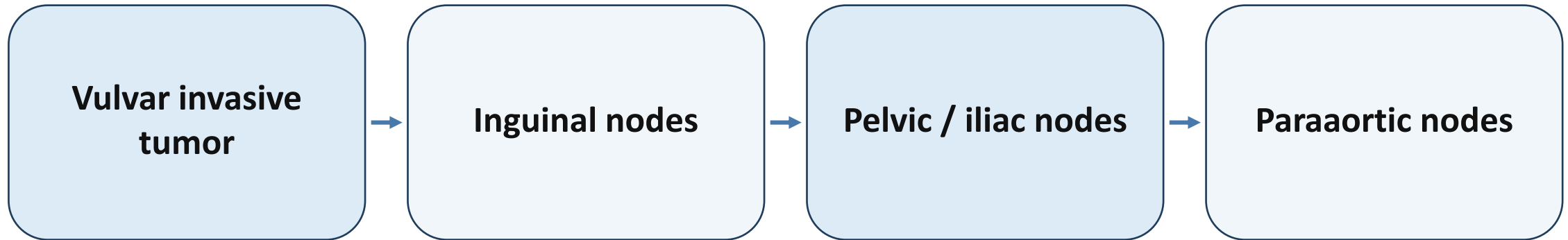
Depth of invasion

Influences spread

Lymphatic invasion

Signals metastatic
potential

Lymphatic spread: Regional progression



Illustrative sites of regional nodal involvement; Not an obligatory order of spread.

Hematogenous dissemination occurs later



Historical survival statement

<2 cm

Tumor diameter in described subgroup

90%

5-year survival after vulvectomy and
lymphadenectomy

Nodal disease and larger tumors worsen prognosis

- Poor prognosis for larger tumors with lymph node involvement.
- Tumor size, invasion depth, and lymphatic invasion inform metastatic risk.
- The prognostic distinction belongs to invasive cancer rather than VIN alone.

Applied case: HPV-associated precursor

A reproductive-age patient has a slightly raised pigmented vulvar lesion. Histology shows squamous thickening, atypical immature cells across the epithelial thickness, and no stromal invasion.

Which precursor pattern is favored, and what feature excludes carcinoma?

Favored: Classic HPV-associated vulvar intraepithelial lesion.

Absence of stromal invasion separates this precursor from invasive carcinoma.

Applied case: HPV-independent precursor

An older patient with long-standing white vulvar plaques has a lesion with pronounced basal epithelial atypia but orderly maturation in upper squamous layers.

Which neoplastic precursor is suggested?

Differentiated VIN is suggested.

Preserved superficial maturation does not exclude basal-layer neoplasia.

Applied case: Invasive keratinizing tumor

A longstanding vulvar lesion becomes indurated. Histology shows irregular invasive squamous nests with conspicuous central keratin pearls.

Which etiologic group is favored by this combination?

HPV-independent keratinizing squamous carcinoma is favored.

Association with lichen disease and keratin pearls fits the described pathway.

Integrated clinicopathologic differential

Setting	Precursor morphology	Invasive correlate
HPV-associated	Diffuse immaturity; High mitotic activity	Basaloid nests or warty papillae
HPV-independent	Basal atypia; Surface maturation	Keratinizing nests and pearls
Benign HPV wart	Koilocytic papillomatous epithelium	Not a precancerous lesion
Reactive lichen simplex	Acanthosis without cytologic atypia	Not itself a precursor

Remember the distinguishing pathology

HPV-associated

High-risk HPV → classic VIN

Immature atypia across thickness

Basaloid / warty carcinoma



HPV-independent

Lichen context → dVIN

Atypia at basal layer

Keratinizing carcinoma with pearls

Final synthesis: Four diagnostic principles

- Vulvar squamous cancer is divided into HPV-associated and HPV-independent pathways.
- Classic VIN and dVIN have different maturation and atypia distributions.
- Invasion is distinct from precursor atypia and drives metastatic potential.
- Clinical appearance can mislead; Correlate with tissue morphology.

Source, scope, and interpretive limits

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 22, “The Female Genital Tract,” pp. 899–902.

Primary section: “Vulvar Intraepithelial Neoplasia and Vulvar Carcinoma,” pp. 900–901; source extraction 108377–108475.

Relevant adjoining context: “Nonneoplastic Epithelial Disorders” and “Condyloma Acuminatum,” pp. 899–900.

All epithelial / invasion drawings are original editable schematics, not histologic photographs. Current classification, staging, and management guidelines were not independently verified.