High-grade vulvar intraepithelial neoplasia: comprehensive characterization and long-term vulvar carcinoma risk

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要旨

外陰扁平上皮癌 vulvar squamous cell carcinoma (VSCC)の前駆病変である vulvar intraepithelial neoplasia (VIN)は、HPV 関連 high-grade squamous intraepithelial lesion (HSIL)、HPV 関連 low-grade SIL (LSIL)、HPV 非依存性 VIN に分類される。HPV 非依存性 VIN は HPV 関連 SIL と比べ高齢者に多く、臨床像および組織像は幅広いスペクトラムをとる。筆者らは HPV 関連 SIL および HPV 非依存性 VIN の特徴を明らかにするため、過去に high-grade VIN と診断された 751 例に対し、臨床病理像学的所見、p53, p16 および Ki-67 の免疫組織化学的解析(IHC)、HPV-DNA 解析を行った。

オランダの人口ベースデータベースから 1991 年から 2001 年に high-grade VIN と診断された 894 例が特定され、791 例の FFPE が収集されたが、このうち十分な組織が含まれない 40 例が除外され、751 例が解析対象となった。癌への進行を確認するために 2020 年までの追跡データが収集された。病変は 2 人の病理医による形態観察と IHC、HPV-DNA 解析を統合し、HPV 関連(VSCC, HSIL, LSIL)、HPV 非依存性(VSCC, HPV 非依存性 VIN, 非腫瘍性病変)に再分類された。

88.4%は HPV 関連(HSIL, 77%; LSIL, 10.9%; VSCC, 0.4%)、10.9%は HPV 非依存性(HPV 非依存性 VIN, 6.1%; 非腫瘍性, 4.7%; VSCC, 0.1%)、1.1%は HPV 関連か非依存性か確定できなかったために分類不能であった(Table 1)。HPV 関連は HPV 非依存性と比べ有意に年齢中央値が低かったが、その分布は広範であった(Table 1)。HSIL の 99%は p16 block 状陽性像を示し、p53 は 99.8%が wild type であった(Table 2)。一方、HPV 非依存性 VIN では p16 block 状陽性像は 2.1%に見られるのみで、p53 は 65.2%で mutated-pattern を呈した(Table 2)。HPV 非依存性 VIN は HPV 関連 SIL 様の未分化形態をとるものから、胞体の大型化といった分化傾向みる分化型まで幅広い形態的スペクトラムがみられた(各組織分類の組織像は Fig. 2-6)。10 年間癌発生リスクは HPV 関連 HSIL が 8%、p53 野生型 HPV 非依存性 VIN は 27.8%、p53 変異型 HPV 非依存性 VIN は 67.4%であった。さらに HPV 非依存性 VIN のうち、分化型の 10 年間癌発生リスクは 39.3%であったが、HPV 関連 SIL 様の未分化形態をとる症例では 73.7%であった(Table 4, Fig. 7)。

抄読会　令和 5 年 11 月 24 日

Take Home Message

1. VIN の診断時には p16 と p53 の IHC を行い、HPV 関連か非依存性かを確認する必要がある。
2. HPV 関連 SIL 様の未分化形態なのか、分化型なのかも報告する必要がある。

抄読者　刑部光正

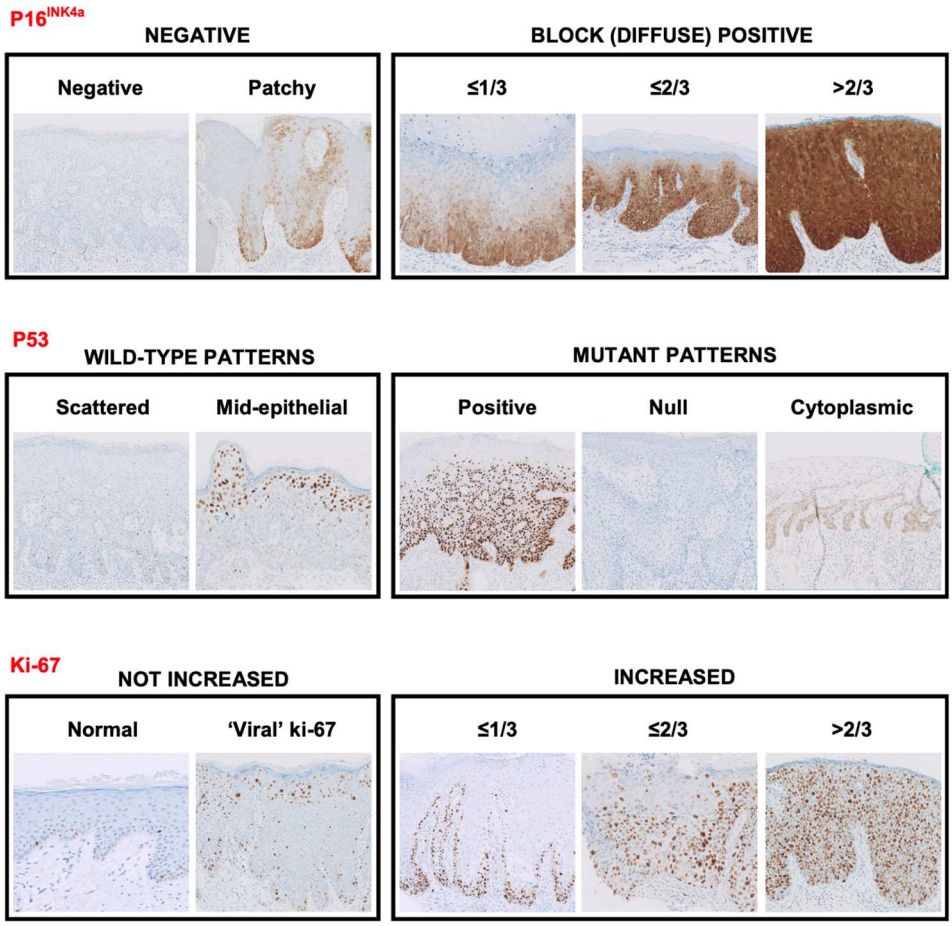

Fig. 1. Representative examples of p16INK4a, p53, and Ki-67 immunohistochemical staining patterns. The p16, p53, and the increased Ki-67 staining patterns haven been described before. The p53 mutant positive pattern includes the earlier described patterns of 'basal overexpression' and 'parabasal/diffuse overexpression'.

Table 1. Categorization of vulvar lesions after reassessment in relation to the original diagnosis and age at baseline

	Original diagnosis			Age, years
	HSIL	DVIN	Total (%)	Median (range)
	743	8	751 (100)	45.0 (16–92)
Final categorization				
HPV-associated	663	1	664 (88.4)	44.0 (17–91)
HSIL	578	0	578 (77.0)	45.0 (17–90)
LSIL	81	1	82 (10.9)	39.0 (19–91)
VSCC	3	0	3 (0.4)	39.0 (37–48)
HPV-independent	75	7	82 (10.9)	67.0 (16–92)
HPV-independent VIN	39	7	46 (6.1)	72.0 (35–92)
Nondysplastic	35	0	35 (4.7)	58.0 (16–79)
VSCC	1	0	1 (0.1)	67.0 (NA)
Inconclusive	6	0	6 (1.1)	75.0 (46–88)

Abbreviations: dVIN, Differentiated vulvar intraepithelial neoplasia; HPV, Human papillomavirus; HSIL, High-grade squamous intraepithelial lesion; LSIL, Low-grade squamous intraepithelial lesion; NA, Not applicable; VSCC, Vulvar squamous cell carcinoma.

Table 2. Immunohistochemical staining patterns of $p16^{INK4a}$, p53, and Ki-67 in human papillomavirus (HPV)-associated and HPV-independent vulvar lesions

	HPV-associated		HPV-independent	
	HSIL+	LSIL	HPV-independent VIN+	Nondysplastic
$P16^{INK4a}$				
Negative				
Negative	1 (0.2)	23 (28.0)	32 (68.1)	26 (74.3)
Patchy	5 (0.9)	34 (41.5)	14 (29.8)	9 (25.7)
Block positive				
≤1/3	50 (8.6)	15 (18.3)	0 (0)	0 (0)
≤2/3	289 (49.8)	10 (12.2)	0 (0)	0 (0)
>2/3	235 (40.5)	0 (0)	1 (2.1)	0 (0)
p53				
Wildtype				
Scattered	278 (48.0)	61 (74.4)	16 (34.8)	35 (100)
Mid-epithelial	300 (51.8)	21 (25.6)	0 (0)	0 (0)
Mutant pattern				
Positive	1 (0.2)	0 (0)	19 (41.3)	0 (0)
Null	0 (0)	0 (0)	11 (23.9)	0 (0)
Cytoplasmic	0 (0)	0 (0)	0 (0)	0 (0)
Ki-67				
Not increased				
Normal	2 (0.3)	20 (24.4)	6 (12.8)	19 (54.3)
'Viral' Ki-67	38 (6.6)	32 (39.0)	0 (0)	0 (0)
Increased				
≤1/3	36 (6.2)	55 (67.1)	36 (76.6)	14 (40.0)
≤2/3	317 (54.7)	7 (8.5)	4 (8.5)	2 (5.7)
>2/3	224 (38.7)	0 (0)	1 (2.1)	0 (0)

In four lesions, one or more stains could not be assessed (1× $p16^{INK4a}$, 4× p53, and 2× Ki-67).
HSIL+, High-grade squamous intraepithelial lesion, including three HPV-associated vulvar squamous cell carcinomas; HPV-independent VIN+, HPV-independent vulvar intraepithelial neoplasia, including one HPV-independent vulvar squamous cell carcinoma; LSIL, Low-grade squamous intraepithelial lesion.

Table 3. High-risk and low-risk human papillomavirus (HPV) genotype distribution per disease category.

	HPV-associated		HPV-independent	
	HSIL+	LSIL	HPV-independent VIN+	Nondysplastic
Overall HPV positive	557/559 (99.6)	56/62 (90.3)	5/34 (14.7)	0/11 (0)
High-risk HPV positive	553 (99.3)	43 (76.8)	4 (80.0)	0 (0.0)
Single high-risk HPV type	535 (96.1)	42 (75.0)	4 (80.0)	0 (0.0)
Multiple high-risk HPV types	18 (3.2)	1 (1.8)	0 (0.0)	0 (0.0)
High-risk HPV genotype 16/18	479 (86.0)	32 (57.1)	3 (60.0)	0 (0.0)
Type 16	453 (81.3)	30 (53.6)	3 (60.0)	0 (0.0)
Type 18	27 (4.8)	3 (5.4)	0 (0.0)	0 (0.0)
High-risk HPV genotype non-16/18	89 (16.0)	11 (19.6)	1 (20.0)	0 (0.0)
Type 31	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Type 33	41 (7.4)	2 (3.6)	0 (0.0)	0 (0.0)
Type 35	1 (0.2)	1 (1.8)	0 (0.0)	0 (0.0)
Type 45	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Type 51	4 (0.7)	1 (1.8)	0 (0.0)	0 (0.0)
Type 52	1 (0.2)	1 (1.8)	0 (0.0)	0 (0.0)
Type 56	2 (0.4)	1 (1.8)	0 (0.0)	0 (0.0)
Type 59	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Type 66[a]	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Type undetermined (variant X)	9 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Type non-16/18, not further specified[b]	21 (3.8)	5 (8.9)	1 (20.0)	0 (0.0)
Tested for additional HPV types	8/559 (1.4)	16/62 (25.8)	15/34 (44.1)	2/11 (18.2)
Low-risk HPV positive	4 (0.7)	13 (23.2)	1 (20.0)	0 (0)
Single low-risk HPV type	3 (0.5)	12 (21.4)	1 (20.0)	0 (0)
Multiple low-risk HPV types	1 (0.2)	1 (1.8)	0 (0)	0 (0)
Low-risk HPV genotype				
Type 6	2 (0.4)	11 (19.6)	0 (0)	0 (0)
Type 11	0 (0.0)	0 (0.0)	1 (20.0)	0 (0)
Type 26[a]	1 (0.2)	0 (0.0)	0 (0)	0 (0)
Type 34[a]	1 (0.2)	0 (0.0)	0 (0)	0 (0)
Type 42	0 (0.0)	3 (5.4)	0 (0)	0 (0)
Type 83	1 (0.2)	0 (0.0)	0 (0)	0 (0)

Type-specific positivity includes those contributed by multiple infections.
HSIL+, High-grade squamous intraepithelial lesion, including three HPV-associated vulvar squamous cell carcinomas; LSIL, Low-grade squamous intraepithelial lesion; HPV-independent VIN+, HPV-independent VIN, including one HPV-independent vulvar squamous cell carcinoma.
[a]IARC (International Agency for Research on Cancer) Group 2b ('possibly carcinogenic').[17]
[b]'High-risk HPV Type non-16/18, not further specified' was used for cases that could not be subtyped due to insufficient DNA.

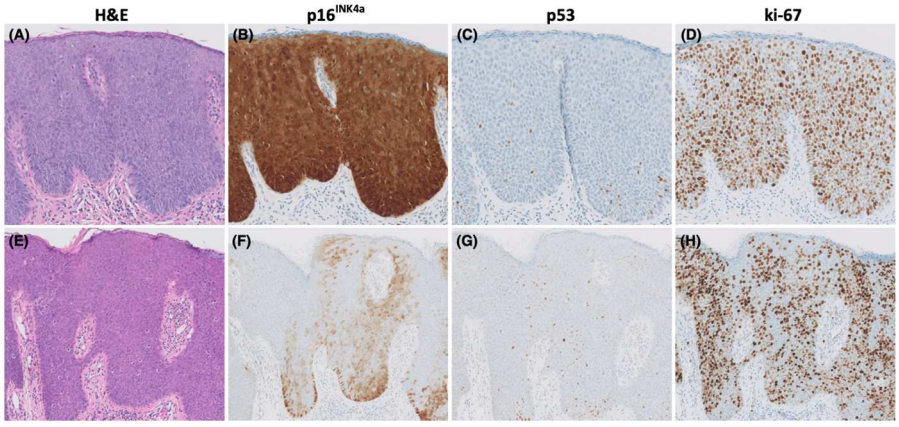

Fig. 2. HPV-associated vulvar high-grade squamous intraepithelial lesion (HSIL). (A–D) Representative example of ‘classical’ HSIL with block-positive p16INK4a, wildtype, scattered p53 staining, and full-thickness increased Ki-67. (E–H) HSIL with patchy (negative)p16INK4a, HSIL morphology, wildtype, scattered p53, and full-thickness increased Ki-67.

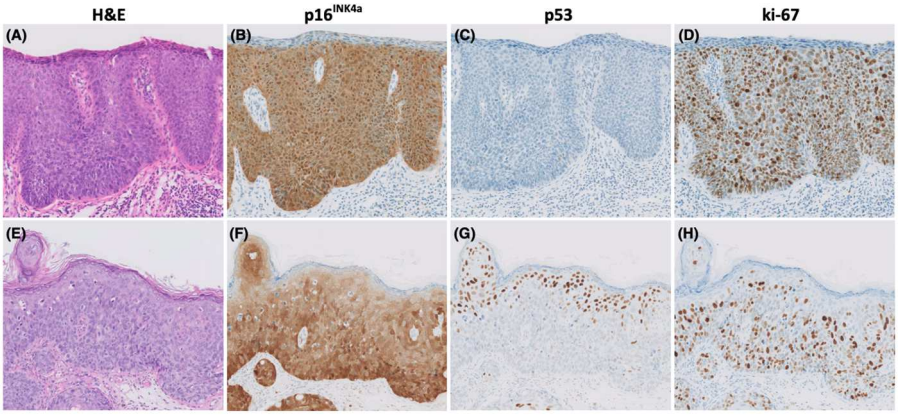

Fig. 3. HPV-associated vulvar high-grade squamous intraepithelial lesion (HSIL). (A–D) HSIL with wildtype, reduced p53 staining, mimicking a mutant null pattern. (E–H) HSIL with wildtype p53 mid-epithelial staining with sparing of the basal cell layer, which can mimic mutant positive staining, and with positive p16INK4a.

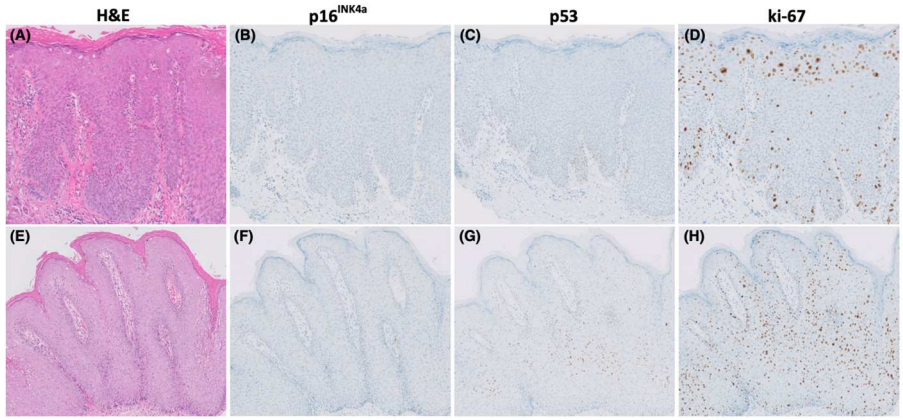

Fig. 4. HPV-associated vulvar low-grade squamous intraepithelial lesion (LSIL). (A–D) LSIL with ‘viral’ Ki-67 in scattered individual koilocytic cells in the upper epithelium with lesser staining in the lower epithelium, mimicking transepithelial increased Ki-67. (E–H) LSIL with wildtype p53 mid-epithelial staining with sparing of the basal cell layer and negative p16INK4a.

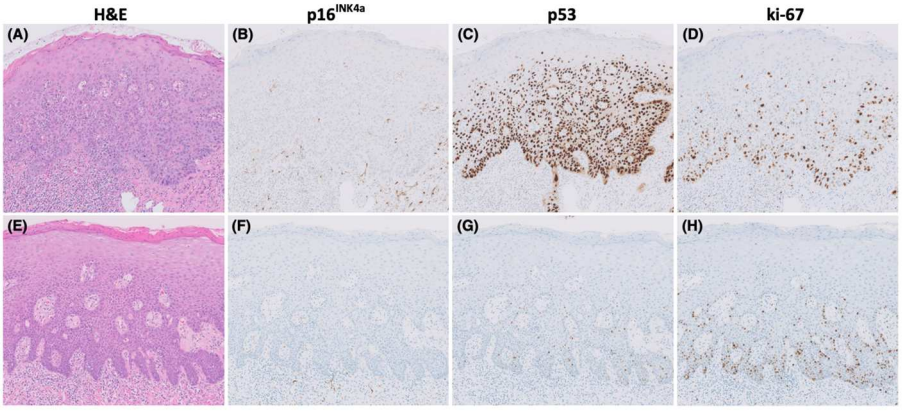

Fig. 5. HPV-independent vulvar intraepithelial neoplasia (VIN). (A–H) Representative examples of HPV-independent VIN with differentiated morphology, negative p16INK4a and respectively mutant (C) versus wildtype scattered p53 staining (G).

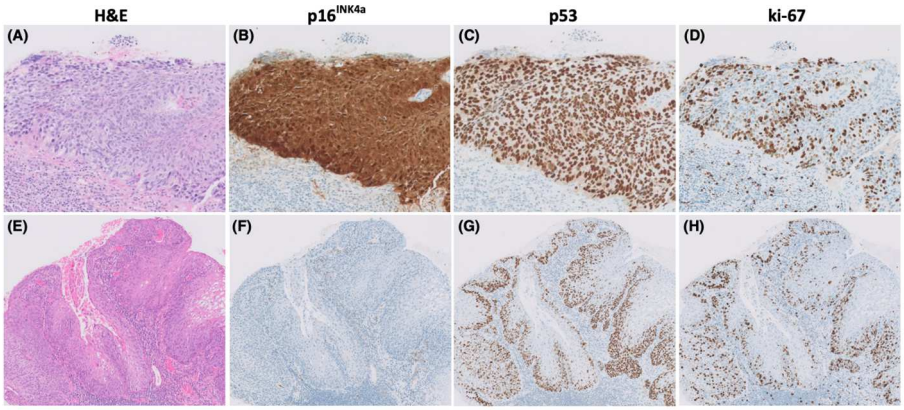

Fig. 6. HPV-independent vulvar intraepithelial neoplasia (VIN) with nondifferentiated (‘HPV-associated-like’) morphology. (A–H) Both cases had negative HPV DNA and mutant positive p53 staining. In (A–D), basaloid morphology is seen, whereas in (E–H) wide and deep rete ridges, with moderate pleomorphism and koilocytic-like changes are seen.

Table 4. Risk of vulvar squamous cell carcinoma (VSCC), including time to VSCC, per disease category

	Absolute VSCC risk	Cumulative incidence of VSCC (95% CI)			Median time to VSCC,
	No. (%)	1 year	5 years	10 years	years (range)
HPV-associated HSIL	61/578 (10.6)	2.1 (0.9–3.3)	4.5 (2.7–6.3)	8.0 (5.8–10.2)	6.0 (0.3–24.2)
HPV-independent VIN	25/46 (54.3)	19.6 (8.2–31.0)	45.7 (31.4–60.0)	53.6 (38.7–68.5)	1.8 (0.3–10.9)
HPV-ind VIN/p53 mutant	20/30 (66.7)	30.0 (13.5–46.5)	63.3 (46.1–80.5)	67.4 (50.3–84.5)	1.5 (0.3–6.7)
HPV-ind VIN/p53 wildtype	5/16 (31.3)	0.0 (NA)	12.5 (0.0–28.8)	27.8 (3.9–51.7)	5.1 (1.2–10.9)
HPV-ind VIN/ differentiated	11/27 (40.7)	3.7 (0.0–10.8)	25.9 (9.4–42.4)	39.3 (19.9–58.7)	3.2 (0.8–23.3)
HPV-ind VIN/ nondifferentiated	14/19 (73.7)	42.1 (20.0–64.2)	73.7 (53.9–93.5)	73.7 (53.9–93.5)	0.5 (0.3–16.5)

HSIL, High-grade squamous intraepithelial lesion; HPV-independent VIN, Human papillomavirus-independent vulvar intraepithelial neoplasia; NA, Not applicable.

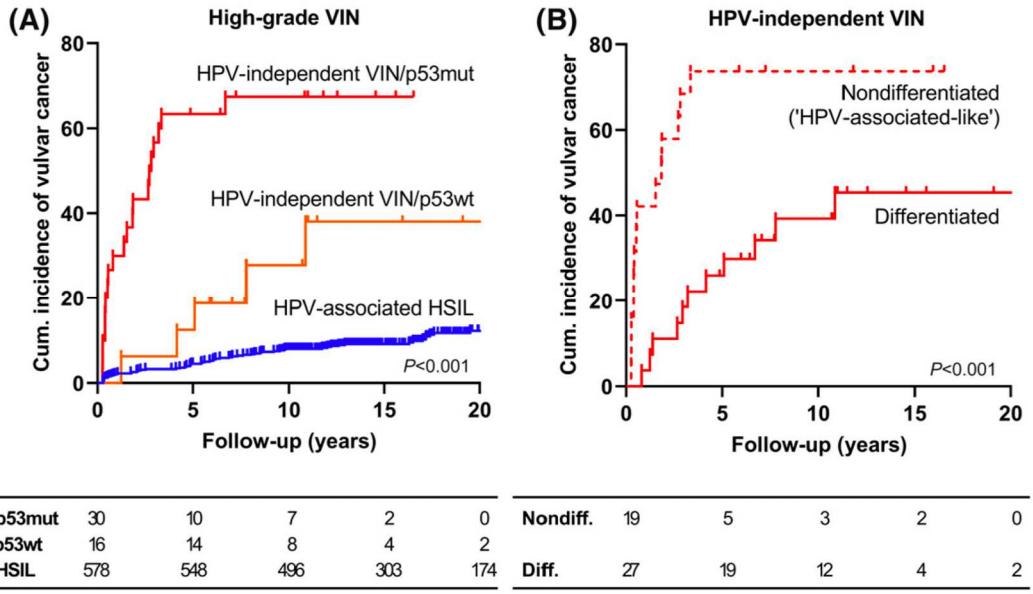

Fig. 7. Cumulative incidence of vulvar cancer in high-grade VIN. (A) Stratified for three subtypes of high-grade VIN: HPV-associated HSIL, HPV-independent VIN/p53 mutant, and HPV-independent VIN/p53 wildtype. (B) HPV-independent VIN with differentiated morphology versus nondifferentiated ('HPV-associated-like') morphology. HPV-independent VIN, Human papillomavirus-independent vulvar intraepithelial neoplasia; HSIL, High-grade squamous intraepithelial lesion.