Premalignant Vulvar Lesions Classification and Clinical Implications

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- **Vulvar intraepithelial neoplasia (VIN)**
- Lichen sclerosus
- Paget disease
- Melanoma in-situ

Vulvar Intraepithelial Neoplasia
VIN

Dysplastic changes of squamous epithelium

Hudelo (1922)	Kaufmann (1965)	ISSVD			
		Friedrich (1976)	Wilkinson (1986)	Sideri (2005)	Bornstein (2016)
Dyskératose erythroplasiforme de la musqueuse vulvaire	Queyrat's erythroplasia Bowenoid carcinoma in situ Carcinoma simplex	Vulvar atypia without or with dystrophy	VIN1	Flat condyloma or HPV effect	LSIL
			VIN2	VIN usual type	HSIL
		Squamous carcinoma in situ	VIN3	VIN usual type	HSIL
			Differentiated VIN	VIN differentiated type	dVIN, differentiated-type VIN

Hudelo ML, Oury C. Dyskeratose erythroplasiforme de la musqueuse vulvaire. Bull Soc Franc Dermatol Et Syph 1922; 29: 139–142.
Friedrich EG. Report of the committee on terminology. New nomenclature for vulvar disease. Obstet Gynecol 1976; 49: 122–124.
Wilkinson EJ, et al. Report of the ISSVD terminology committee. Reprod Med 1986; 31: 973–974.
Sideri M, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med 2005; 50: 807–810.
Bornstein J, et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of vulvar Squamous Intraepithelial Lesions. J Lower Gen Tract Dis 2016; 20:11–14.

Pathways	ISSVD		
	Wilkinson (1986)	Sideri (2005)	Bornstein (2016)
HPV-associated	VIN1	Flat condyloma or HPV effect	LSIL
	VIN2	VIN usual type Basaloid and/or Warty	HSIL
	VIN3	VIN usual type Basaloid and/or Warty	HSIL
HPV-independent	Differentiated VIN	VIN differentiated type	dVIN, differentiated-type VIN

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van de Nieuwenhof HP, et al: Review of squamous premalignant vulvar lesions H.P. Critical Reviews in Oncology/Hematology 68 (2008) 131–156.
Sideri M, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med. 2005 Nov;50(11):807-10.
Crum CP, et al. ed. WHO Classification of Tumours of Female Reproductive Organs. 4th Edition. IARC Press, Lyon 2014.

Pathways	ISSVD			
	Wilkinson (1986)	Sideri (2005)	Bornstein (2016)	
HPV-associated	VIN1	Flat condyloma or HPV effect	LSIL	**NOT precancerous**
	VIN2	VIN usual type	HSIL	**PRECANCEROUS**
	VIN3	VIN usual type	HSIL	
HPV-independent	Differentiated VIN	VIN differentiated type	dVIN, differentiated-type VIN	

Bornstein J, et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of vulvar Squamous Intraepithelial Lesions. J Lower Gen Tract Dis 2016; 20:11–14
Srodon M, et al. The distribution of low risk and high risk types in vulvar and vaginal intraepithelial neoplasia (VIN and VAIN). Am J Surg Pathol 2006;30:1513-1518.
Crum CP, et al. ed. WHO Classification of Tumours of Female Reproductive Organs. 4th Edition. IARC Press, Lyon 2014.

Pathways	ISSVD			
	Wilkinson (1986)	Sideri (2005)	Bornstein (2016)	
	VIN1	Flat condyloma or HPV effect	LSIL	NOT precancerous
HPV-associated 90-95% of VIN	VIN2	VIN usual type	HSIL	PRECANCEROUS
	VIN3	VIN usual type	HSIL	
<5-10% HPV-independent of VIN	Differentiated VIN	VIN differentiated type	dVIN, differentiated-type VIN	

Del Pino M, et al. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology. 2013;62:161-75.
Eva LJ, et al. Differentiated type vulval intraepithelial neoplasia has a high risk association with vulval squamous cell carcinoma. Int J Gynecol Cancer. 2009;19(4):7414.

Pathways	ISSVD			
	Wilkinson (1986)	Sideri (2005)	Bornstein (2016)	
	VIN1	Flat condyloma or HPV effect	LSIL	NOT precancerous
HPV-associated 20-40% of burden of invasive cancer	VIN2	VIN usual type	HSIL	PRECANCEROUS
	VIN3	VIN usual type	HSIL	
60-80% independent of burden of invasive cancer	Differentiated VIN	VIN differentiated type	dVIN, differentiated-type VIN	

Del Pino M, et al. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology. 2013;62:161-75.
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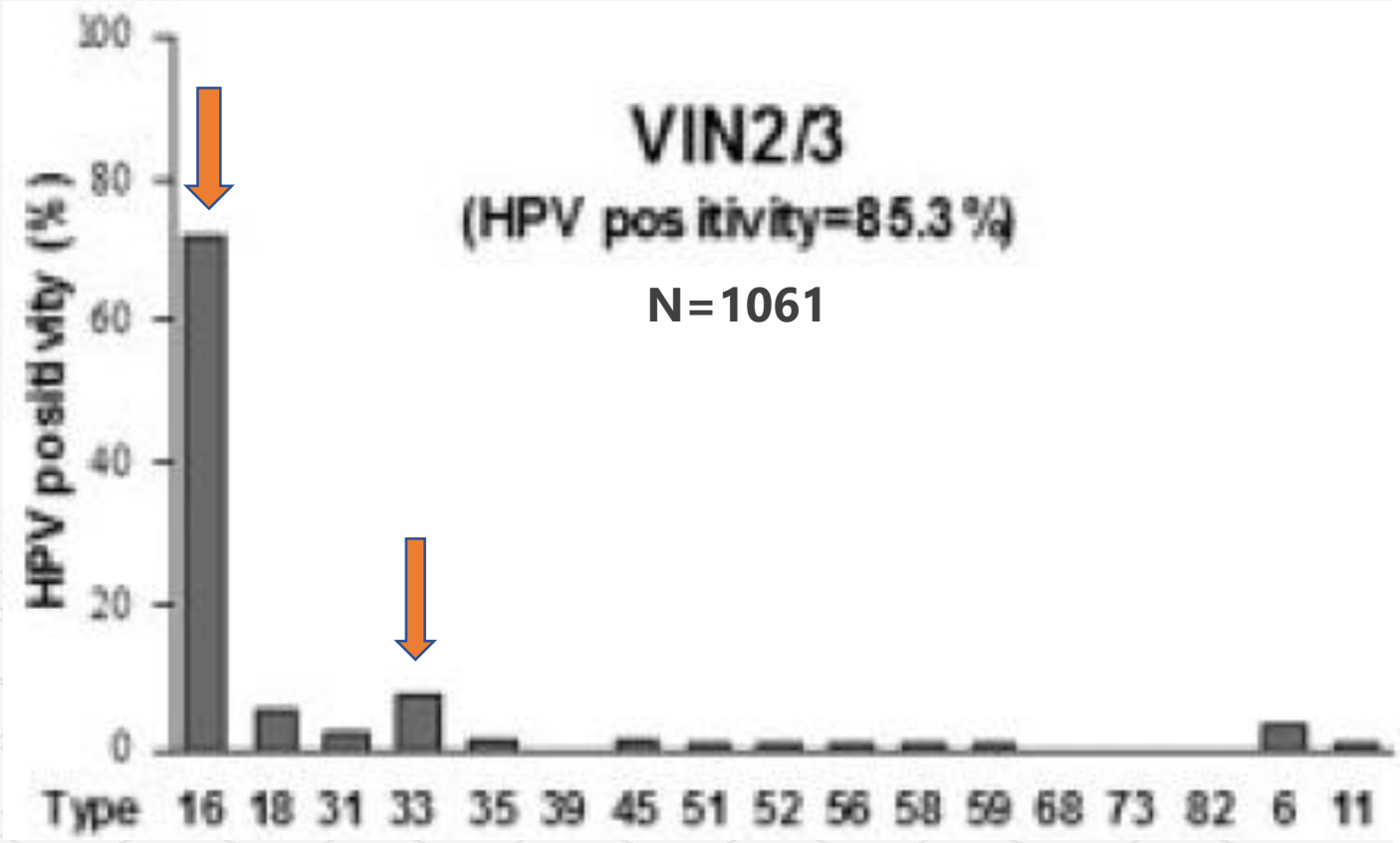
HSIL/uVIN

Epidemiology- HSIL uVIN

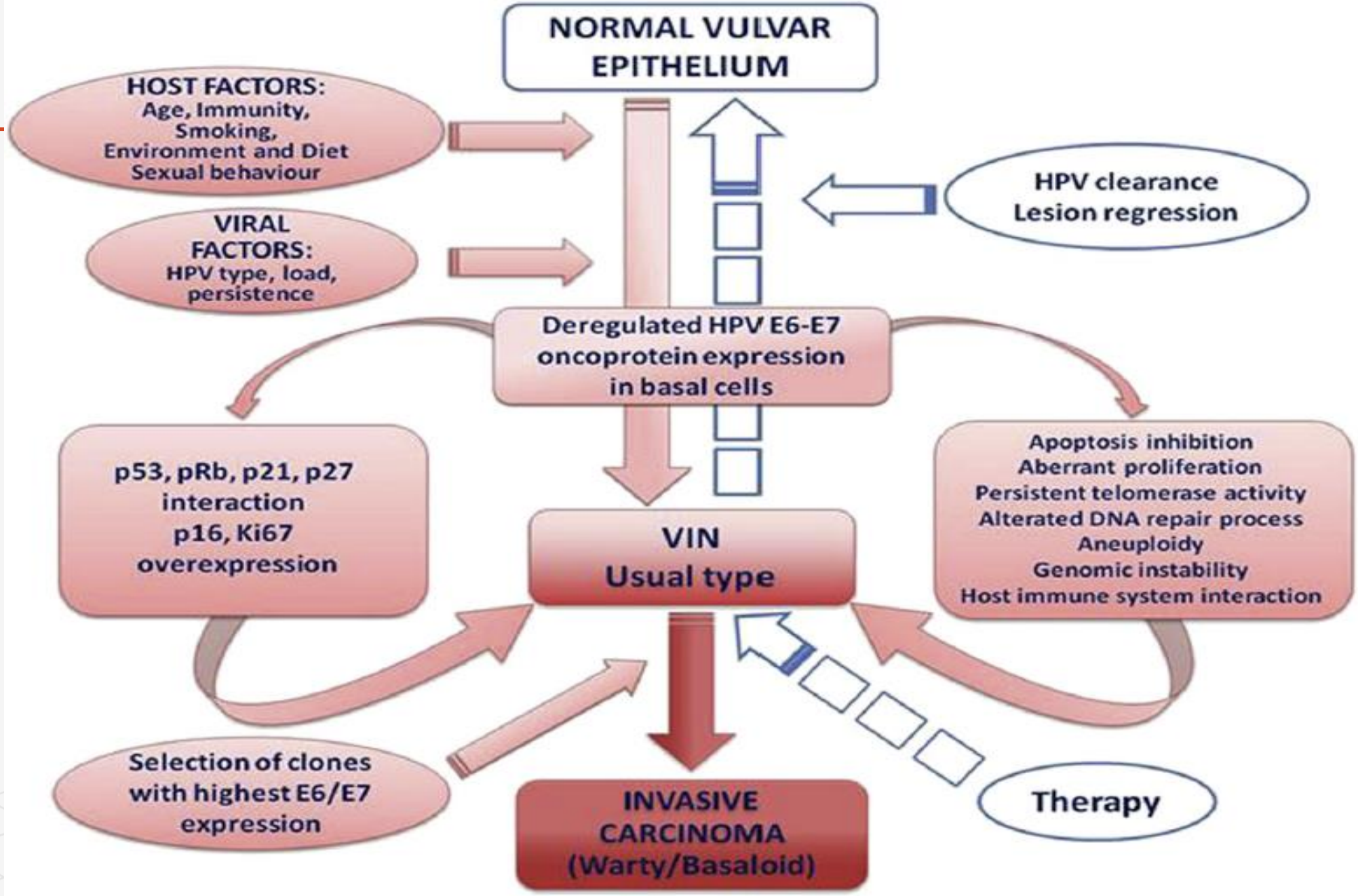
- 90-95% of VIN
- **HPV-related**
  - 85-100% (type of VIN studied, DNA detection method, HPV types determined)
  - Single infection 92%

HPV 16	70-77%
HPV 33	7-10%
HPV 18	2.5-5%
HPV 31	1.2-2.5%



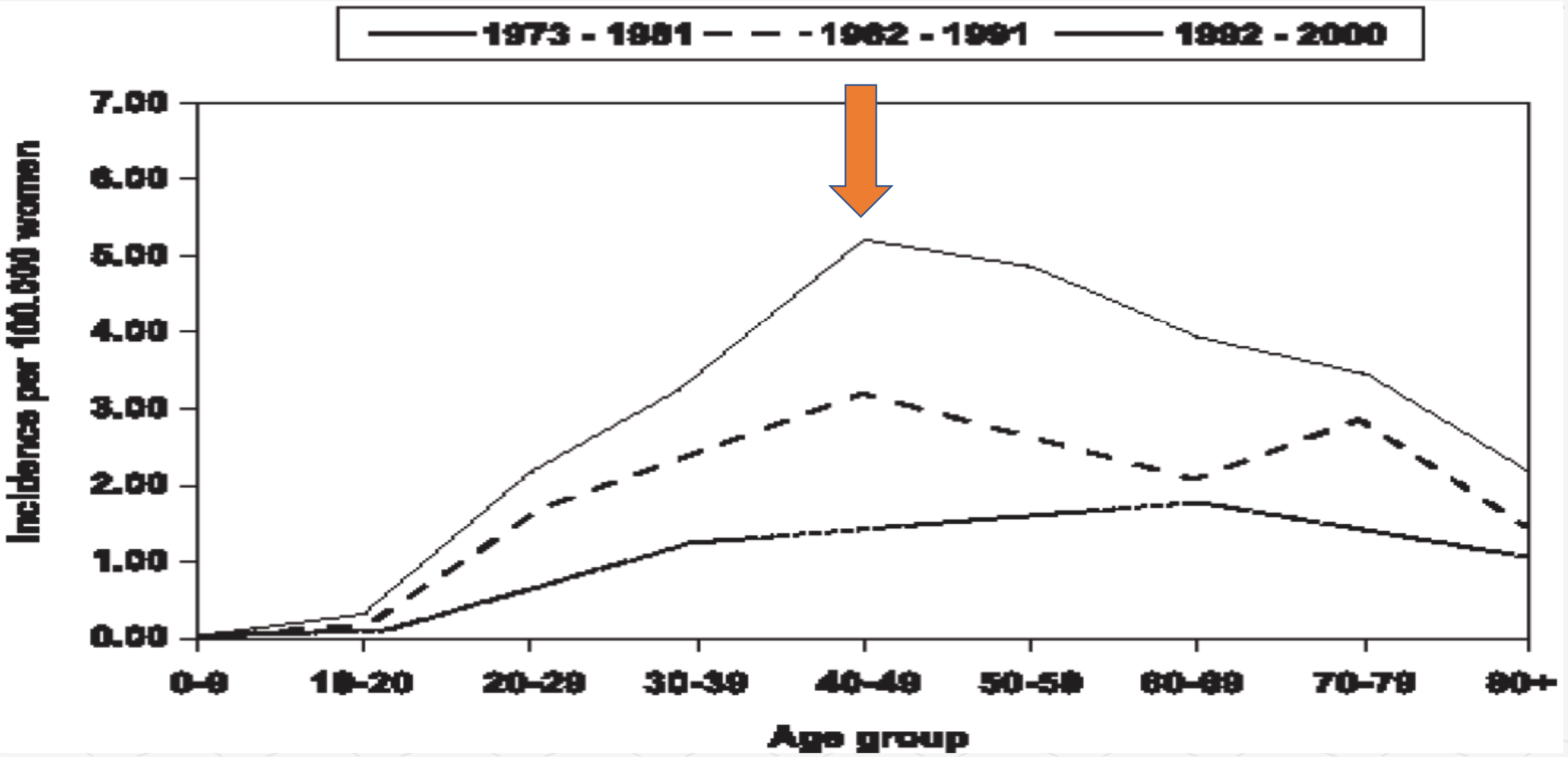
de Sanjose S, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. European Journal of Cancer (2013) 49, 3450–3461.
De Vuyst H, et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: A meta-analysis. Int. J. Cancer: 124, 1626–1636 (2009).
Van de Nieuwenhof HP, et al. Review of squamous premalignant vulvar lesions. Crit Rev Oncol Hematol 2008; 68:131–156.

Vulvar oncogenesis: HPV-related pathway

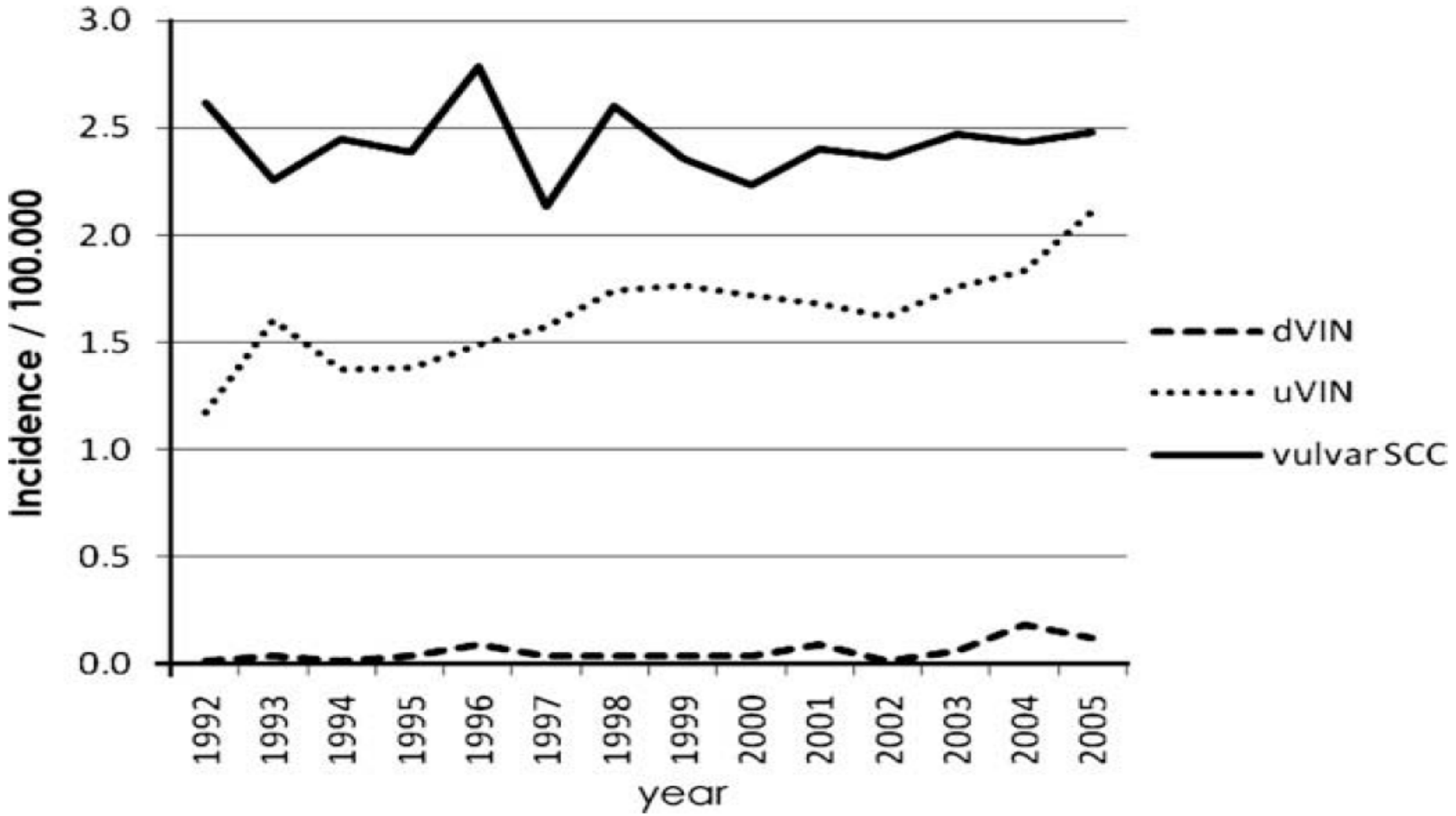


M. Preti et al. Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 1051-1062

Epidemiology- HSIL uVIN



Epidemiology- HSIL uVIN



Epidemiology- HSIL uVIN

- **Young**, 30-50

- Risk factors:
  - Smoking (60-80%)
  - Immunosuppression
  - Sexual behavior
  - History of STI

Epidemiology- HSIL uVIN

Multifocal >50%

Multicentric HPV infection affecting cervix, vagina, anus

22% concurrent CIN

up to 71% had a previous, concomitant or subsequent history of VAIN, CIN or cervical carcinoma

Young+++ (59% in women aged 20-34 and 10% in patients >50 years of age)

Older patients: uncommon sites (vaginal, anal, periurethral)

Immune system role in clearance and persistence

HIV infection

- 4X more likely to have HPV infection
- Prevalence of uVIN 0.5-37%

Immunosuppressants

- 10-30X risk of vulvar ca, mainly HPV 16 and 18

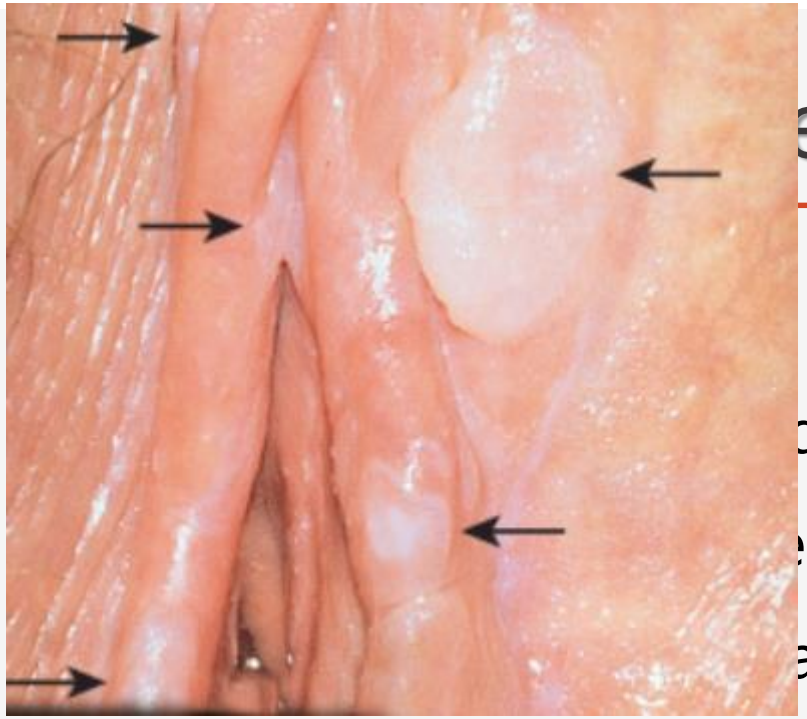
Epidemiology- HSIL uVIN

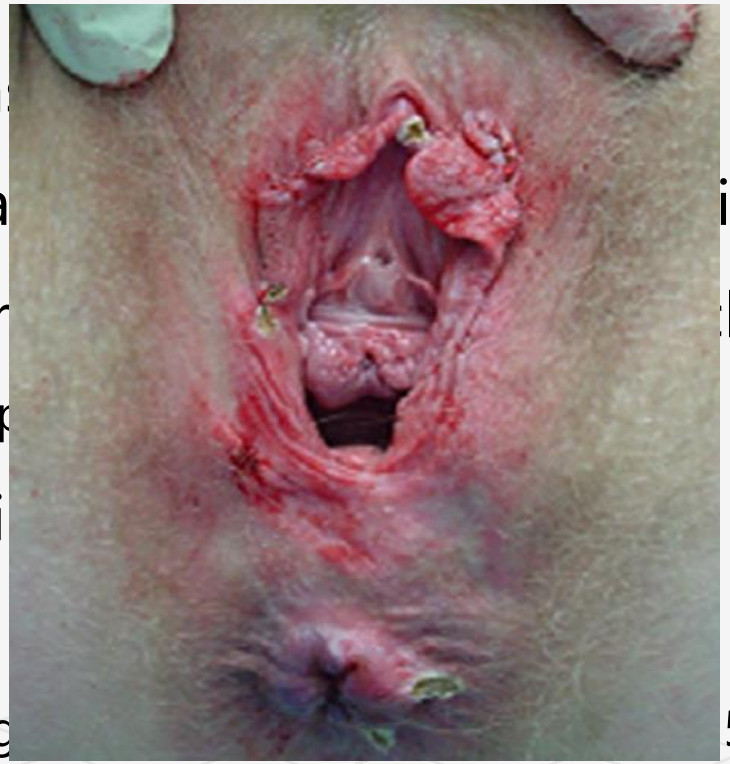
- Subtypes:
  - Warty (previously Bowen's disease)
  - Basaloid
    - older age
    - More likely to become invasive
    - Less likely to regress
  - Mixed, common

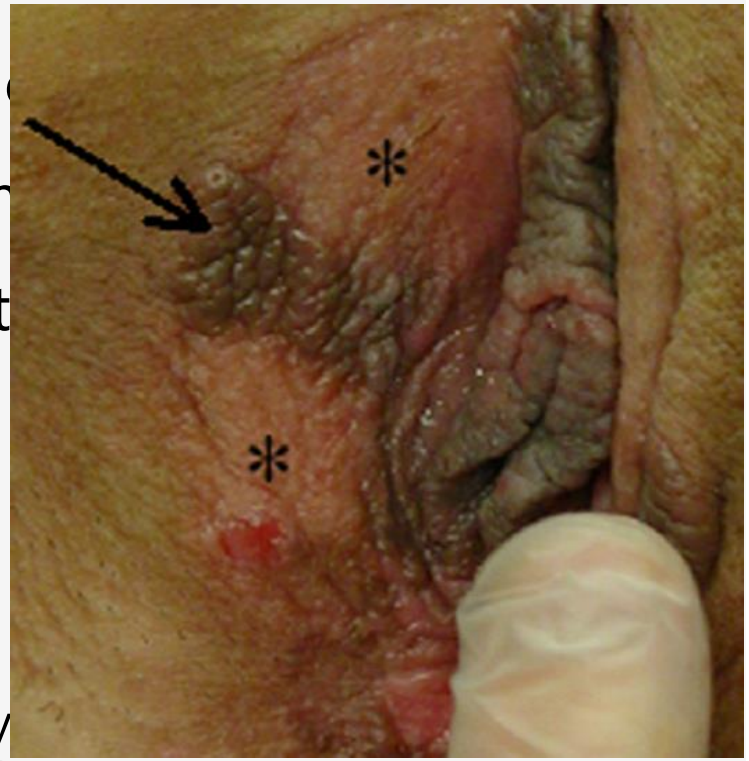
Symptoms- HSIL uVIN

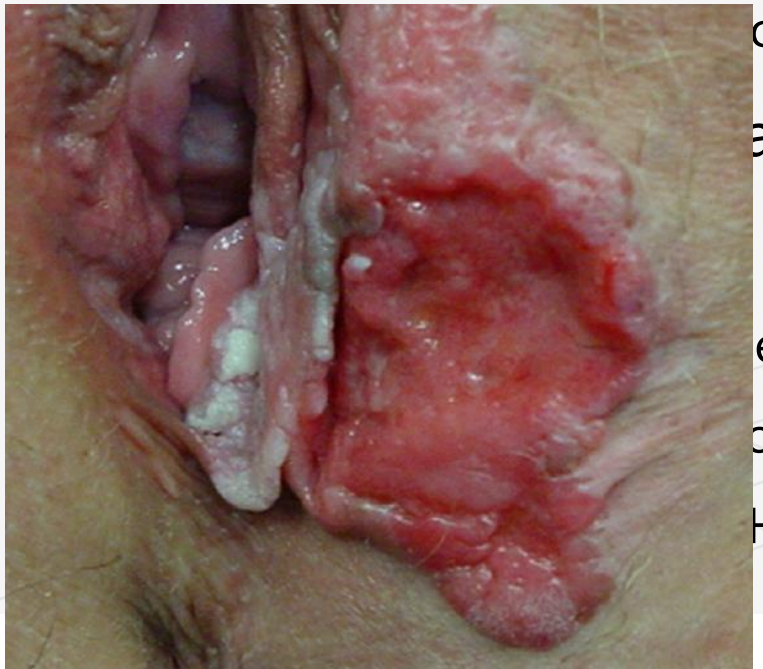
- Itching 60%,
- burning, pain, psychosexual sx
- Asymptomatic 20%

e- HSIL uVIN









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on sites (vaginal, anal, periurethral)

HPV positive than unicentric

Natural history- HSIL uVIN

Malignant progression relatively low,

- **After primary treatment:** 1.4-20%
  - Metaanalysis: **3.3%** (108/3322) (van Seters 2005)
  - Jones 2005: **4.9%** (17/342)
- **Untreated patients:**
  - First study: 7/8 (Jones 1994)
  - Metaanalysis: **9%** (8/88) (van Seters 2005), **mean 4 years (1-8 years)**
  - Jones 2005: **15.8%** (10/63), mean 3.9 years (1.1-7.3 years)
- **71% superficial**
- **Non-keratinizing SCC**
- **Mean time to progression 55 months (4-216)** → long follow up

Occult carcinoma

- **3.2-18.8%**

Natural history- HSIL uVIN- Risk Factors for progression

Advanced age, >45

- ***Increases risk of progression:*** *2.7% <29 years vs 8.5% >75 years*
- ***Shortens time to progression:*** *50 months for<29 vs 25 months for>75*

Raised lesions

Radiation therapy

Immunosuppression

Basaloid type

Focality? controversial

No difference by type of surgery

- except cryosurgery (van Seters 2005)

Free margins do not prevent progression

- 50% of SCC after trt had free margins

Natural history- HSIL uVIN

- **Two patterns of invasive vulvar ca in treated patients**

Early occurring within 7 years of trt
(median 2.4 years) (50%)= inadequate trt

- At site of previous trt
- Previous positive margins

Late occurring many years after trt
(median 13.8 years) (50%)

- At some distance from previous lesions= ***de novo tumors***
- HPV-induced field of risk

Jones RW, et al. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. Obstet Gynecol 2005;106(December (6)):1319–26.

Natural history- HSIL uVIN

Spontaneous regression

- 47-75% (metaanalysis, van Seters 2005; Jones 2005)
  - 1.2%?? (metaanalysis, van Seters 2005)
- Most regressed **10 months** after diagnosis

Young, <35

Multifocal pigmented

Delivery in **pregnant** pts (40% of regression related to pregnancy)

Improvement of immunosuppression

Smoking cessation

Jones RW, et al. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. Obstet Gynecol 2005;106(December (6)):1319–26.

Natural history- HSIL uVIN

Recurrence

- Common, 13-36%
- even after extensive surgeries
- viral ≡ immune
- True recurrences vs de novo lesions (HPV field effect)
- Most within the first 3 years of F/U

Natural history- HSIL uVIN- Risk Factors for recurrence

Type of surgery

- **No difference**
- Cryocoagulation?

Surgical margins

- Controversial
- Often positive irrespective of type of surgery
- Recurrence significantly lower with free margins (17% vs 47%)

Immunosuppression, HIV

Smoking

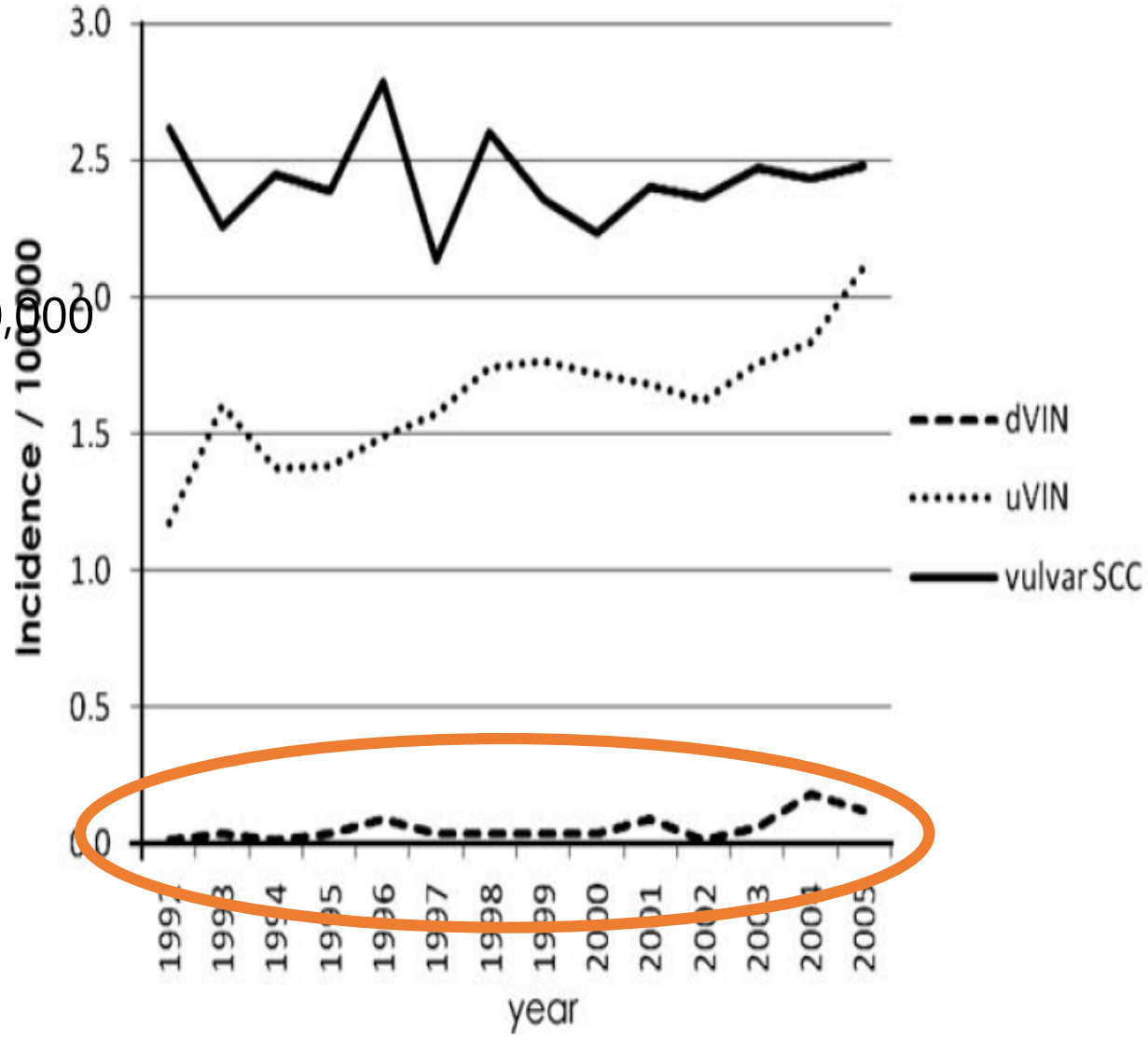
Multifocal

P53 gene mutation

dVIN

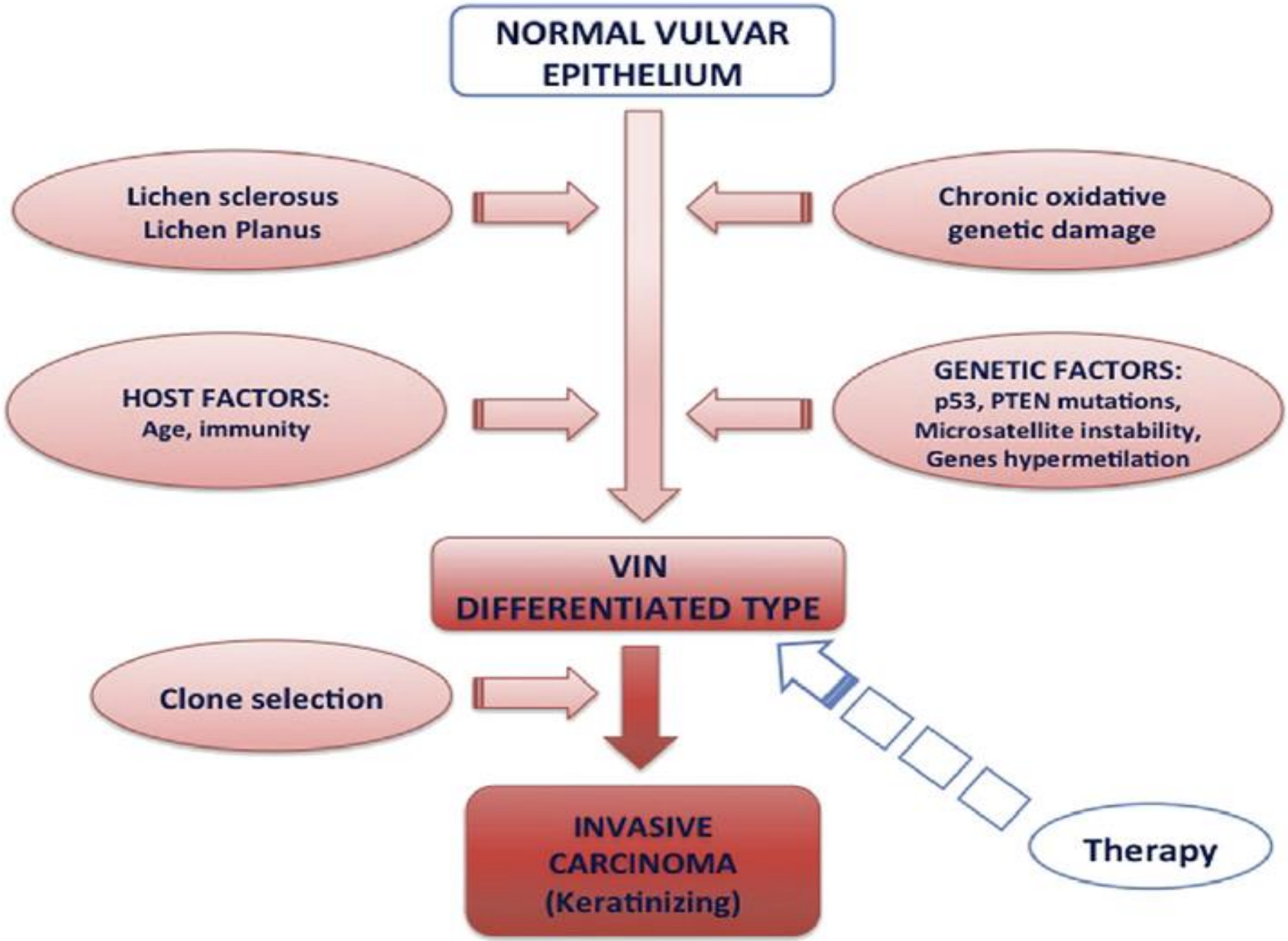
Epidemiology- dVIN

- <5% of VIN
- Incidence low
  - increased 9x from 1992-2005: 0.013 to 0.121/100,000
  - Incidence of vulvar ca stable
- **Probably underdiagnosed/underreported**
  - Difficult clinical and histological diagnosis
  - Brief intraepithelial phase before invasion
- HPV uncommon (1.5%)



Van de Nieuwenhof HP, et al. Review of squamous premalignant vulvar lesions. Crit Rev Oncol Hematol 2008; 68:131–156.
van de Nieuwenhof HP, et al. Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age. Eur J Cancer 2009;45:851e6.

Vulvar oncogenesis: Non-HPV-related pathway



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Epidemiology- HSIL uVIN

Elderly mainly, **Postmenopausal** Median age 67

Associated with **vulvar dermatoses** (LS, LSC, LP)

Rarely found in an isolated form

Mostly **Unicentric, Unifocal** 3% cervical, anal, and/or vaginal intraepithelial lesion

Symptoms- dVIN

- Often symptomatic
- due to underlying dermatosis
- Itching, pain, burning, dyspareunia, dryness, urinary and GI complaints, bleeding

Clinical appearance- dVIN

- Less specific
- ary les nt to L
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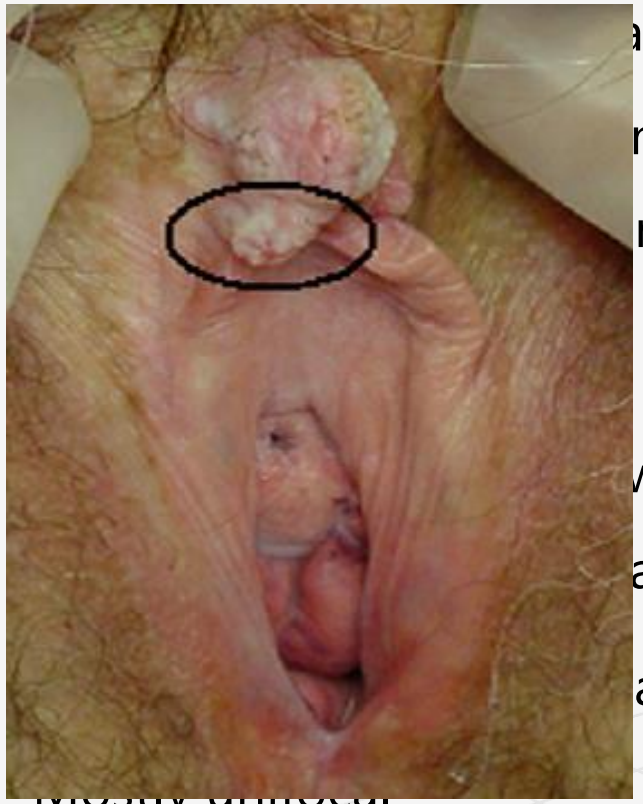
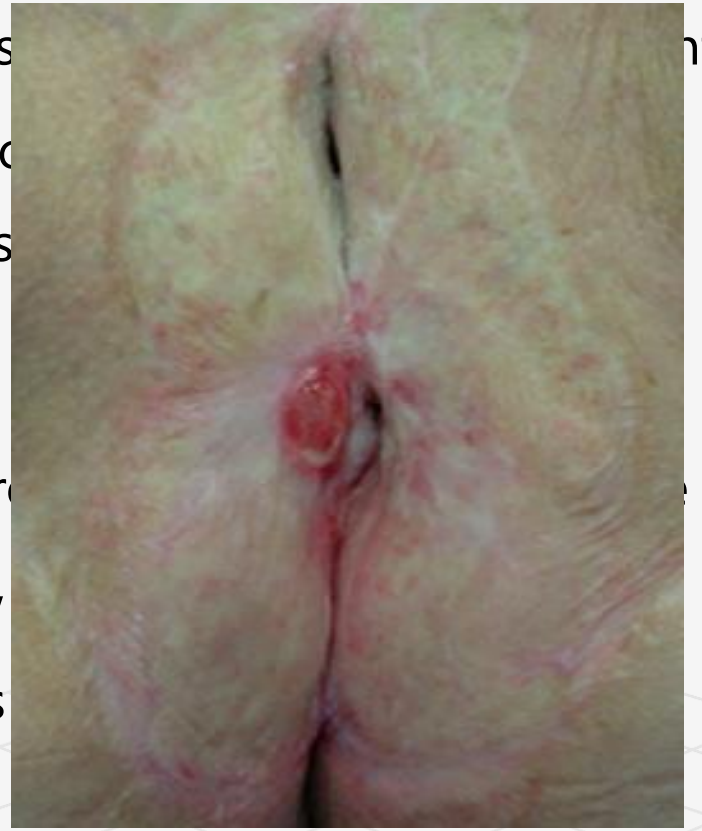
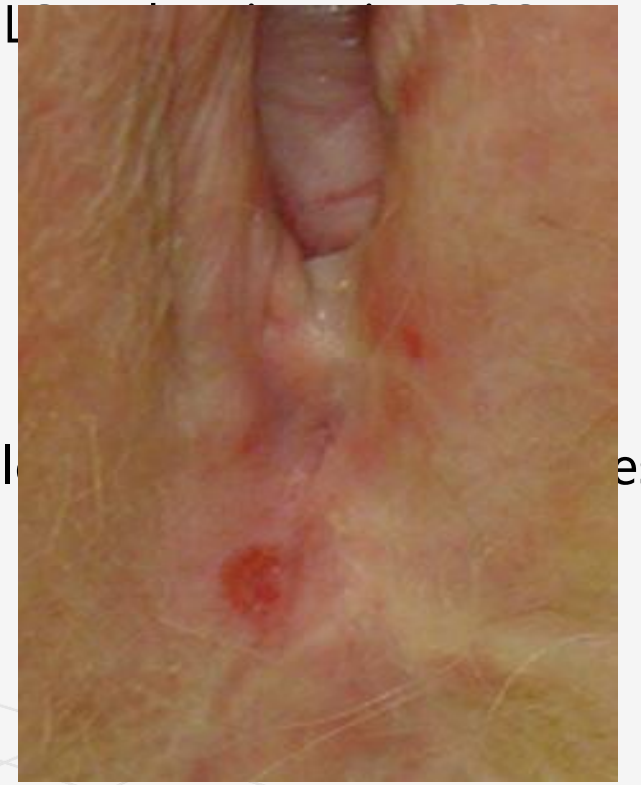
- areas
- Mostly unifocal
- Mostly unicentric (2.9% have concommitant intraepithelial neoplasia of lower genital tract)







Natural history- dVIN

Malignant progression

- **Higher**, 33% vs 5.7%
- **Time to progression shorter** (22.8 months vs 41.4 months)
- **Keratinizing SCC**

Prior, synchronous or subsequent SCC

- 85.7% vs 25.7%

SCC **more likely to recur** and **worse prognosis**

- Local recurrence 35% vs 10%, OR recurrence 3.86 vs 1.35
- 5-year survival 42% vs 87%

ISSVD 2015-PREMALIGNANT LESIONS

	HSIL	DVIN
Prevalence	More common, 95% of VIN	Less common, <2-5% of VIN
Age	Young, Peak 35-49	Mainly Elderly, Postmenopausal, 66-69
HPV association	Persistent infection HR-HPV (16, 18, 33)	Non-HPV related
Risk Factors	Smoking Immunosuppression	Vulvar dermatoses, Chronic skin inflammatory conditions (Lichen sclerosus, Lichen planus, Squamous cell hyperplasia)
Distribution	Multicentric, Multifocal	Usually Unicentric, Unifocal
Progression to invasive cancer	5-12%	33%, Shorter period
Type of SCC	Non-keratinizing SCC (Basaloid/Warty)	Keratinizing SCC
Occult cancer	3%	Significantly higher
Immunohistochemistry	p16+ (diffuse, band-like), p53−	p53+(85%), p16− or focally +

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Van de Nieuwenhof HP, et al. Review of squamous premalignant vulvar lesions. Crit Rev Oncol Hematol 2008; 68:131–156.
Reyes MC, et al. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis J Clin Pathol 2014;67:290–294

Lichen Sclerosus

- **Chronic** inflammatory skin disease
  - 7-13% of women with chronic vulvar sx
- Underdiagnosed
- Anogenital area +++
  - Does not affect vagina, very rarely oral mucosa
- **Bimodal peak incidence prepubertal and menopausal**
  - Adult +++ (50-70), Children 5-15%
  - Signs in young girls difficult to distinguish from sexual abuse
- Should be diagnosed ASAP
  - Early trt prevents scarring and possibly malignant changes

Etiology-LS

- Unknown

Hormonal factors

- **Hypoestrogenic? Androgen?**

Genetic predisposition

- Family hx 10%

Autoimmune

- *22-34% have AID,*
- *up to 75% have autoantibodies,*
- *early onset?*

Oxidative damage

Infectious

- *HCV, B. Burgdorferi, Mycobacteria*

Itch-scratch LS hypothesis

- Kobner phenomenon

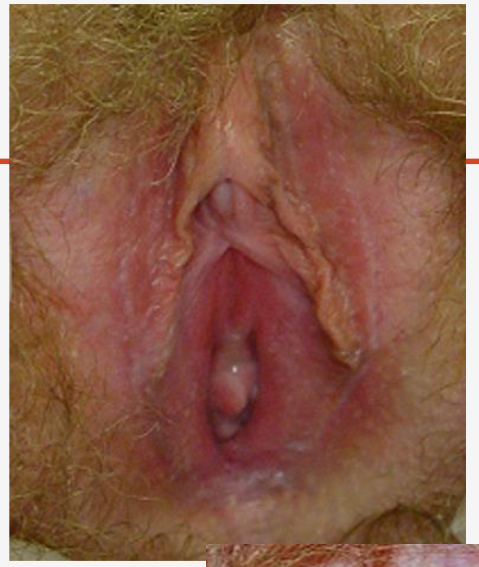
P53 mutation

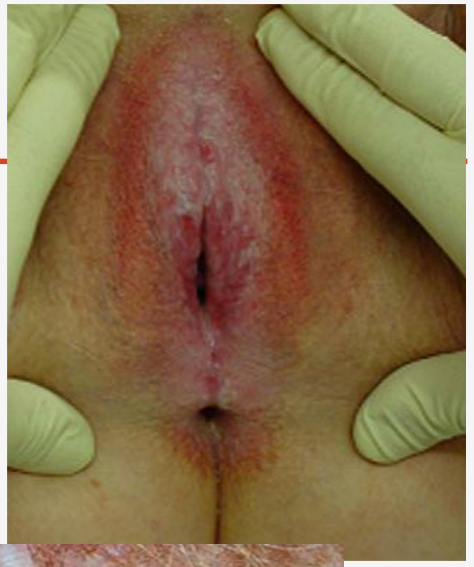
Clinical characteristics-LS

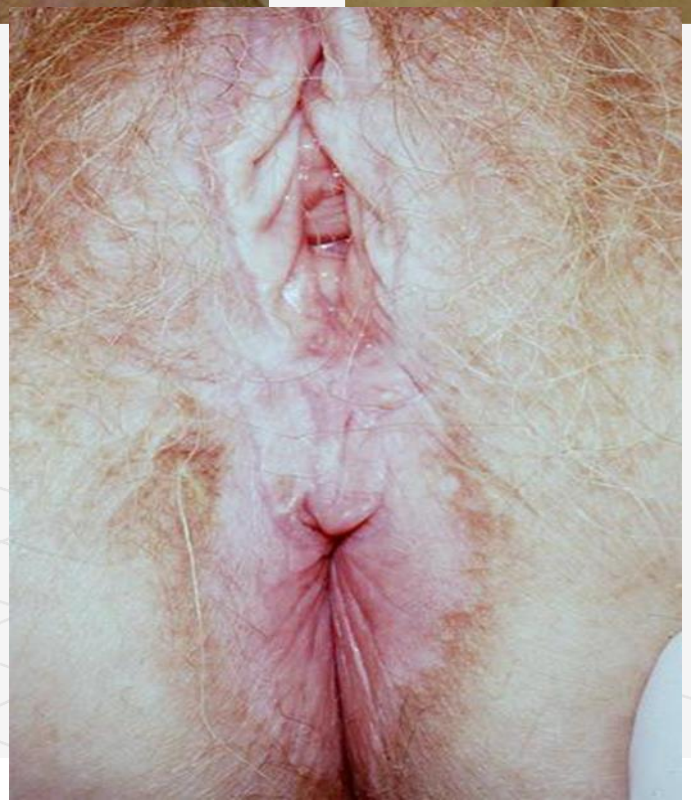
- **Relapse and remission**
- **Poor correlation between extent and sx**
- Itching, pain, dyspareunia, urinary sx, irritation, constipation, bleeding
- Asymptomatic 30%

Clinical characteristics-LS

- Variable signs
- **Wrinkled skin and textural change**, pallor, atrophy +++
  - Erythema, purpura, sclerosis, hyperkeratosis, erosions,
- **Figure of 8**
- **Labia minora and majora** +++, vagina usually spared
- Young: confused with sexual abuse
- Associated extragenital 10-20%, asymptomatic+++
- Severe complicated cases:
  - **scarring, loss of architecture**
  - 2ry infection
  - Adhesions, narrowing introitus, urethra
  - Clitoral pseudocyst







Complications-LS

Severe complicated cases

- **scarring, loss of architecture**
- 2ry infection
- Adhesions, narrowing introitus, urethra
- Clitoral pseudocyst

Sexual dysfunction

Urinary dysfunction

Dysesthesia

Loss of self-esteem

Malignant potential-LS

Majority of SCC has LS (30-60%), squamous cell hyperplasia, dVIN

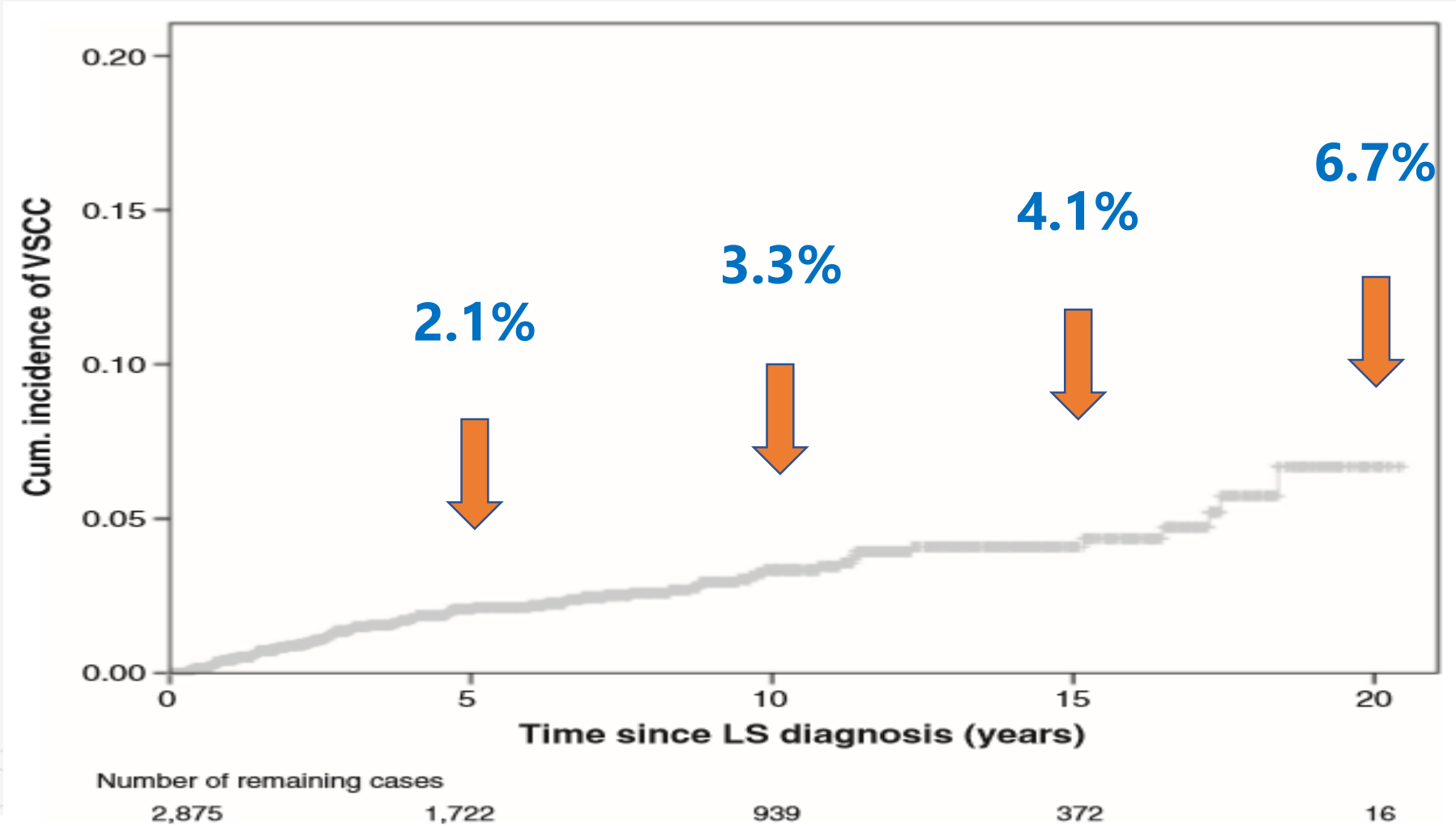
SCC 2-6%

- 976 women, 1% at 2 year FU to nearly 37% at 25 year (Micheletti 2016)
- 2875 women, 2.1% at 5 y, 3.3% at 10, 4.1% at 15, 6.7% at 20 (Bleeker 2016)

- **Protective effect from sx control?:**
  - 507 trt corticosteroid, mean 4.7 y: VSSC none in compliant vs 4.7% in non-compliant ($p<0.001$)
- Sx, duration, loss of architecture: not a useful indicator of malignant potential
- Itch-scratch damage?
- Immunogenetic profile?
- P53?

Malignant potential-LS

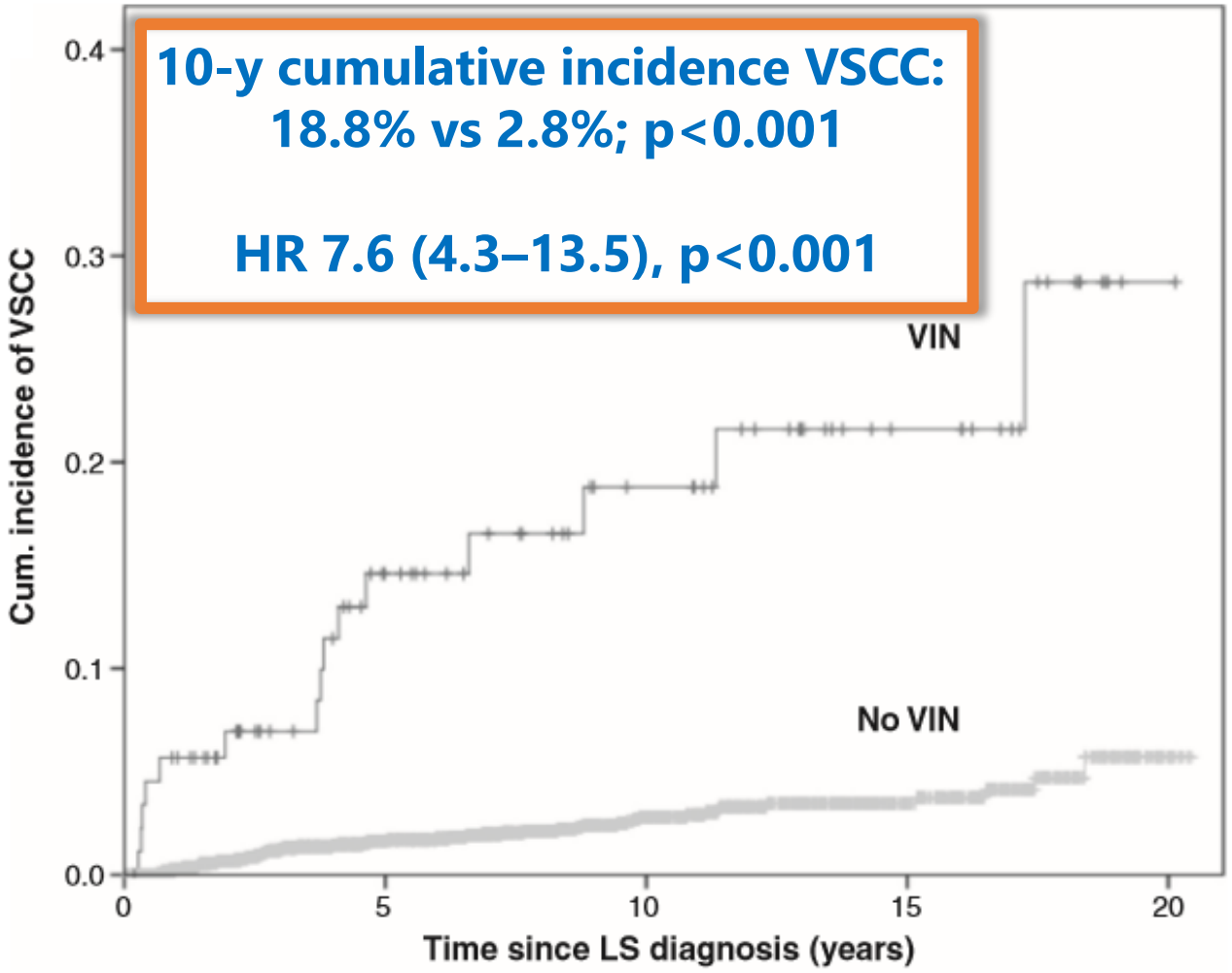
- 2875 women, (Bleeker 2016)



Malignant potential-LS

10-y cumulative incidence VSCC: 18.8% vs 2.8%; p<0.001

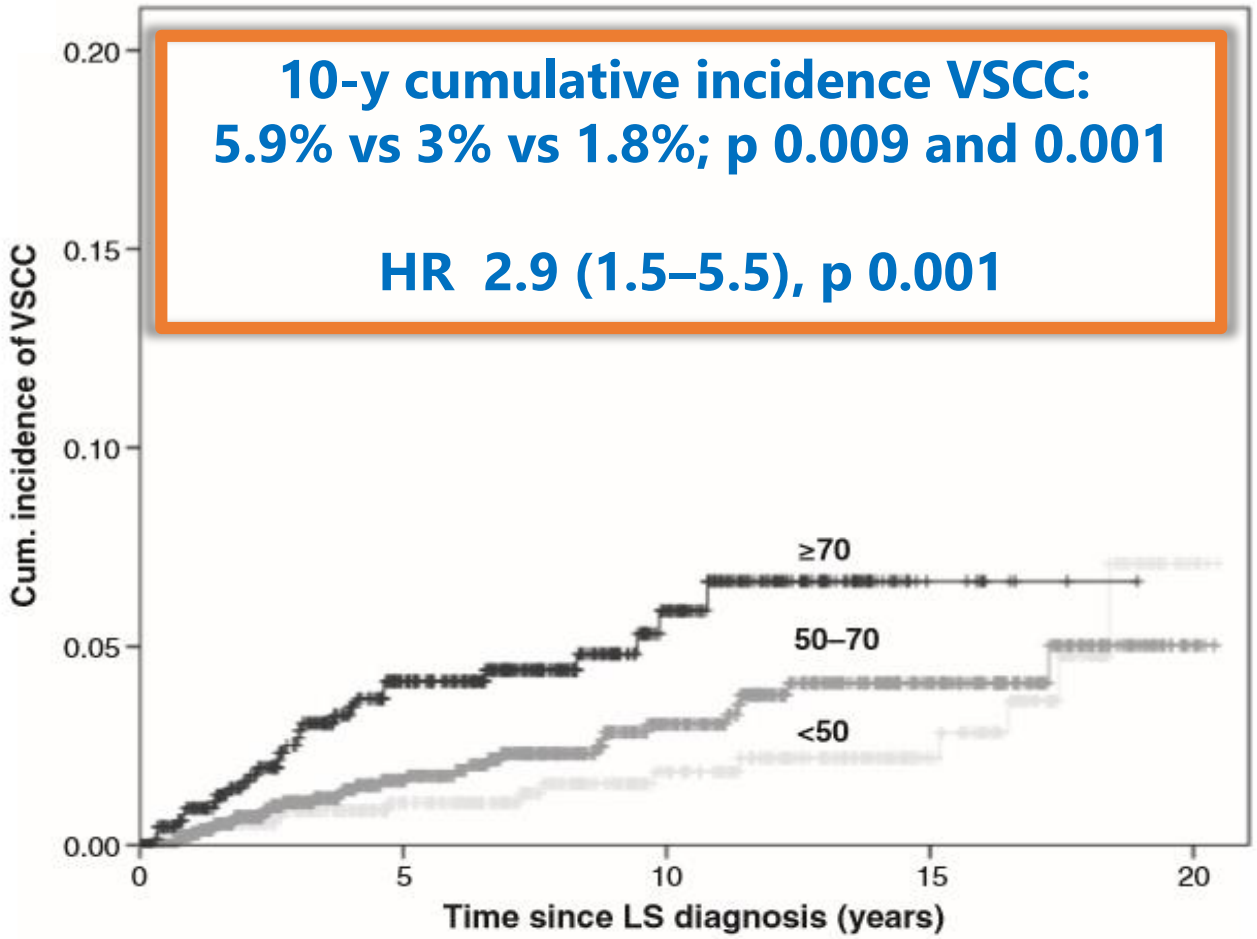
HR 7.6 (4.3–13.5), p<0.001



Number of remaining cases					
No VIN	2,786	1,672	906	358	15
VIN	89	50	33	17	1

10-y cumulative incidence VSCC: 5.9% vs 3% vs 1.8%; p 0.009 and 0.001

HR 2.9 (1.5–5.5), p 0.001



Number of remaining cases Age group (years)					
<50	766	509	323	157	6
50–70	1,431	802	458	205	10
≥70	678	414	158	13	0

THANK YOU