

Carcinomas escamosos de vulva y vagina. Relación con HPV



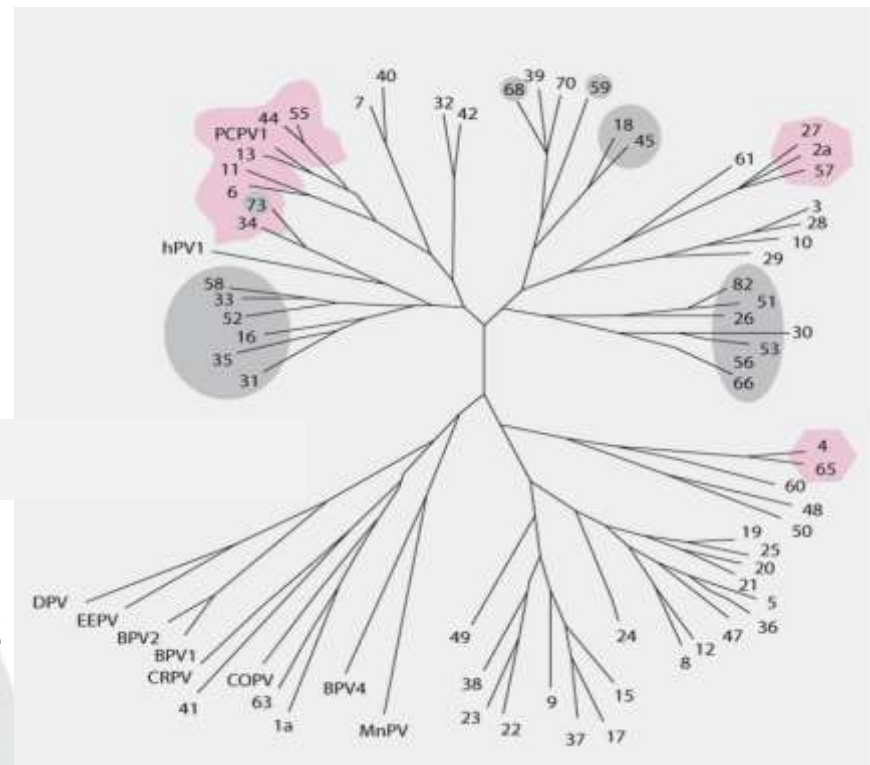
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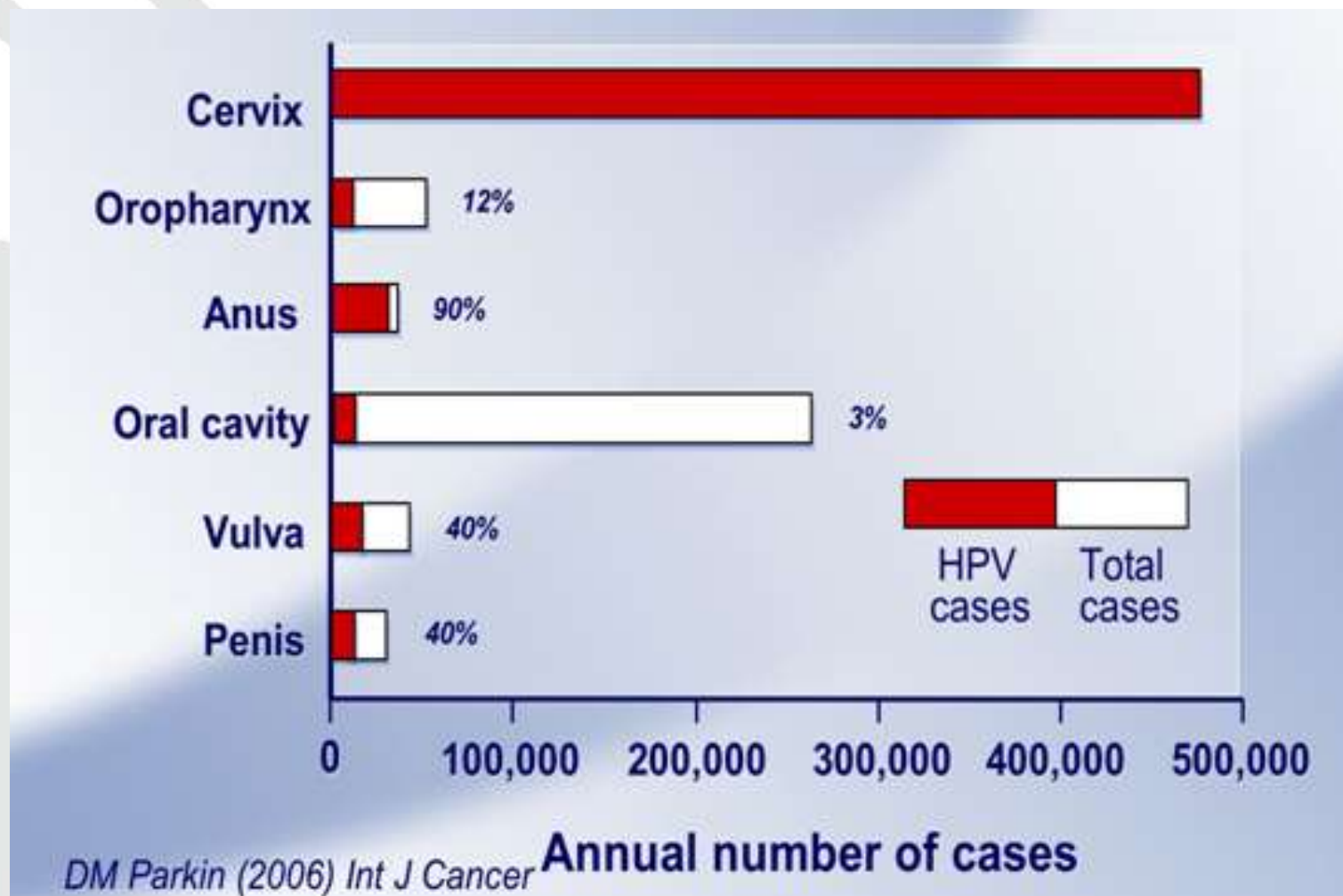
Carcinoma de cérvix y VPH

- International Biological Study on Cervical Cancer:
 - >1000 carcinomas de 22 países utilizando PCR: 99.7% HPV (Bosch et al, *J Natl Cancer Inst* 1995; 87:796) (Wallboomers et al, *J Pathol* 1999; 189:12)
 - HPV 16 el tipo más prevalente en casi todos los países

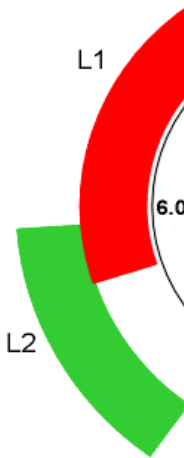


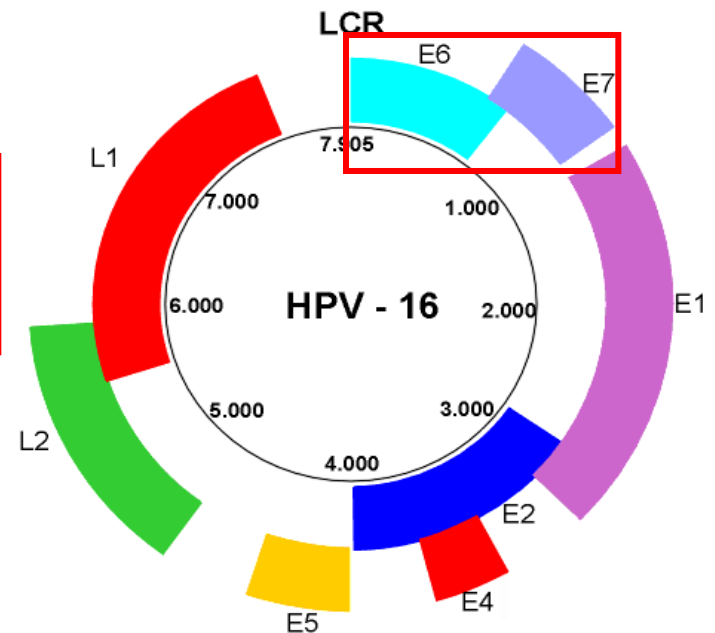


HPV and cancer



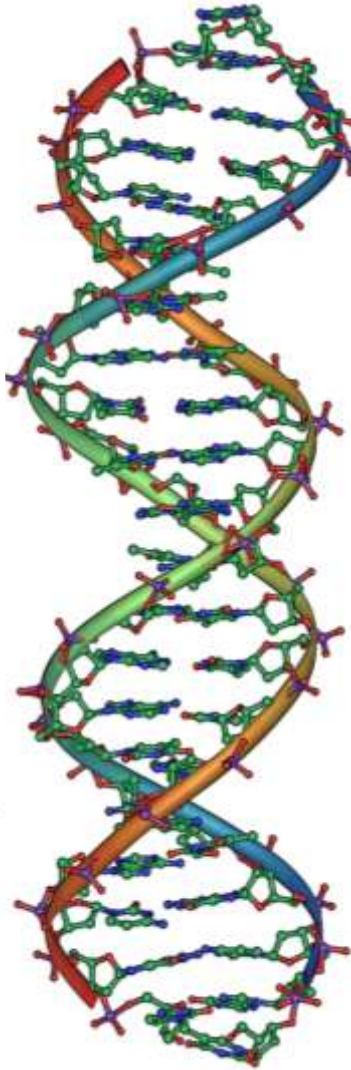
HPV genome

- Double strand DNA (≈ 8.000 base pairs)
 - Regulatory region (LCR)
 - Early region
 - E1 - E8 genes (DNA replication)
 - **E6 and E7 involved in neoplastic transformation**
 - Late region
 - Genes L1 and L2 (Capsid)
- 
- A circular diagram of the SV40 genome. The circle is divided into two main colored segments: a red segment labeled 'L1' and a green segment labeled 'L2'. The red segment represents the Early region, and the green segment represents the Late region. A scale of '6.0' is indicated on the right side of the circle.

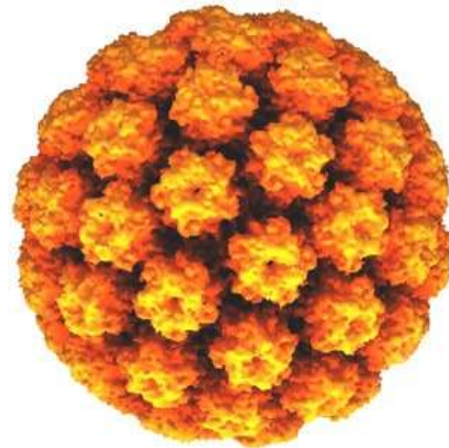




HPV: Mechanisms of transformation

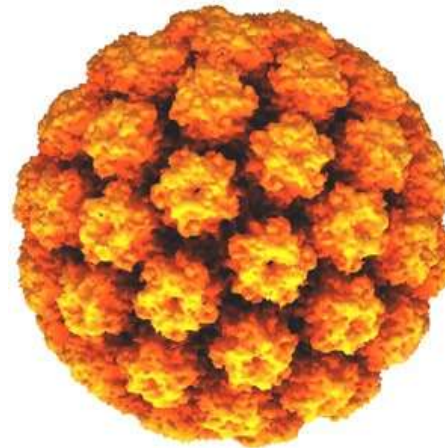
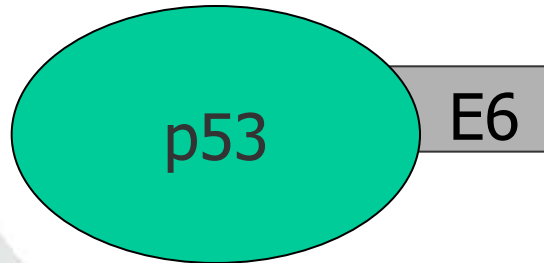
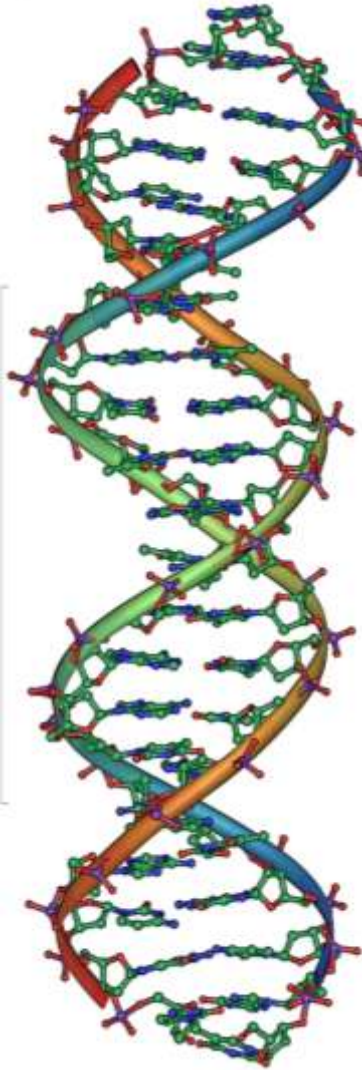


p53

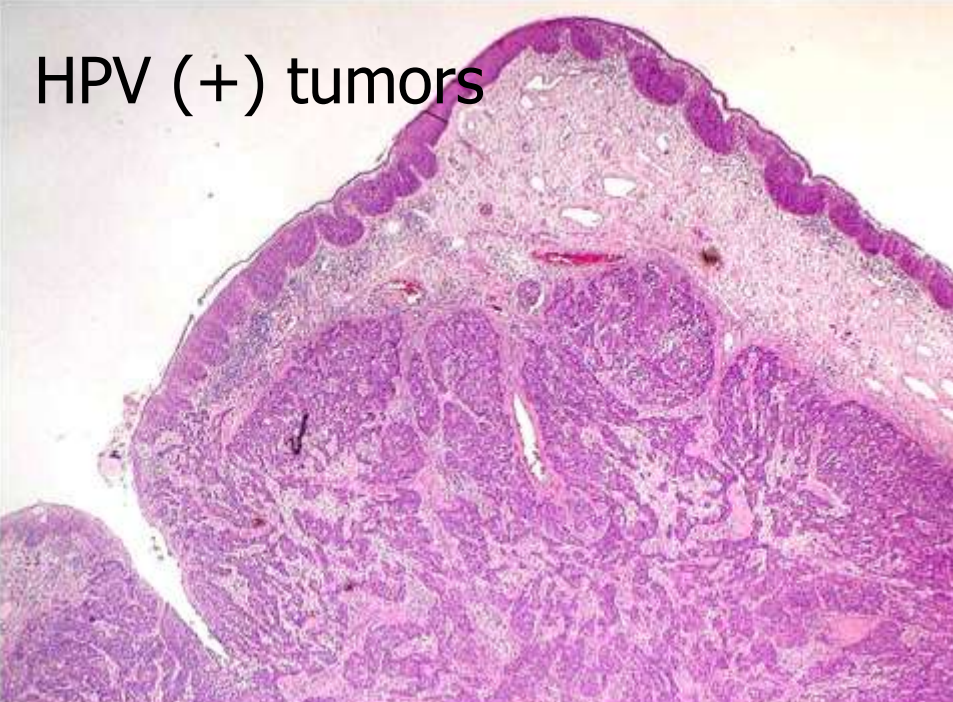




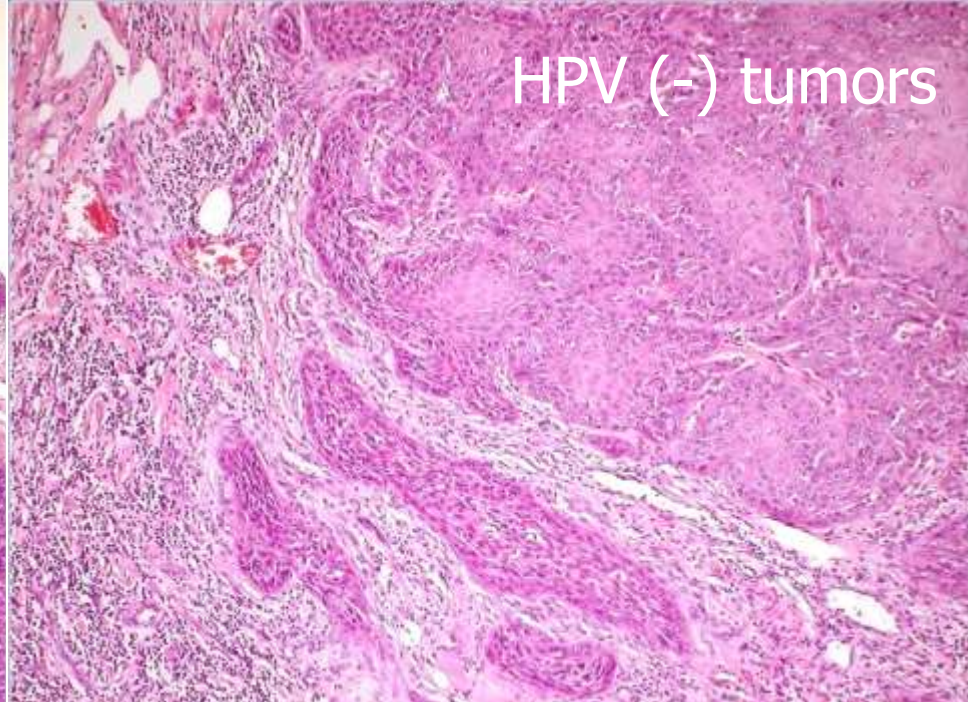
HPV: Mechanisms of transformation



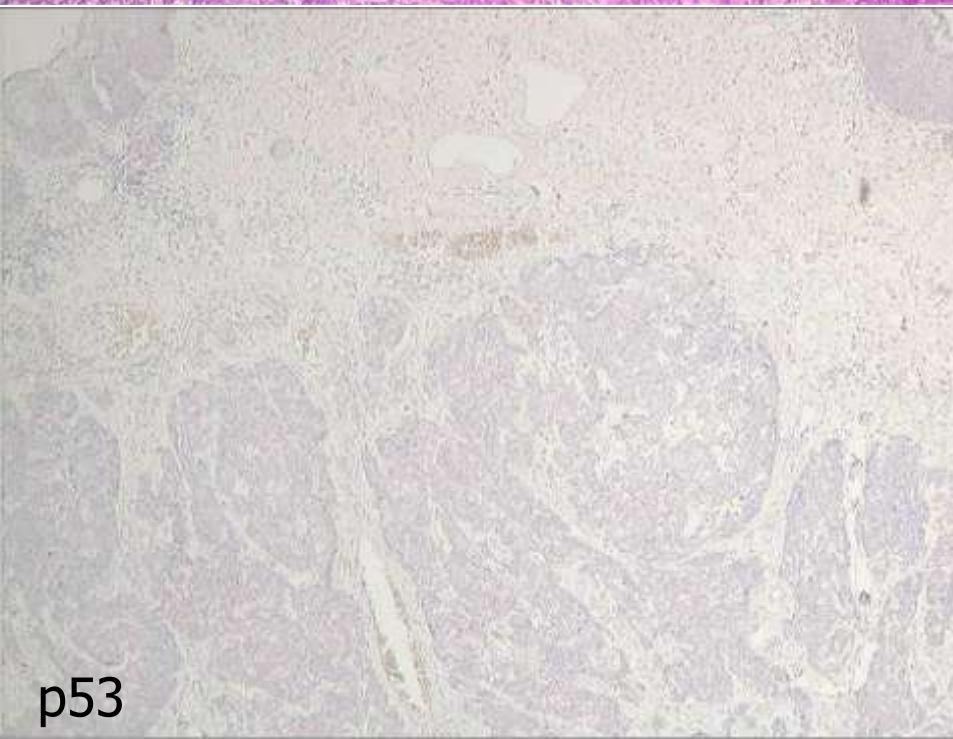
HPV (+) tumors



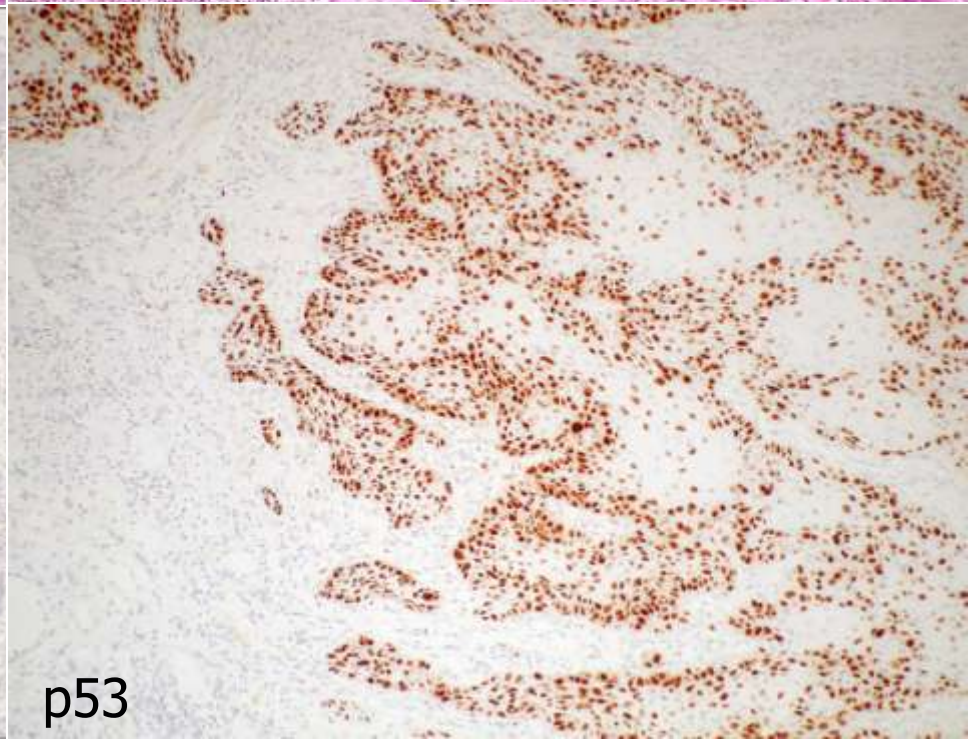
HPV (-) tumors



p53

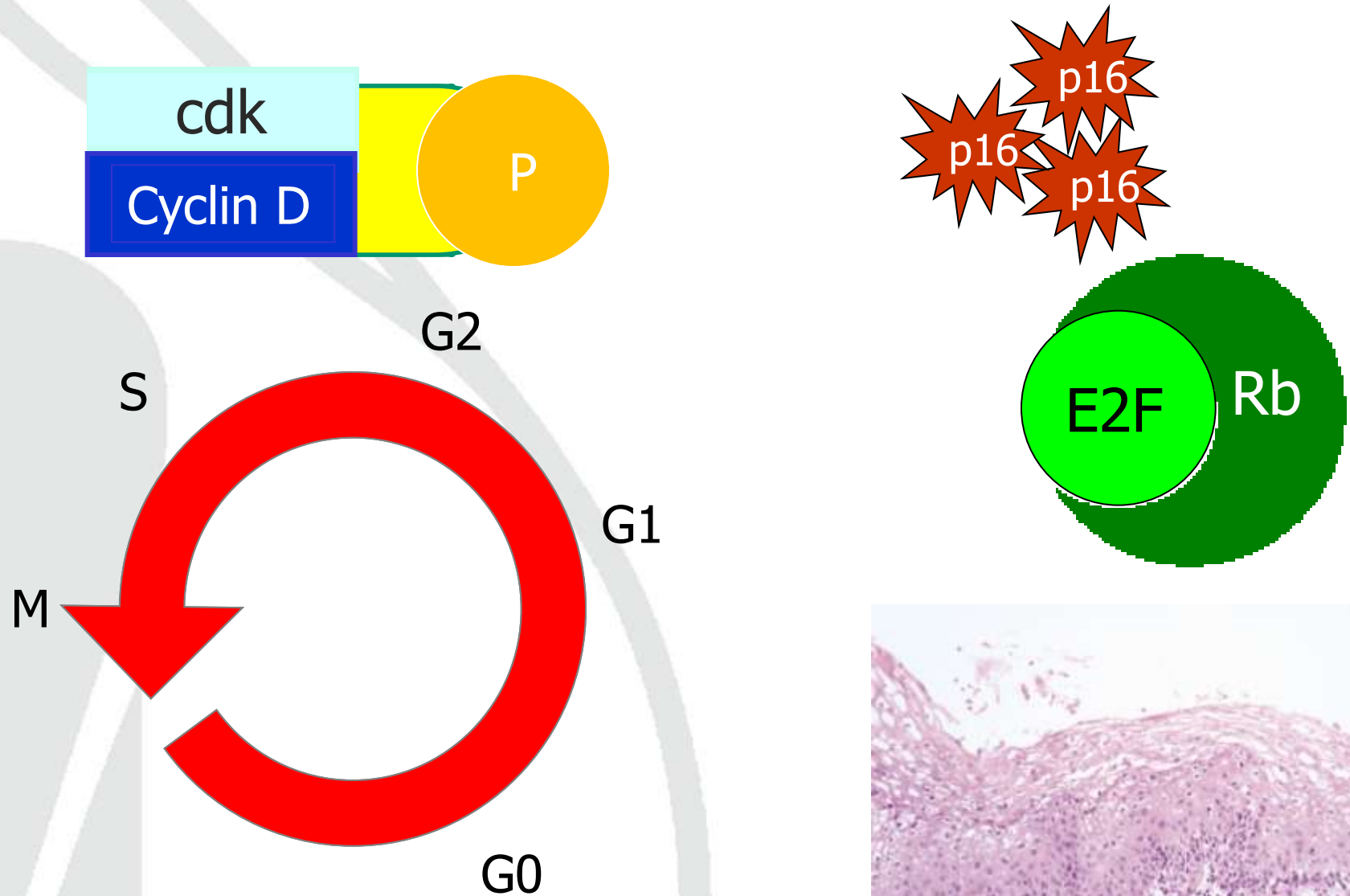


p53



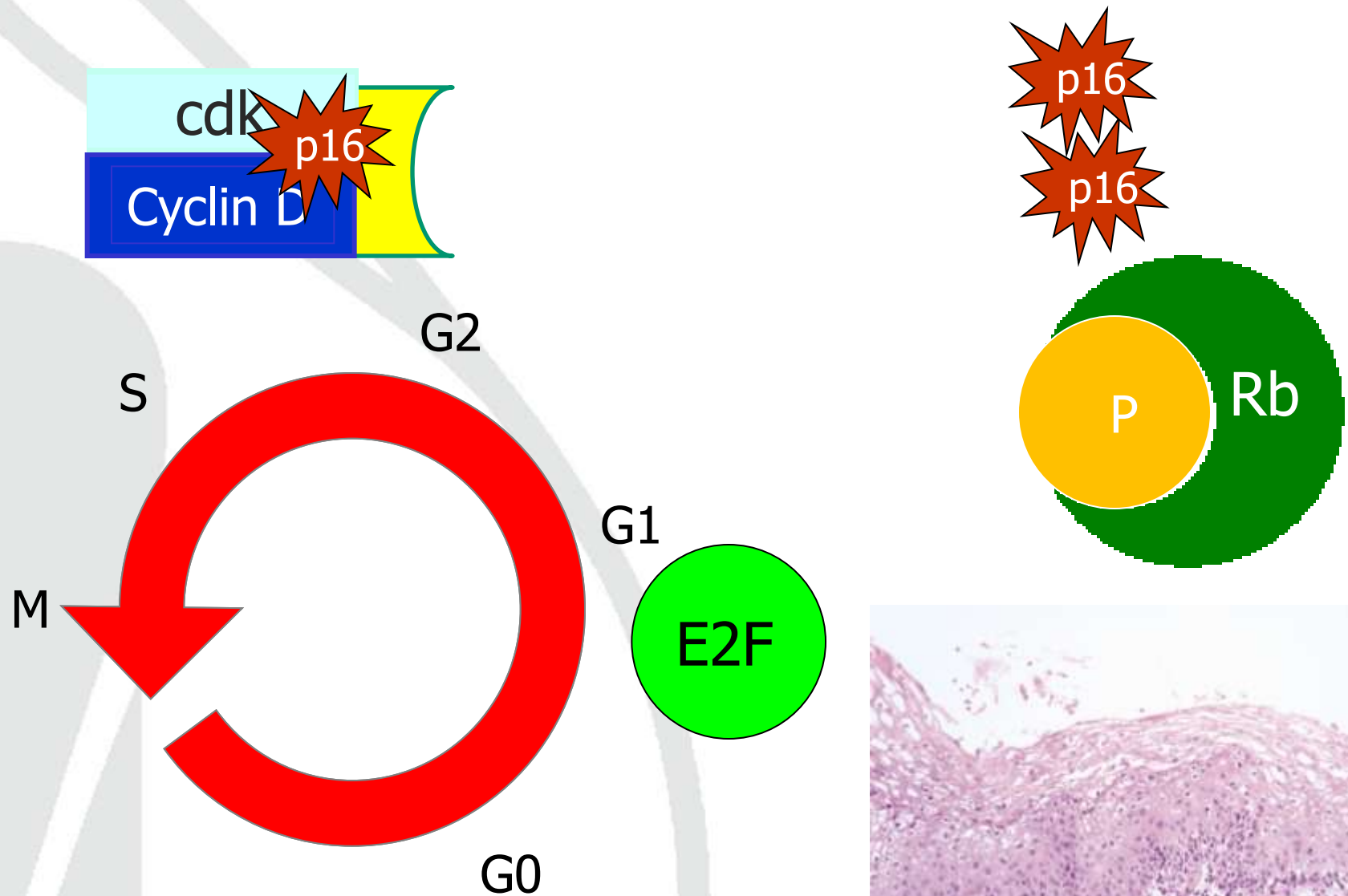


HPV: Mechanisms of transformation



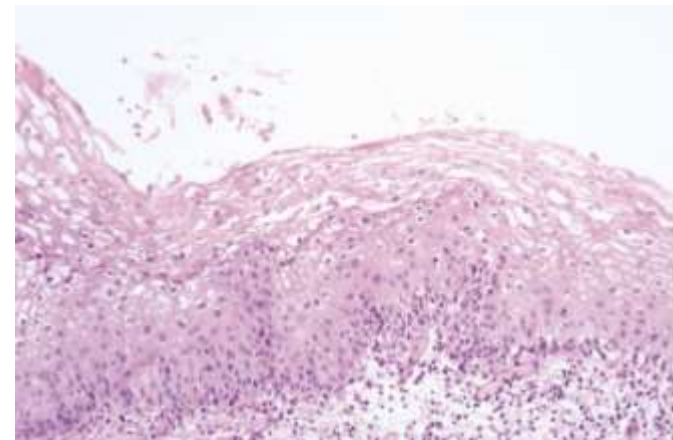
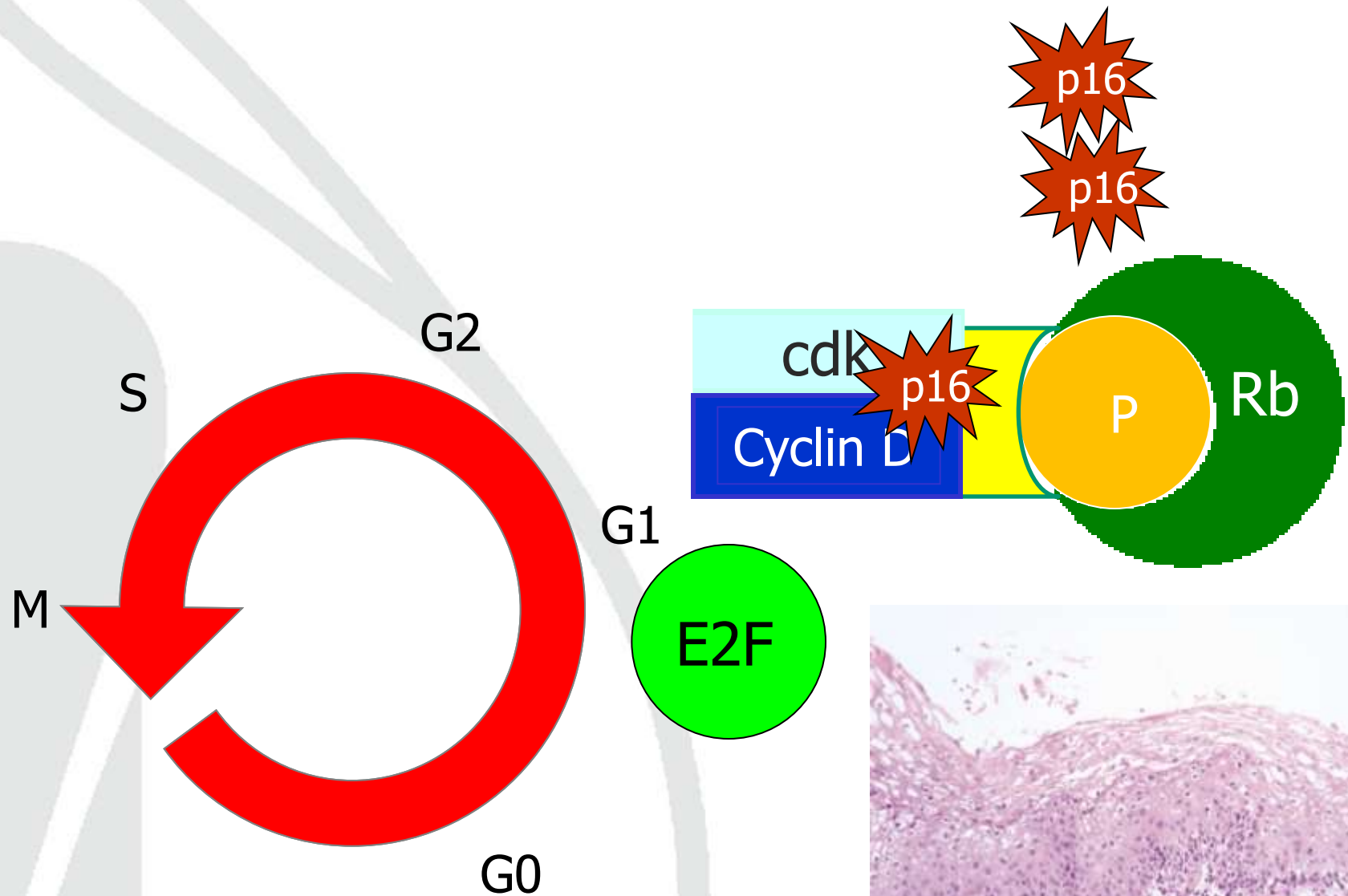


HPV: Mechanisms of transformation



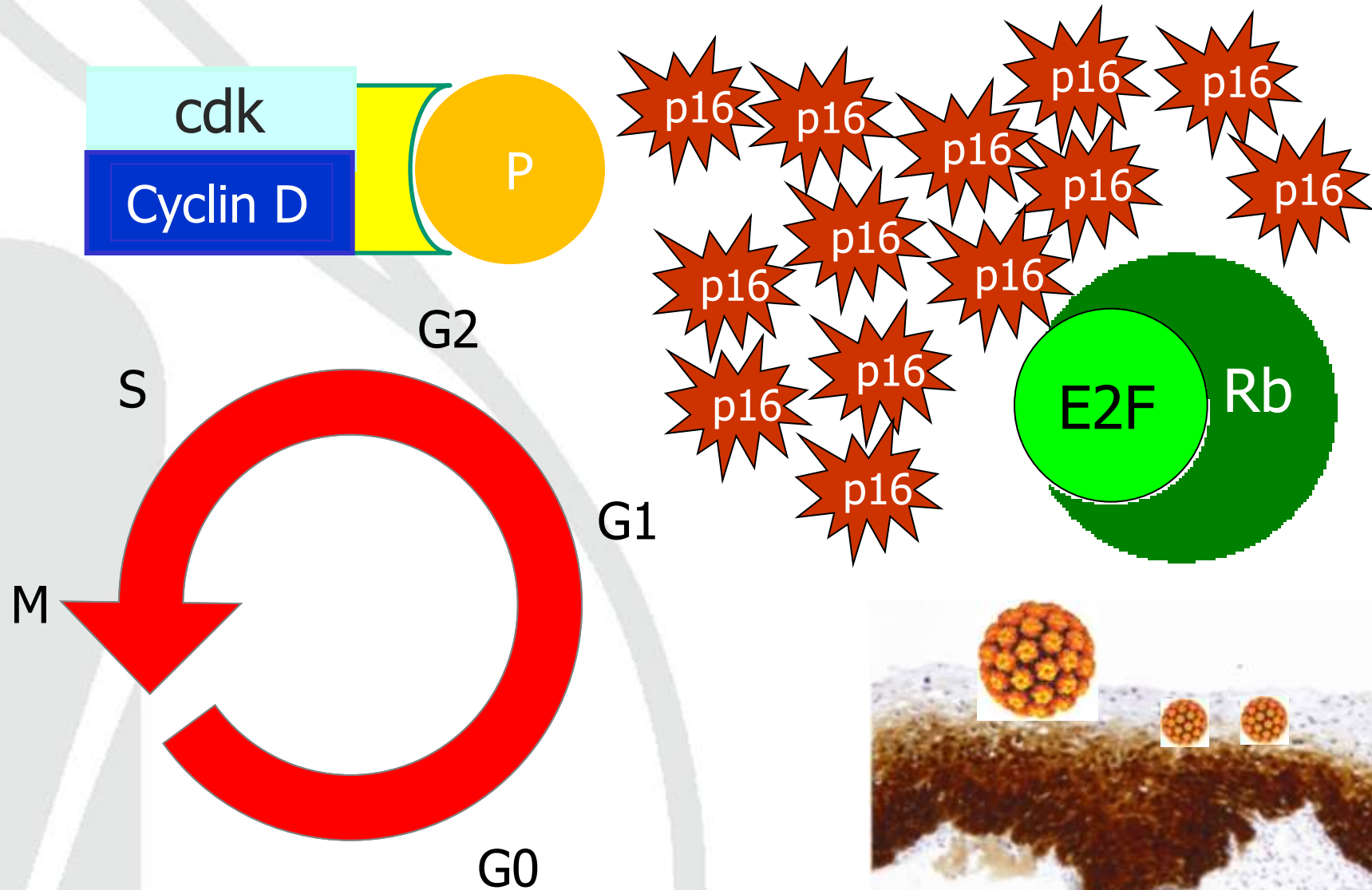


HPV: Mechanisms of transformation

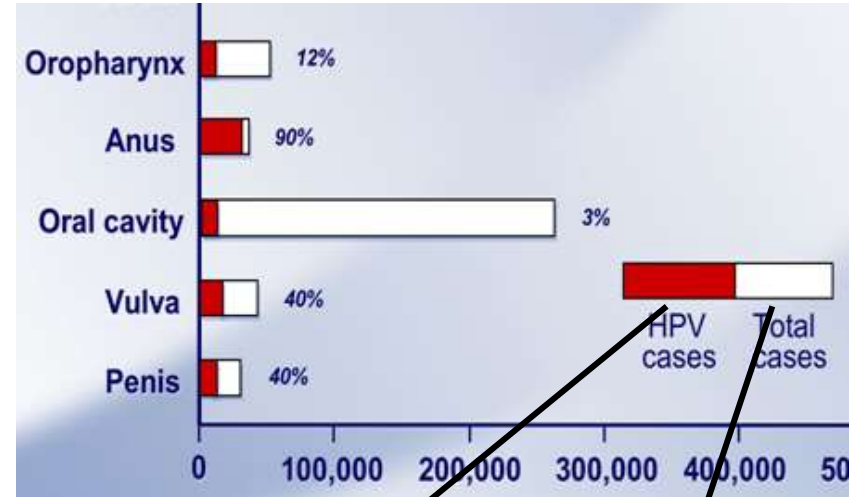




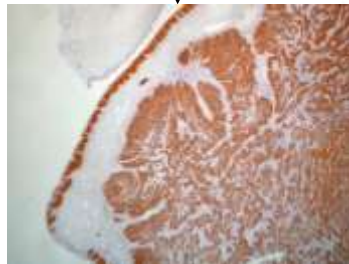
HPV: Mechanisms of transformation



p16^{INK4a} and p53 in SCC



P16 (+)



P53 (-)



P16 (+)

P53 (-)

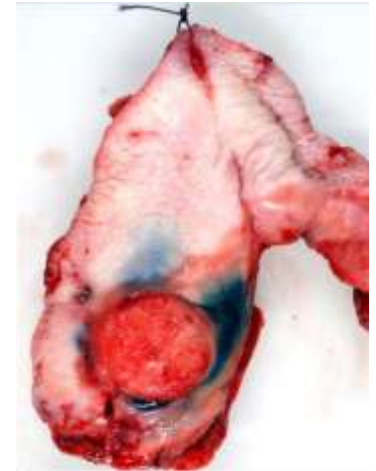
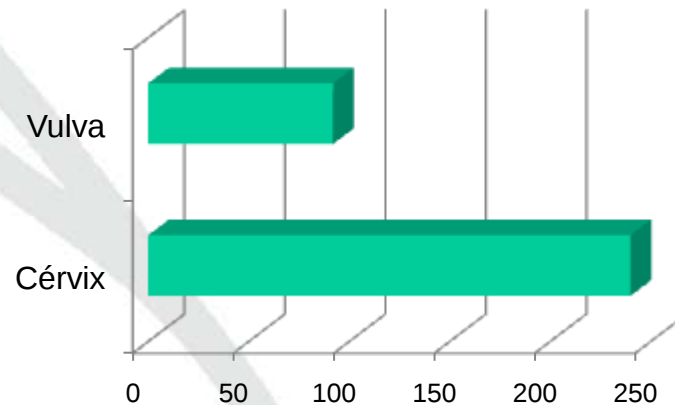
P16 (-)

P53 (+)



Carcinomas of the Vulva

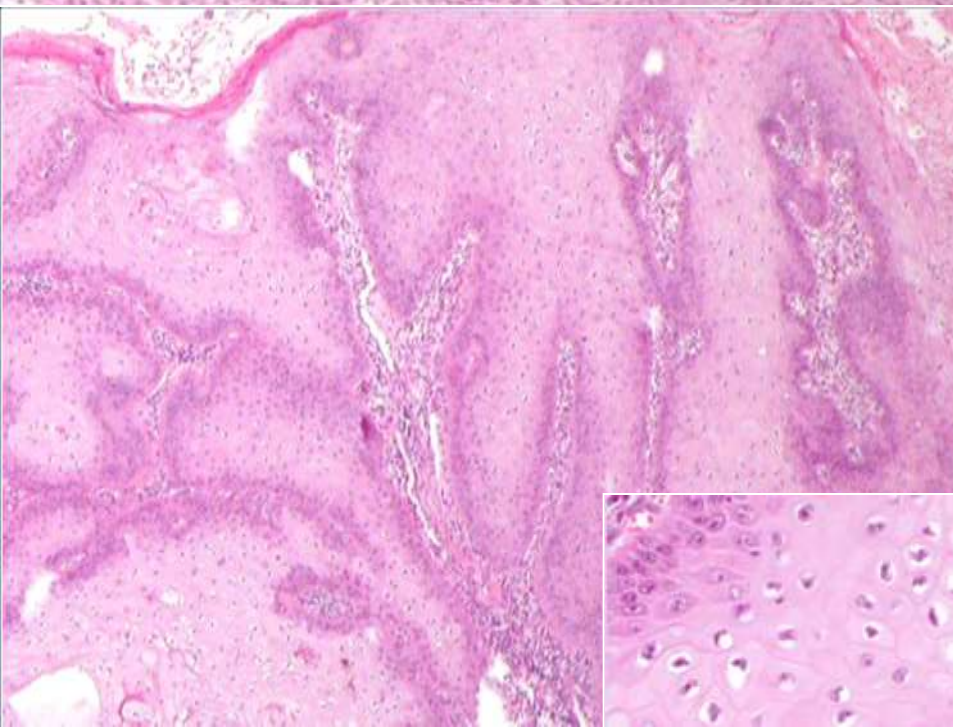
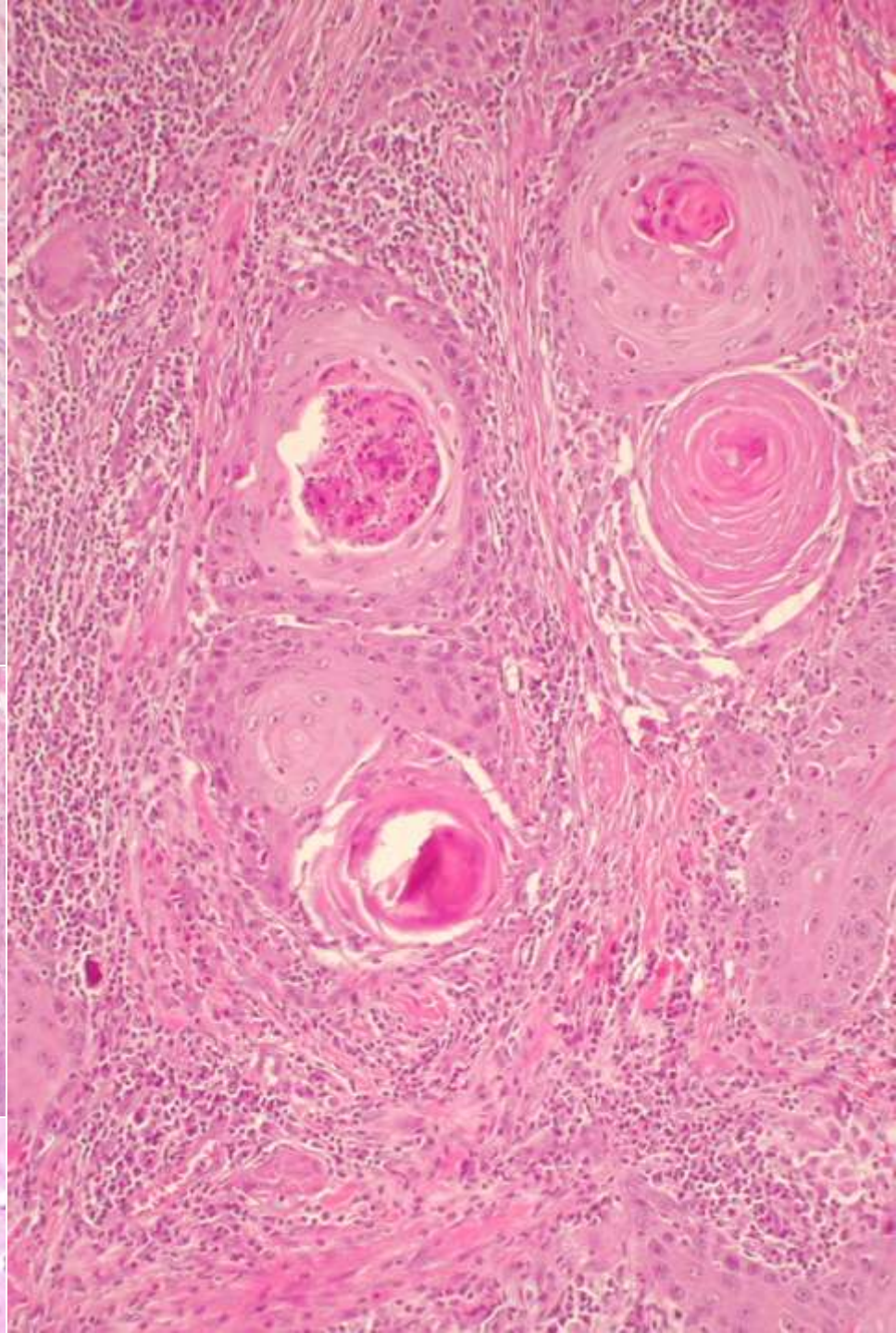
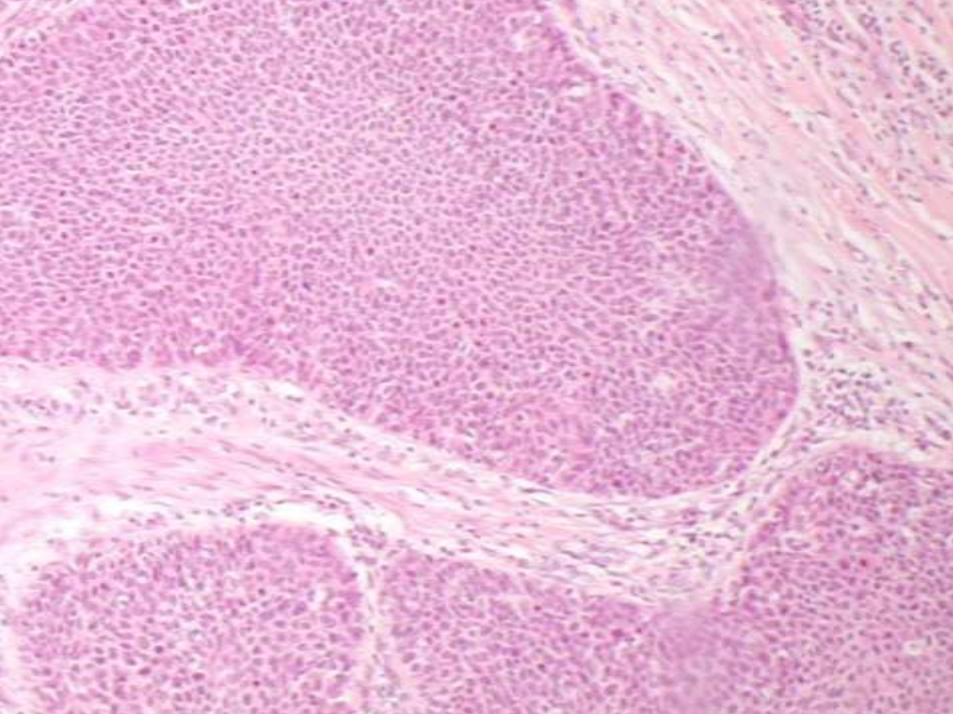
- Low frequency (4% GYN neoplasms)



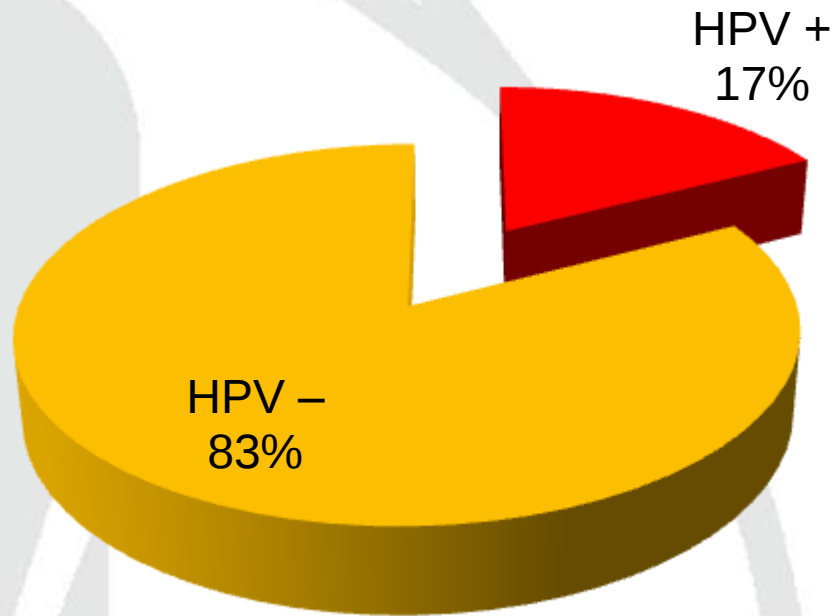
- Squamous cell carcinoma (SCC) >95%
- Two different etiopathogenic types
 - HPV negative
 - HPV positive

SCCs of the vulva (vSCCs)

	HPV-positive	HPV-negative
Frequency	1/3	2/3
Age	Young	Old
Skin lesions	No	Lichen sclerosis Squamous cell hyperplasia
Histolog. type	Basaloid/warty	Keratinizing
VIN	Basaloid/warty	Differentiated
Molecular changes	Inactivation of p53 & Rb by products of HPV	Mutations of p53



SCCs of the Vulva: HPV



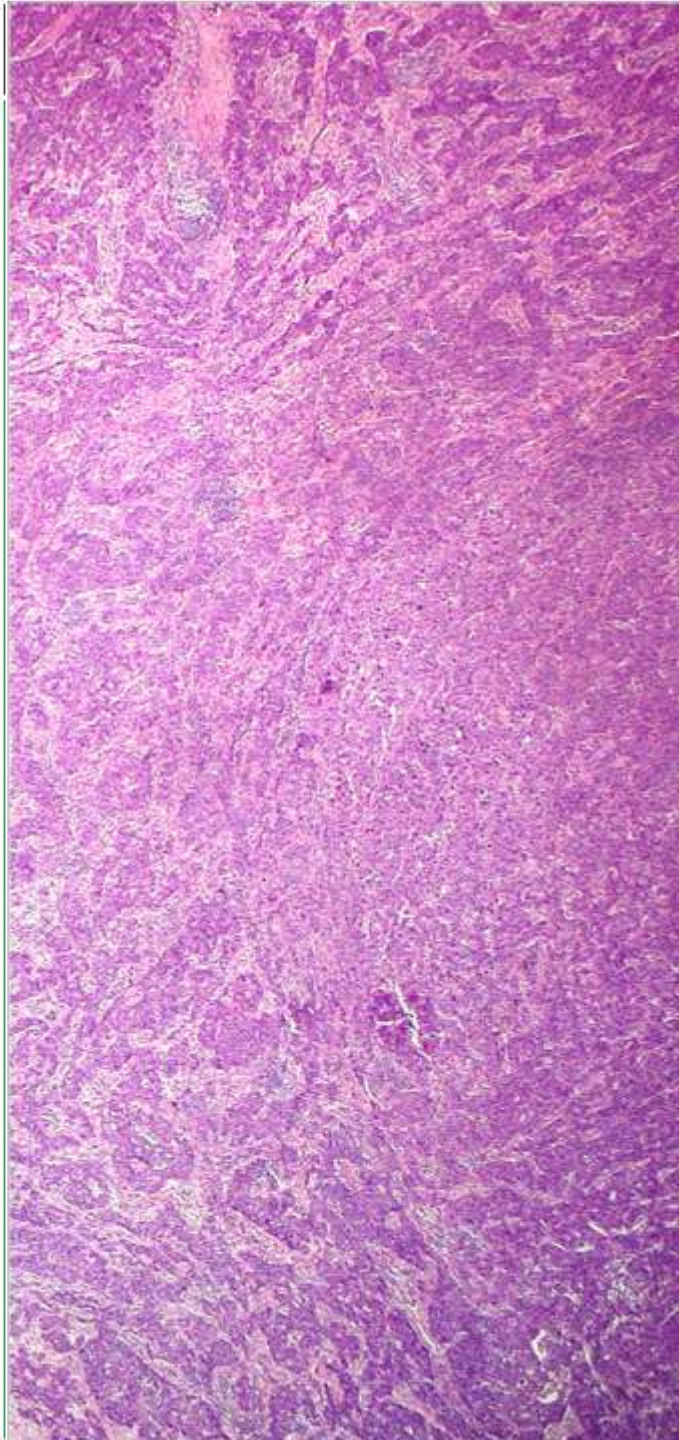
Case number	HPV
C14	33
C23	16
C32	33
C46	16
C62	16
C75	16
C76	16
C22	51
C49	16
C83	31
C33	16
C34	6 and 16
C35	16
C36	6 and 16
C56	16
C84	16

Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347

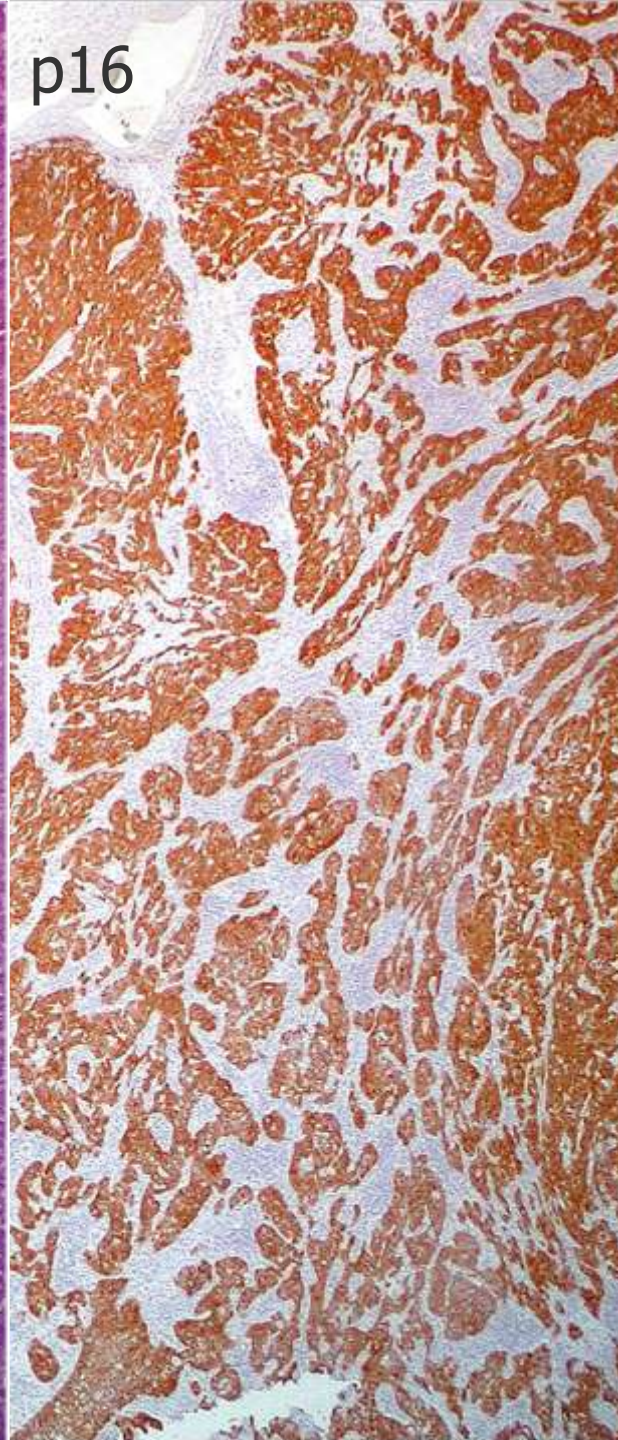
vSCCs: p16^{INK4a}, p53

		High-risk human papillomavirus				
		Positive(n=16)		Negative (n=76)		p value
IHC						
	p16 +	16	(100.0 %)	1	(1.3 %)	<0.000001
	p53 +	1	(6.2 %)	49	(64.5 %)	0.00007

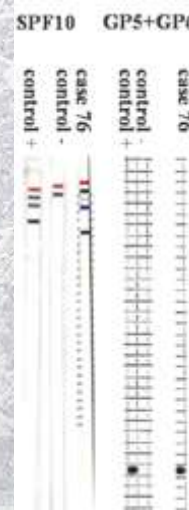
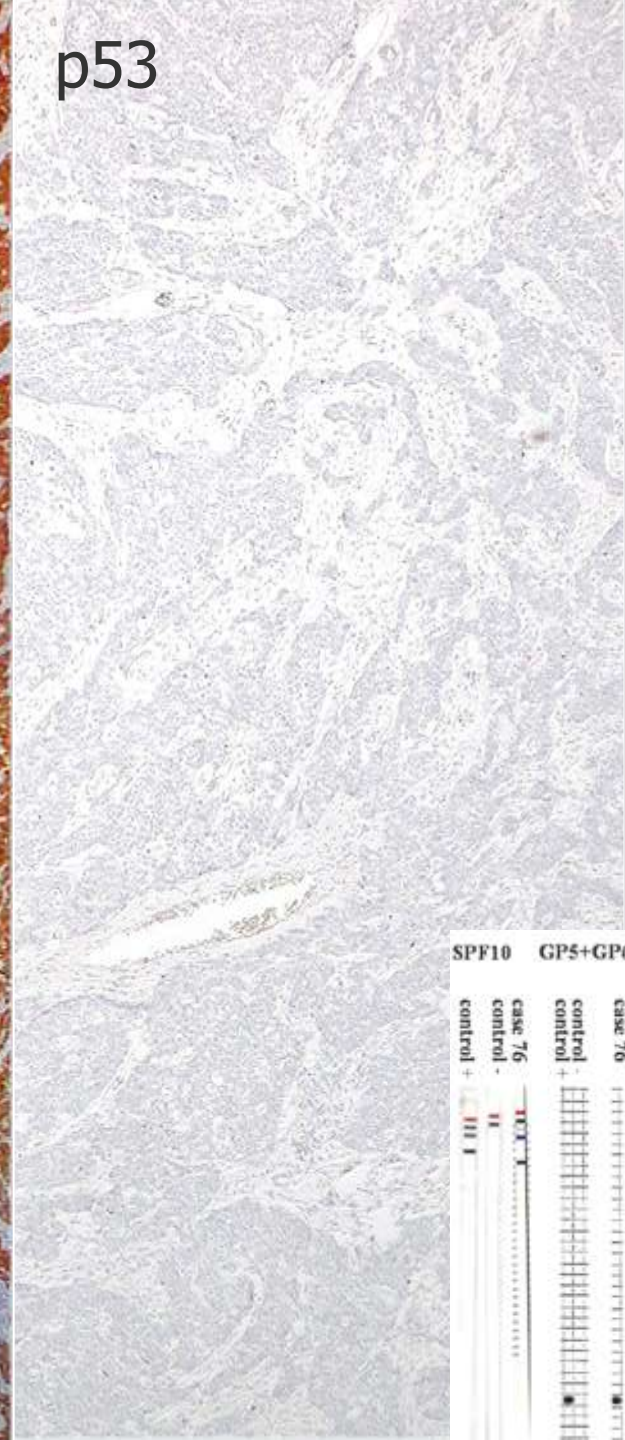
Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347-1356

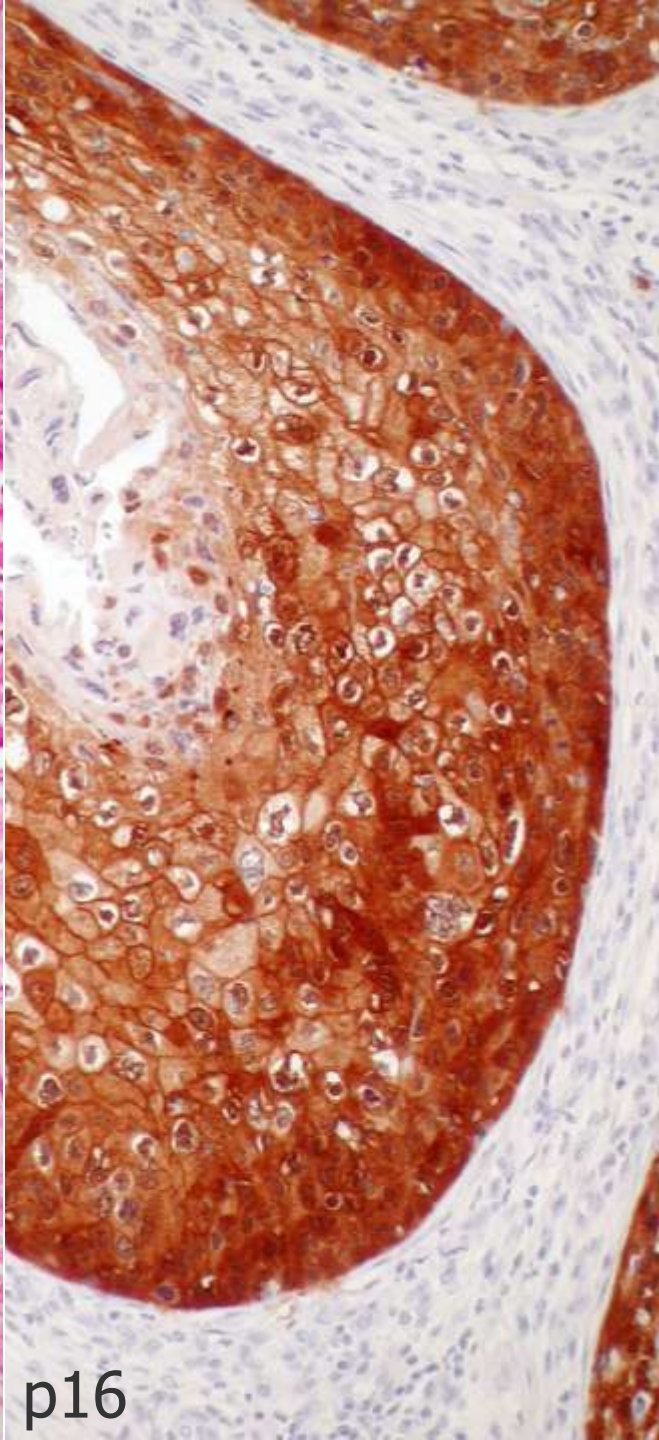
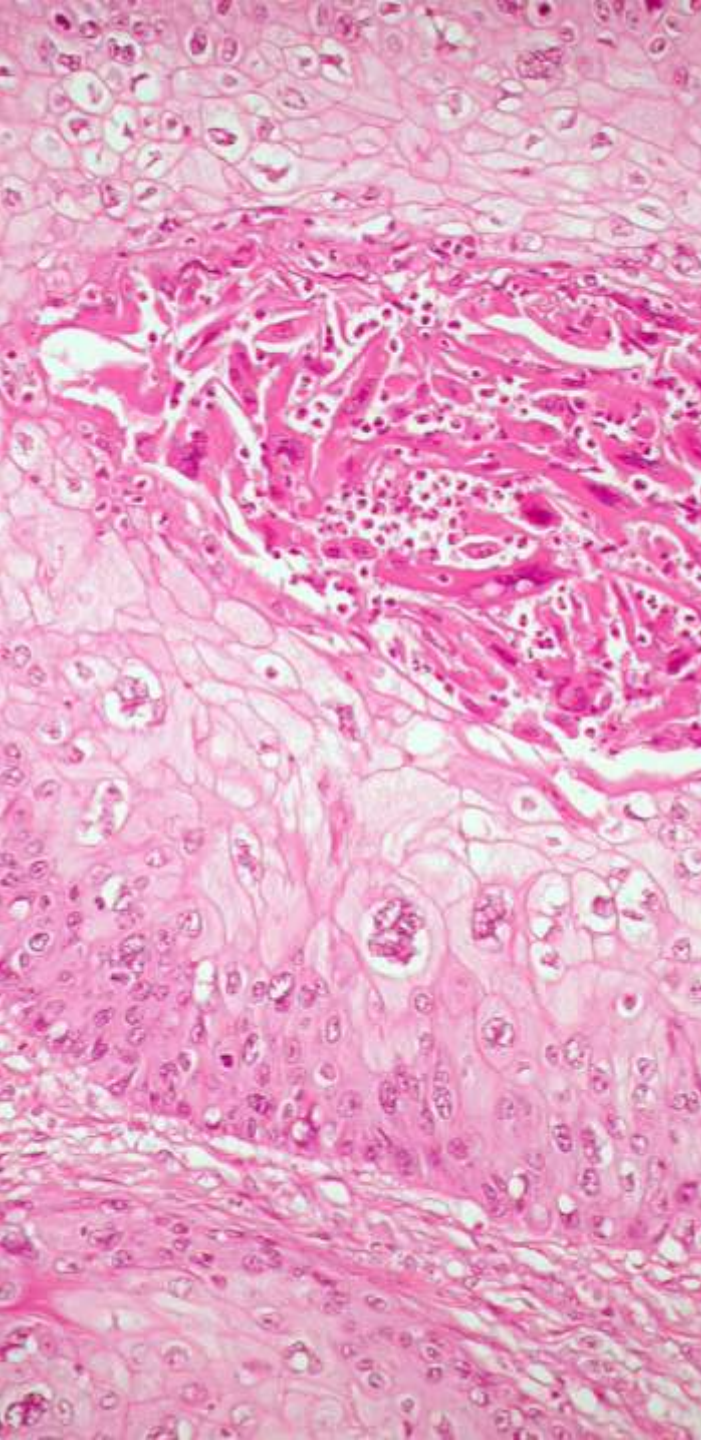


p16



p53

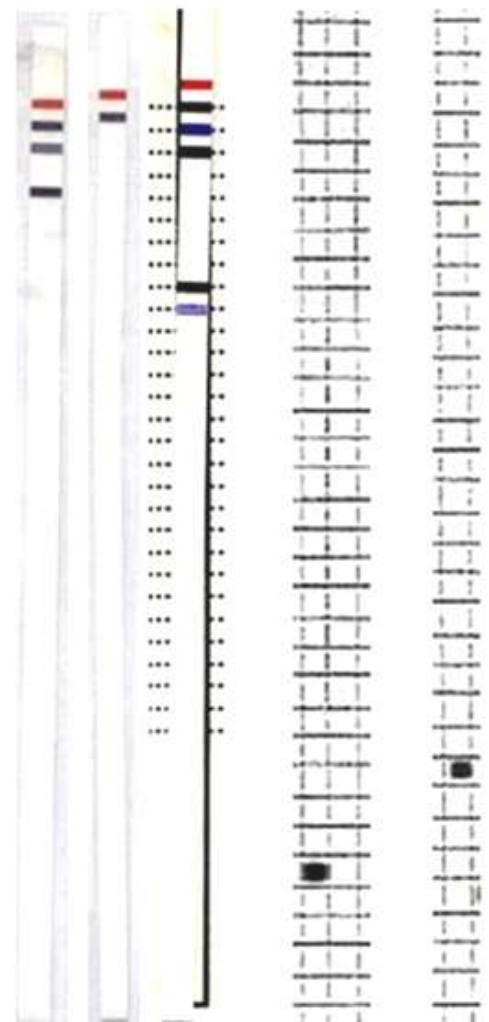


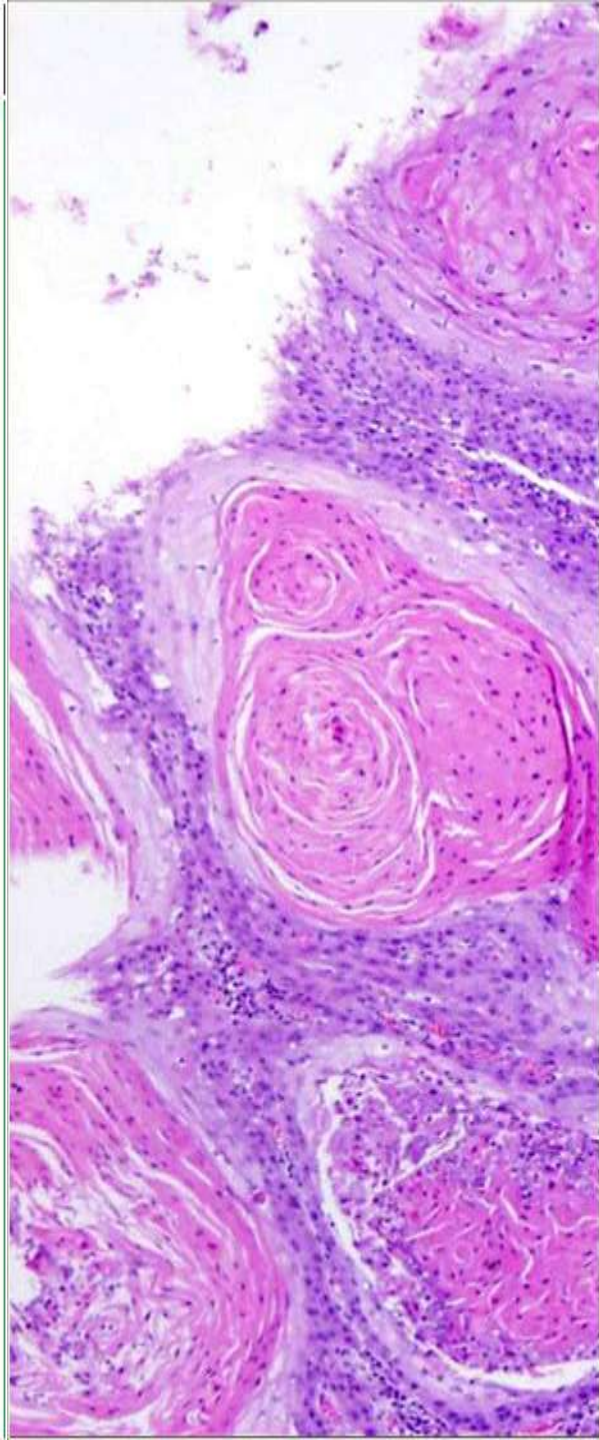


p16

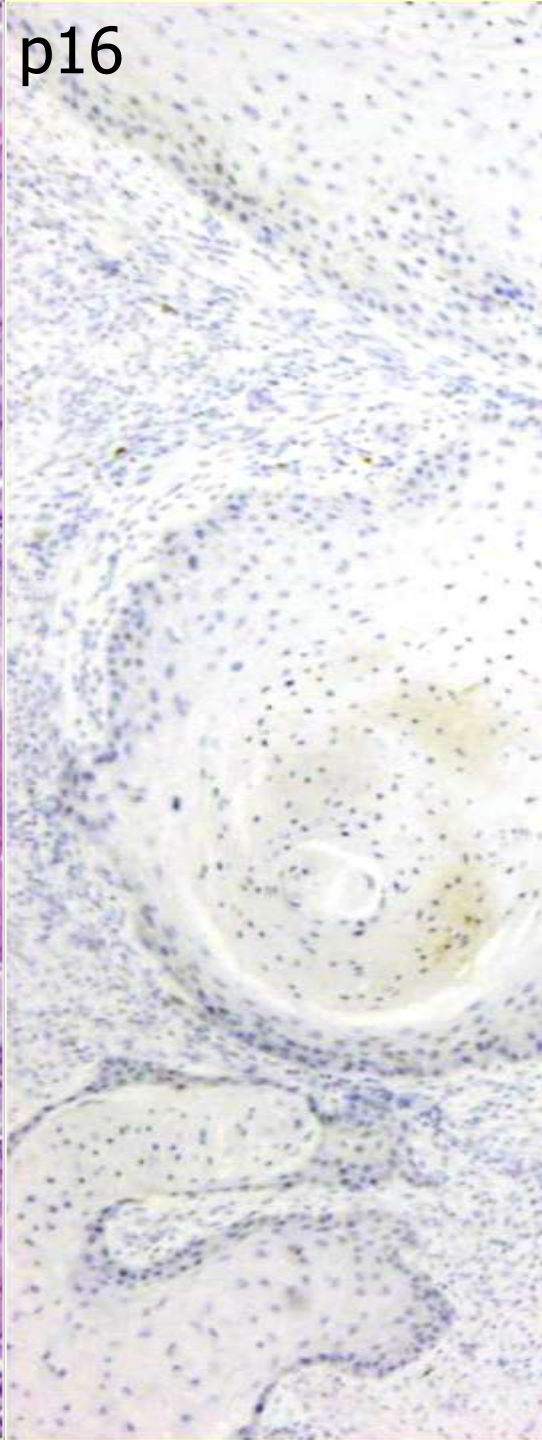
SPF10 GP5+GP6+

case 83
control -
control +
case 83
control -
control +

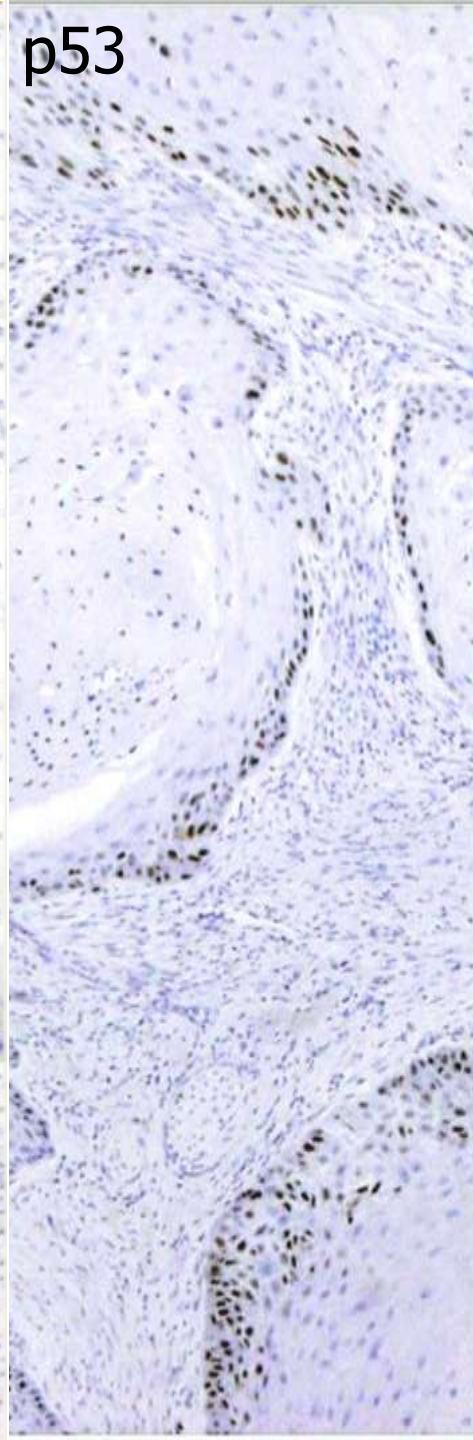




p16



p53



SPF10

control +

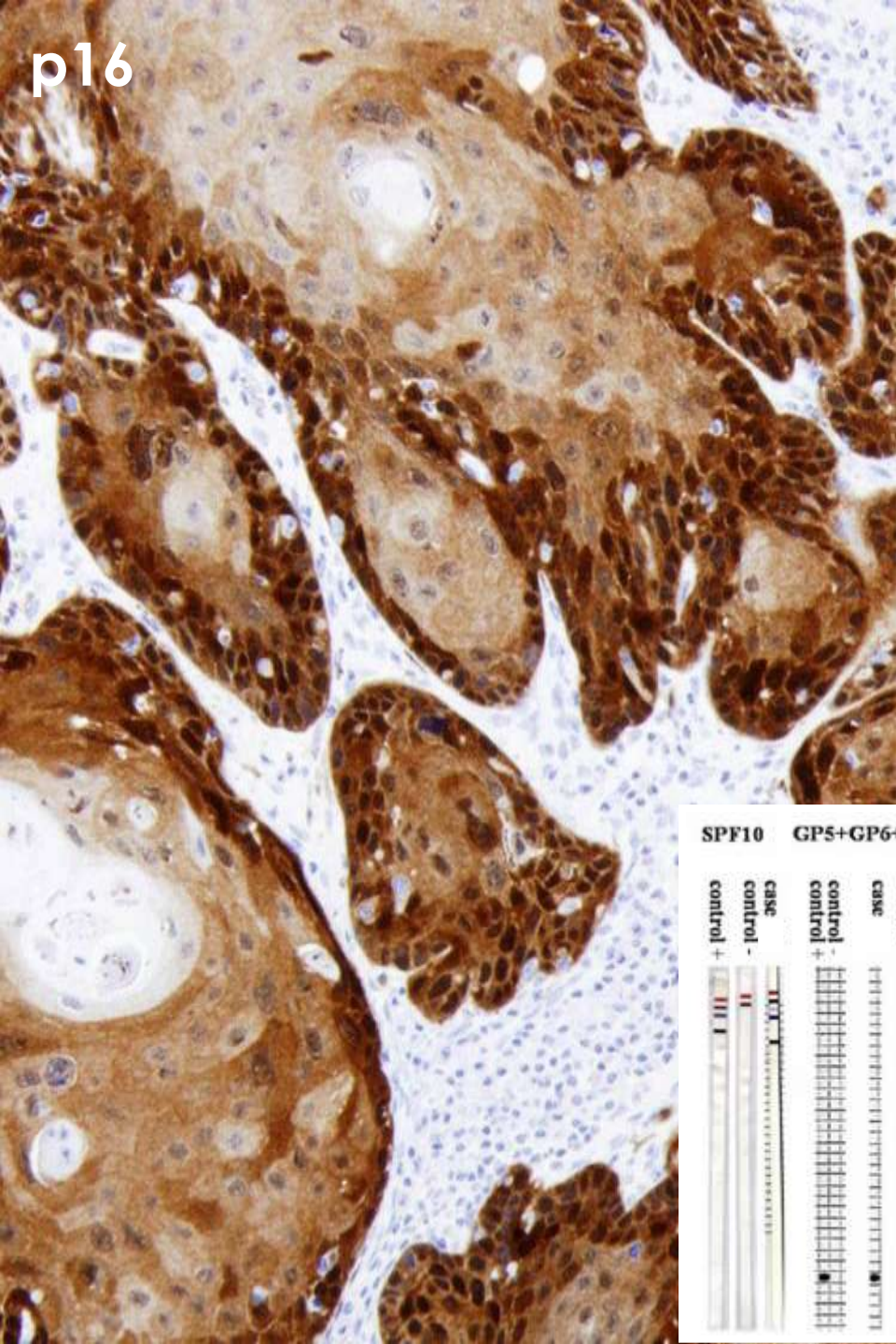
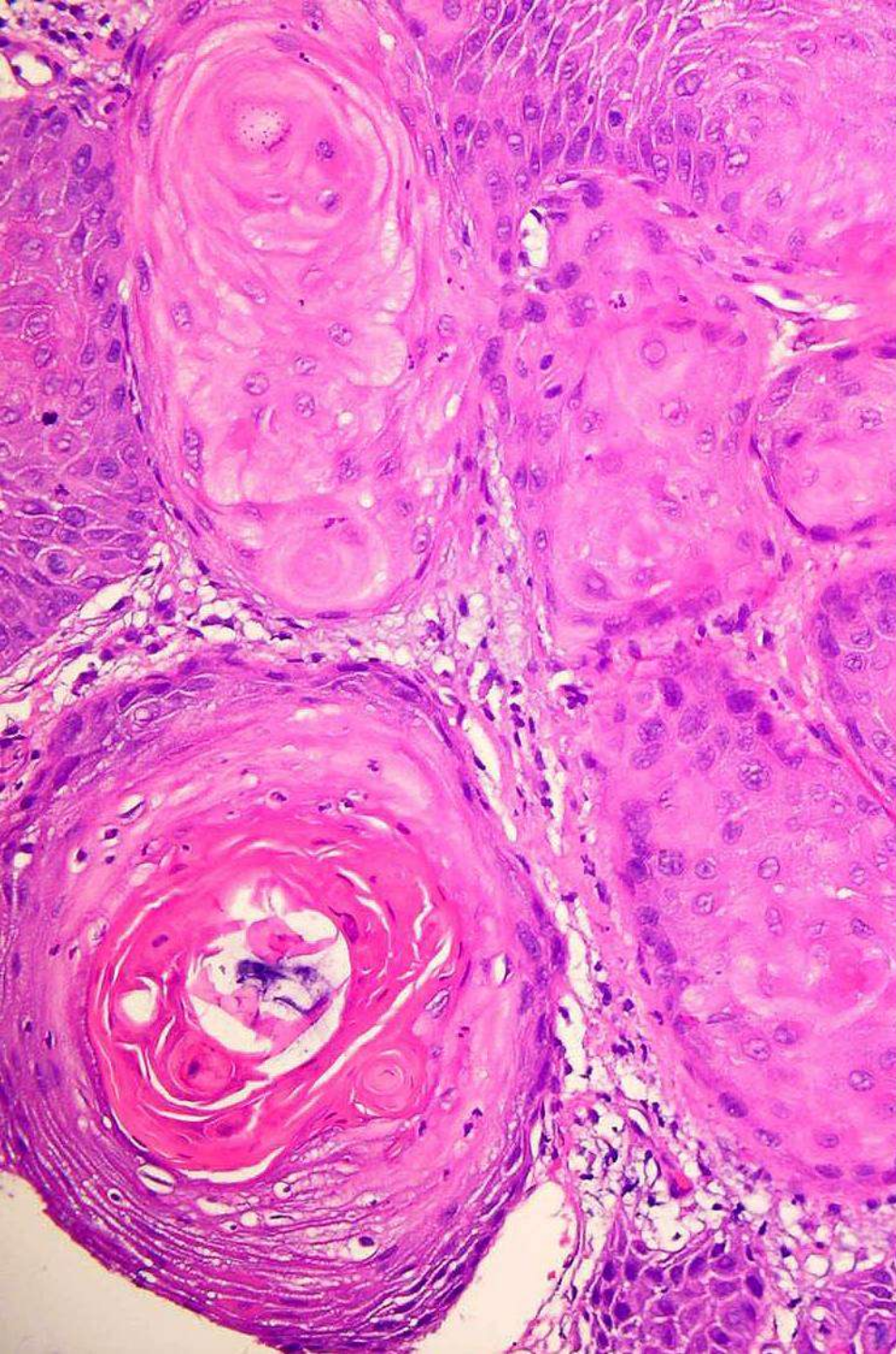


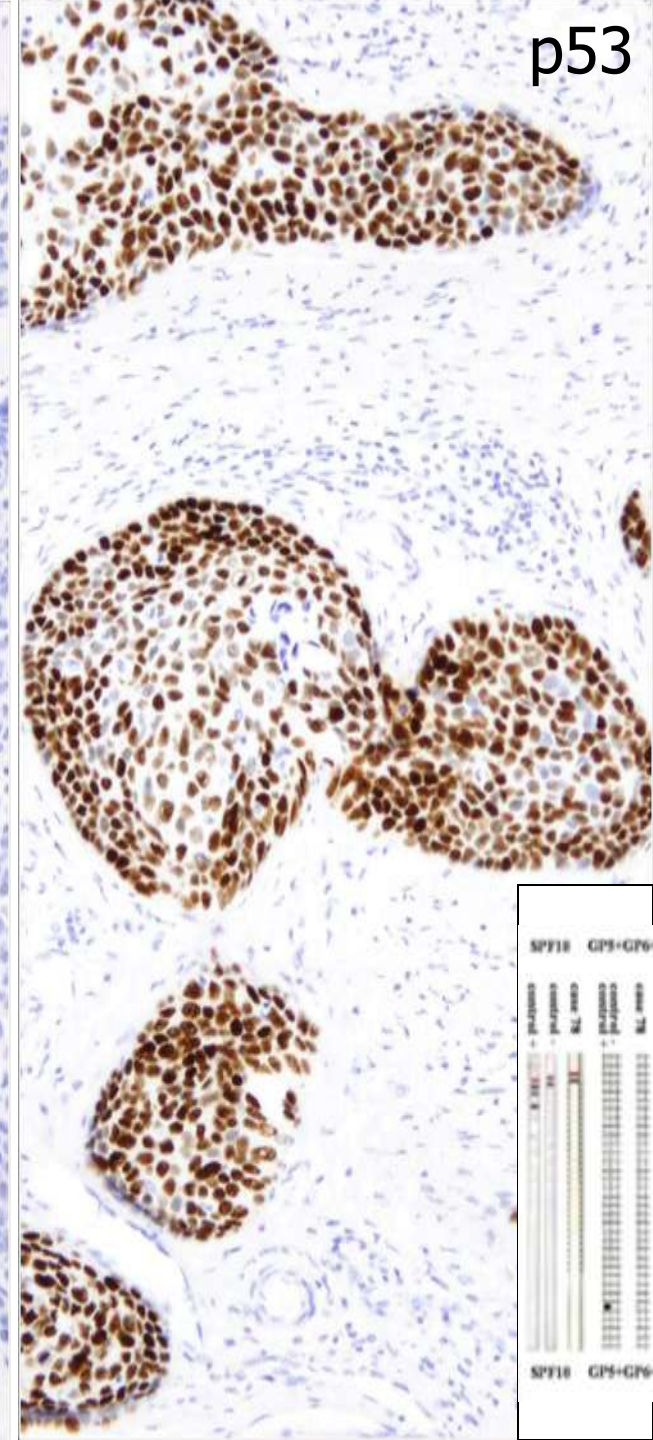
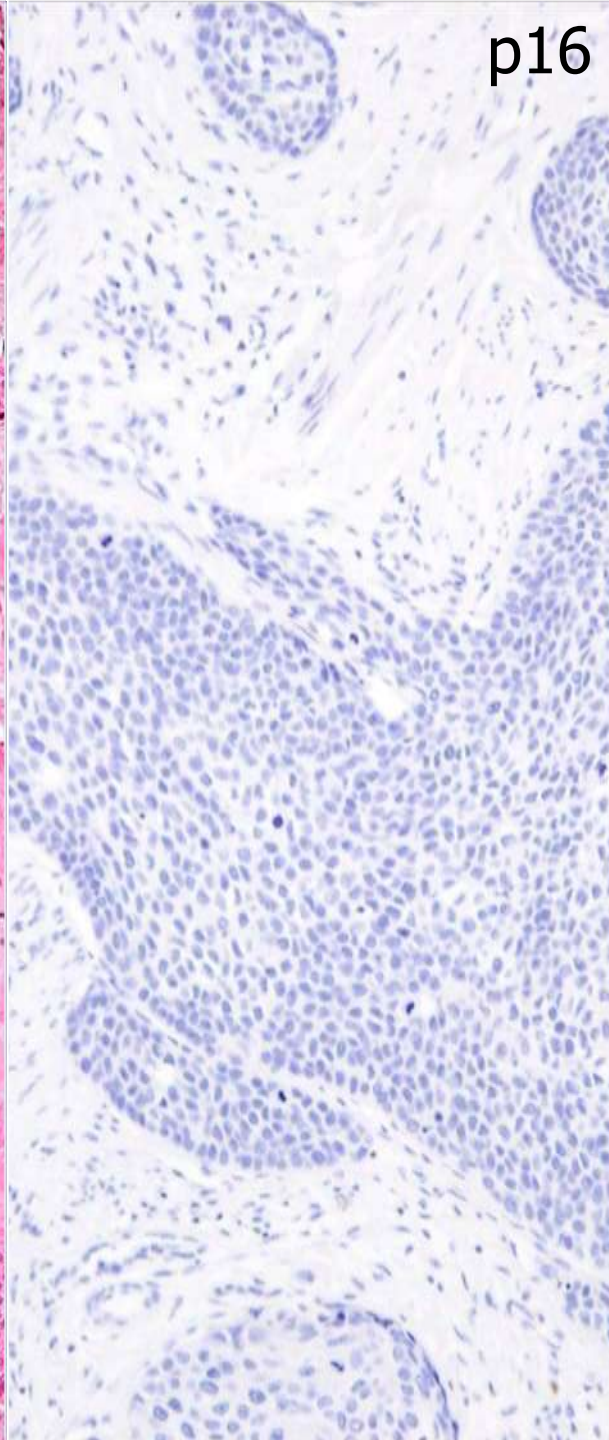
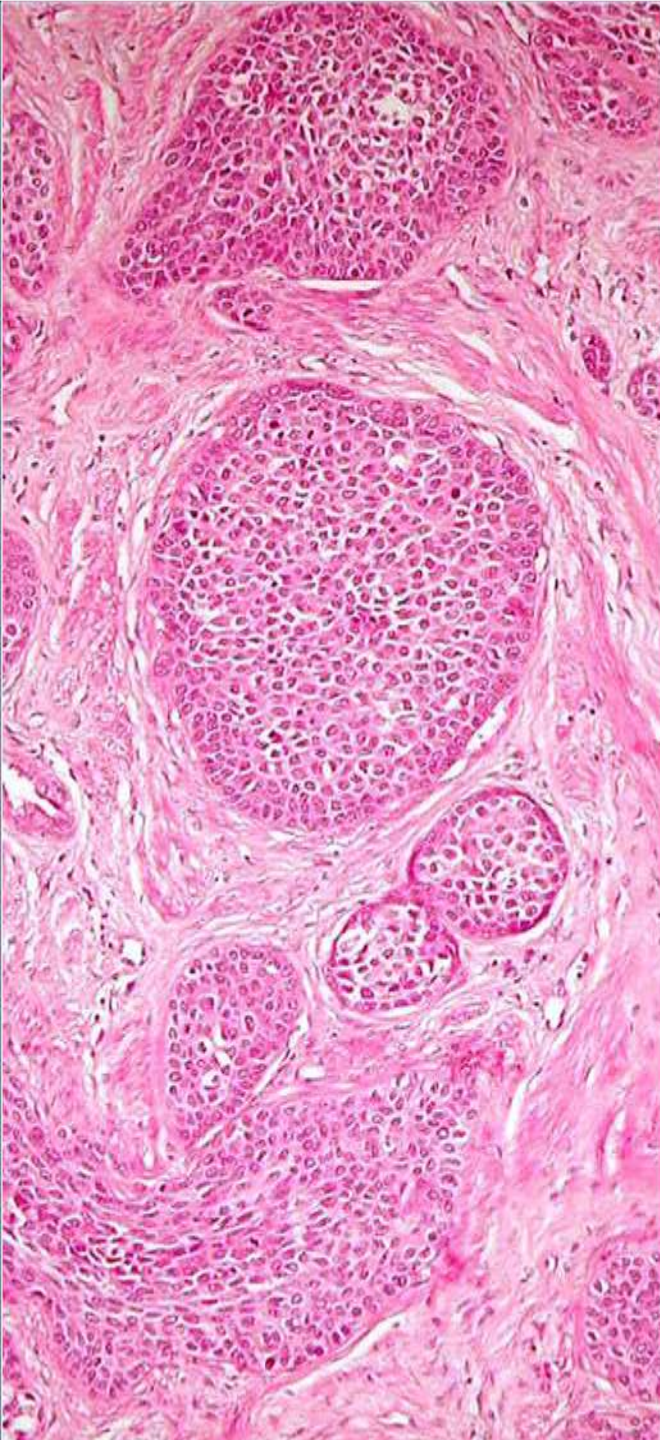
control -



case 50







vSCCs: Histology, p16^{INK4a}, p53

		High-risk human papillomavirus				
		Positive(n=16)		Negative (n=76)		p value
Histologic type						
	Basaloid	7	(43.7 %)	4	(5.3 %)	0.0003
	Warty	3	(18.7 %)	3	(3.9 %)	NS
	Keratinizing	6	(37.5 %)	69	(90.8 %)	0.00001
IHC						
	p16 +	16	(100.0 %)	1	(1.3 %)	<0.000001
	p53 +	1	(6.2 %)	49	(64.5 %)	0.00007

Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347-1356



Identification of HPV relationship

	p16 (+++)	p53 (-)	basaloid/warty histology
Sensitivity	100%	93.8%	62.5%
Specificity	98.7%	35.5%	93.4%
Positive PV	94.1%	23.4%	66.7%
Negative PV	100%	96.4%	92.2%

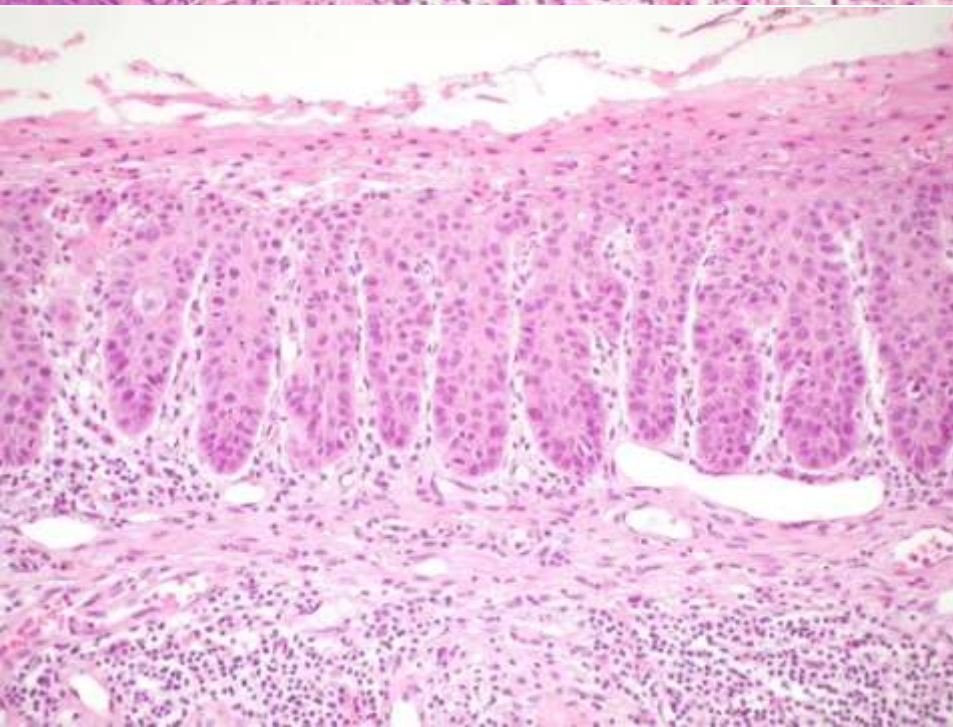
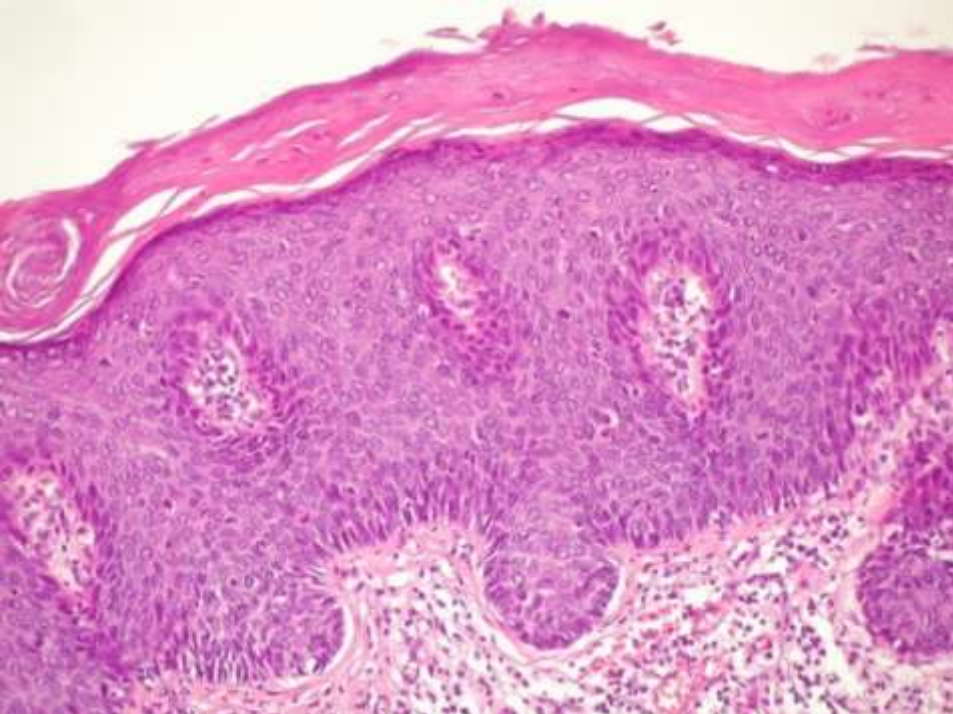
Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347-1356



Vulvar SCCs: Associated lesions

Premalignant and other associated skin lesions	High- risk human papillomavirus				p value
	Positive (n=13)		Negative (n=68)		
VIN basaloid/warty type	7	(53.8 %)	0	(0 %)	<0.001
VIN differentiated type	0	(0 %)	31	(45.6 %)	0.001
Squamous cell hyperplasia	2	(15.4 %)	43	(63.2 %)	0.002
Lichen sclerosis	0	(0 %)	27	(39.7%)	0.004

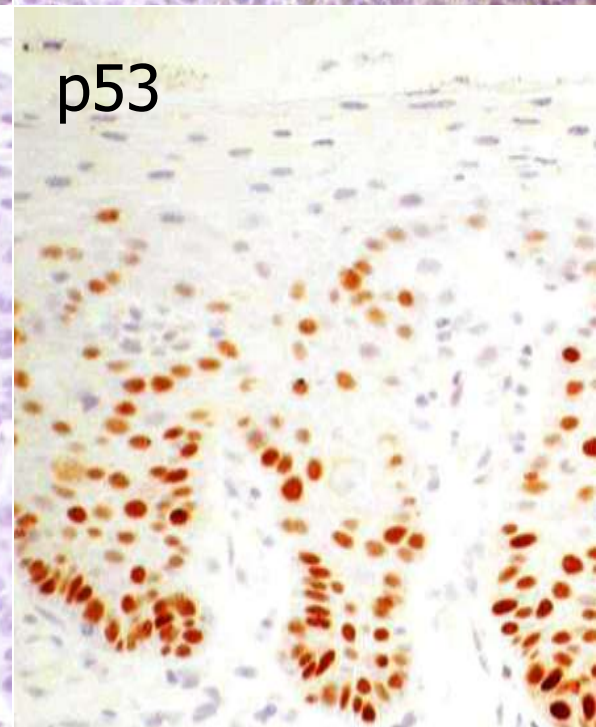
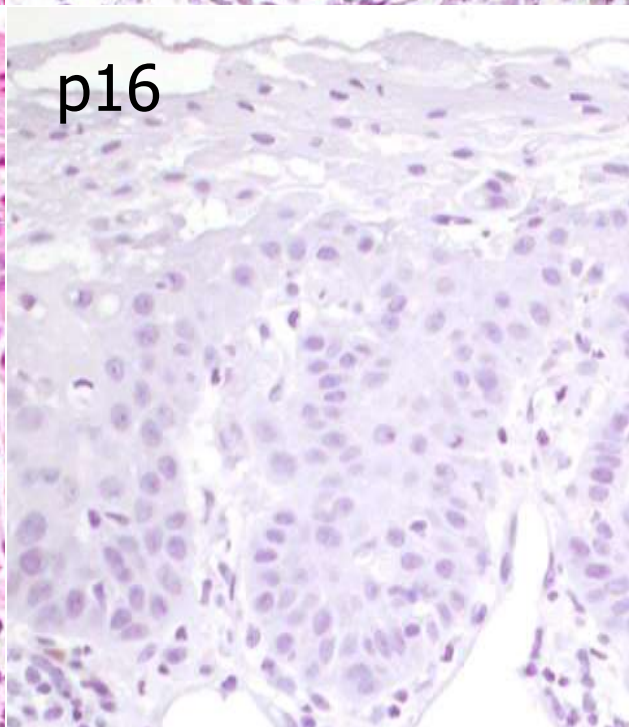
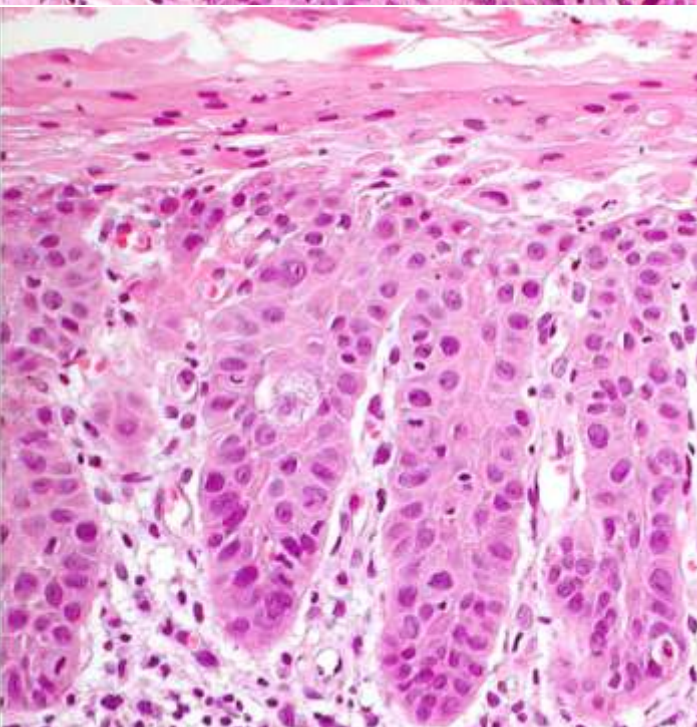
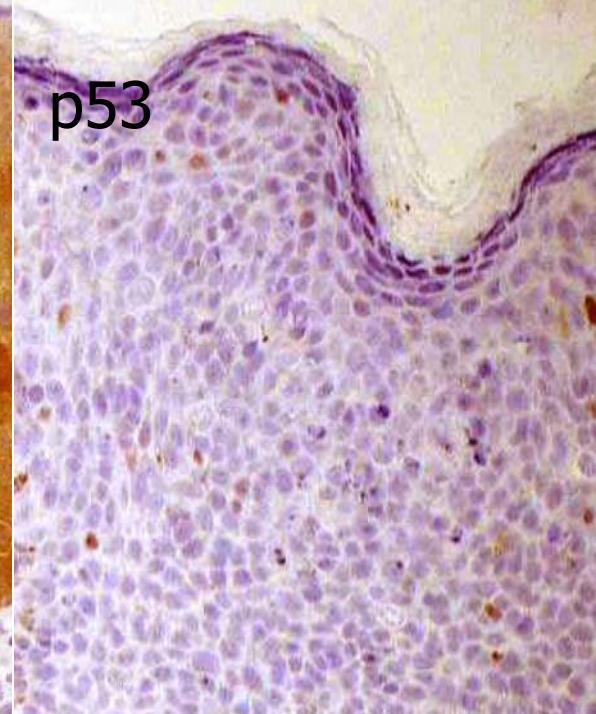
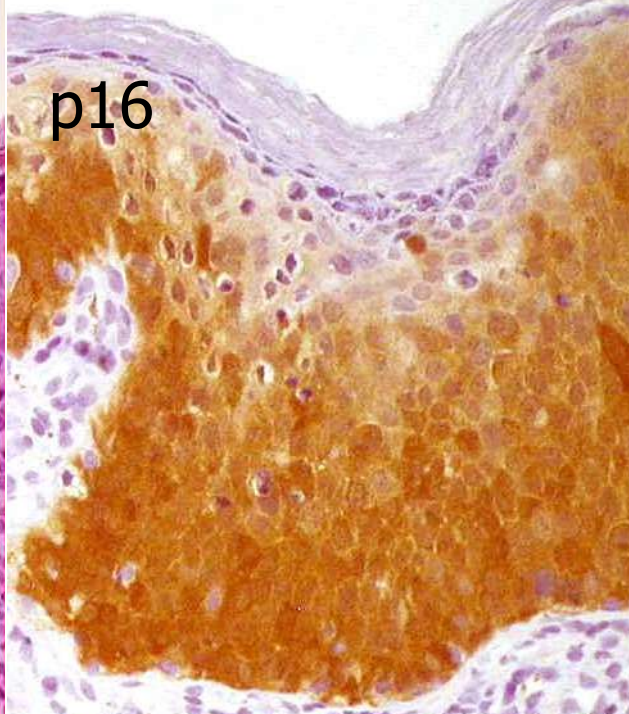
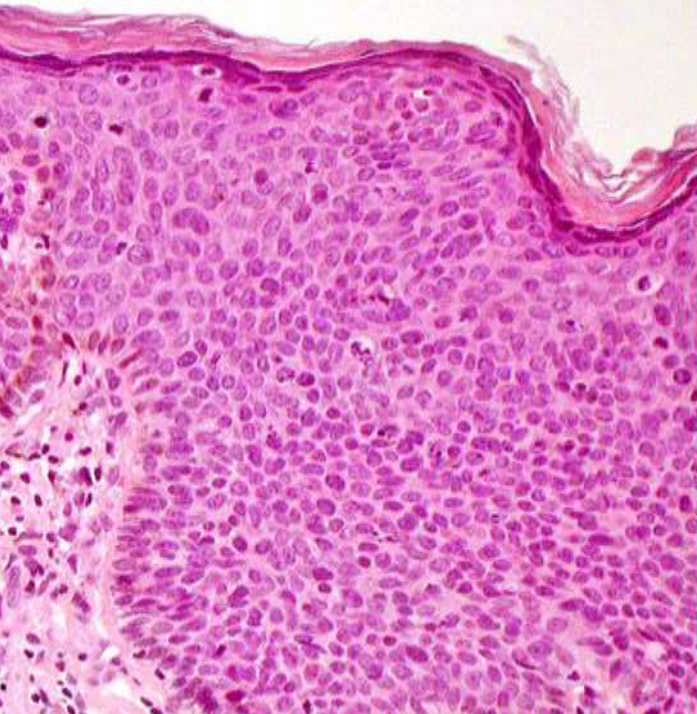
Santos M, et al. *Am J Surg Pathol* 2006; 30: 1347-1356



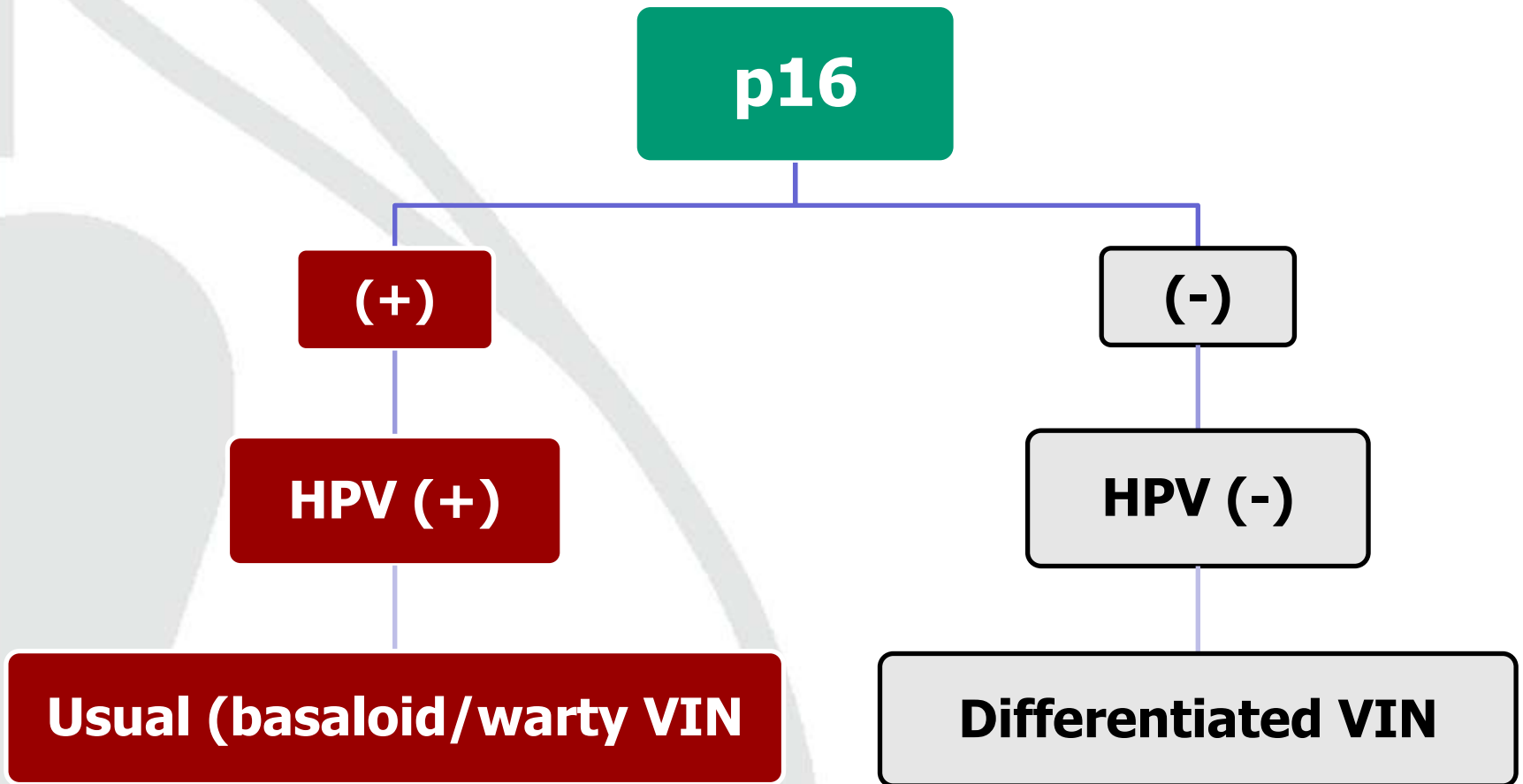
p16^{INK4a} in VIN and benign lesions

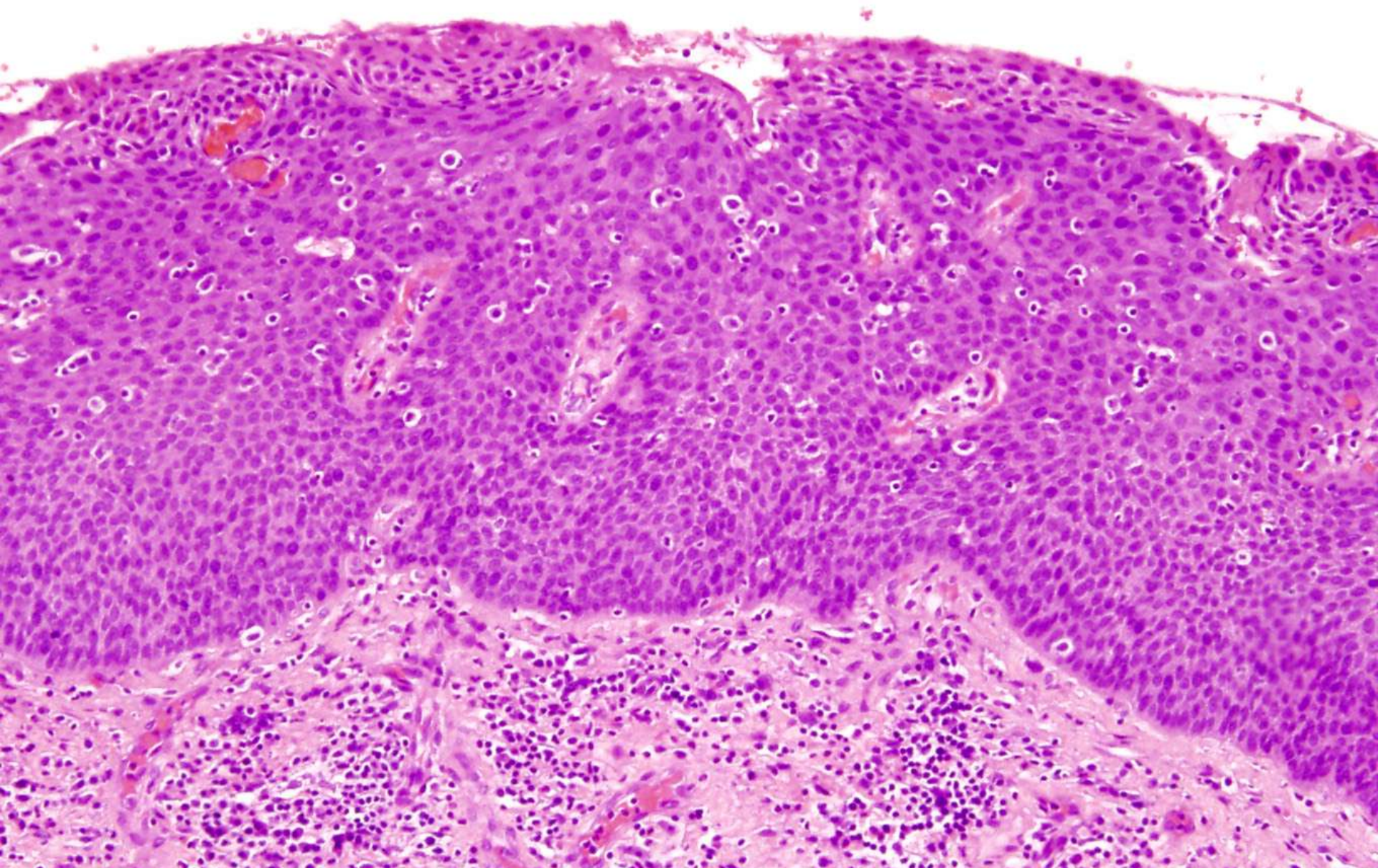
	p16 (%)	p53 (%)
Benign lesions		
Normal skin	0	2
Squamous cell hyperplasia	0	0
Lichen sclerosus	0	11
VIN		
VIN 3 basaloid / warty	100	0
VIN3 differentiated (simplex)	0	81

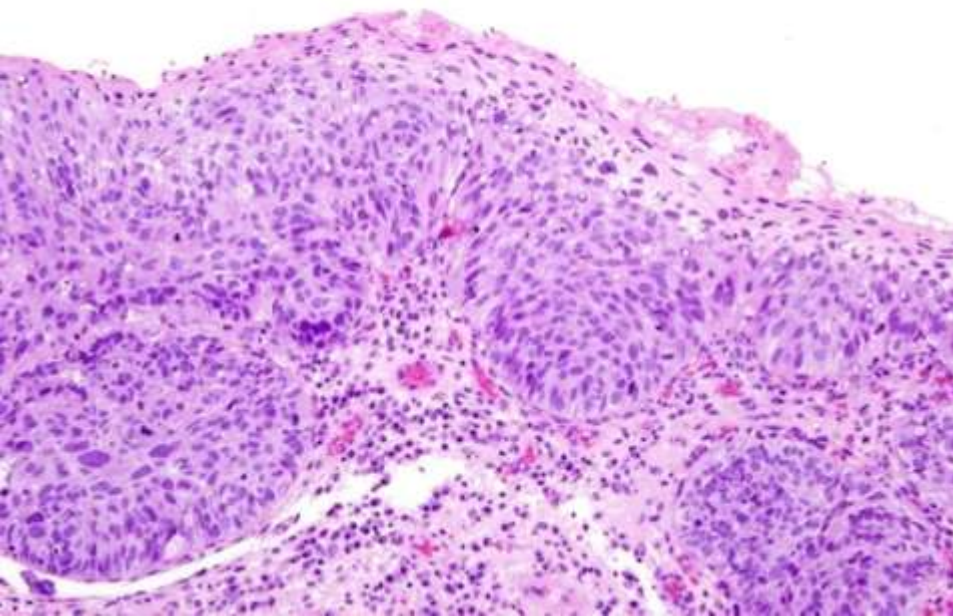
Santos M, et al *Int J Gynecol Pathol* 2004; 23:206-214



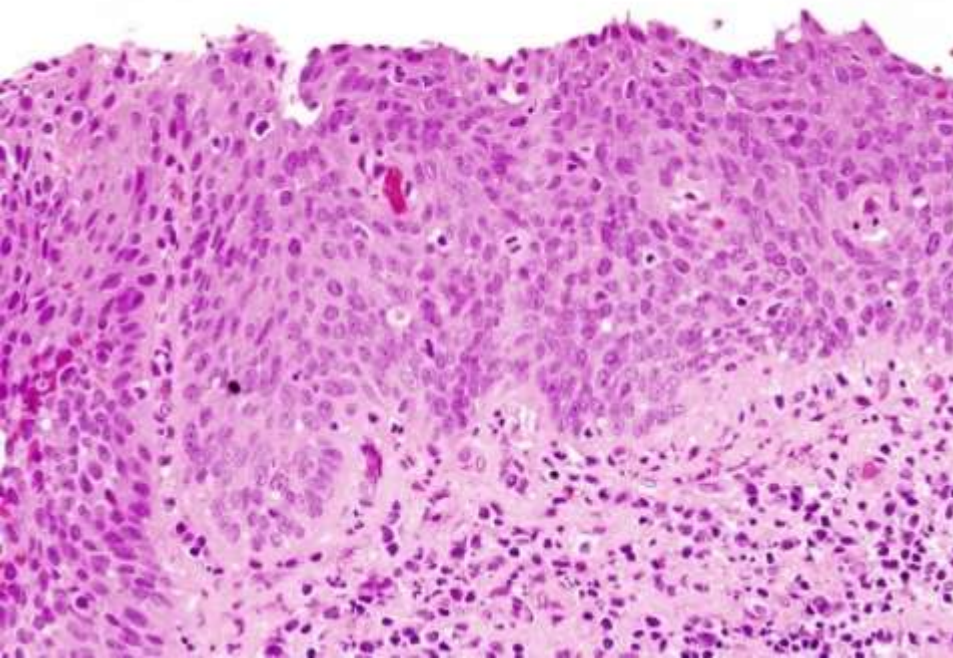
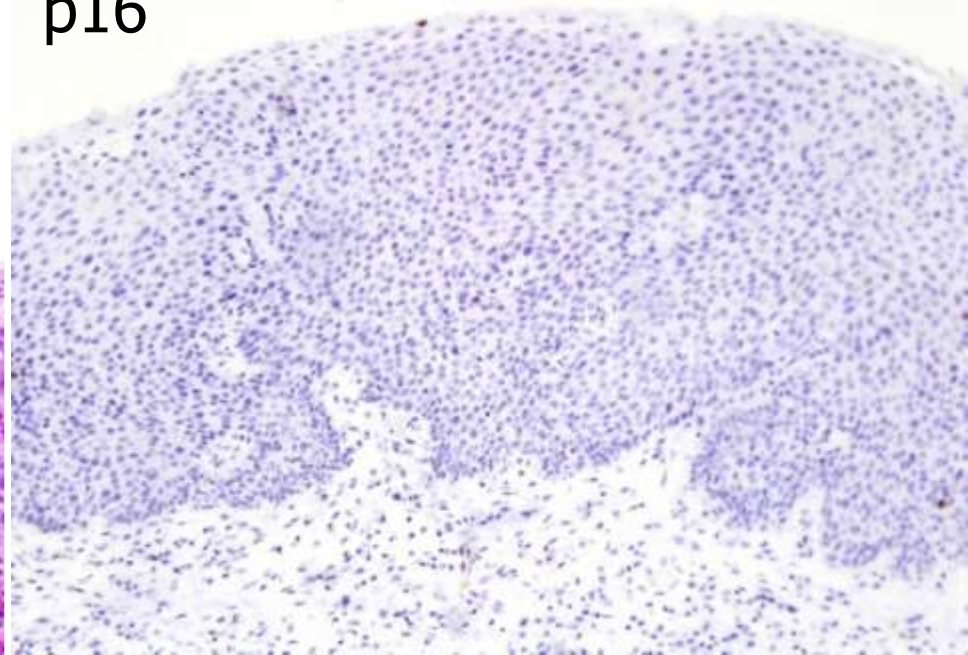
p16^{INK4a} and VIN



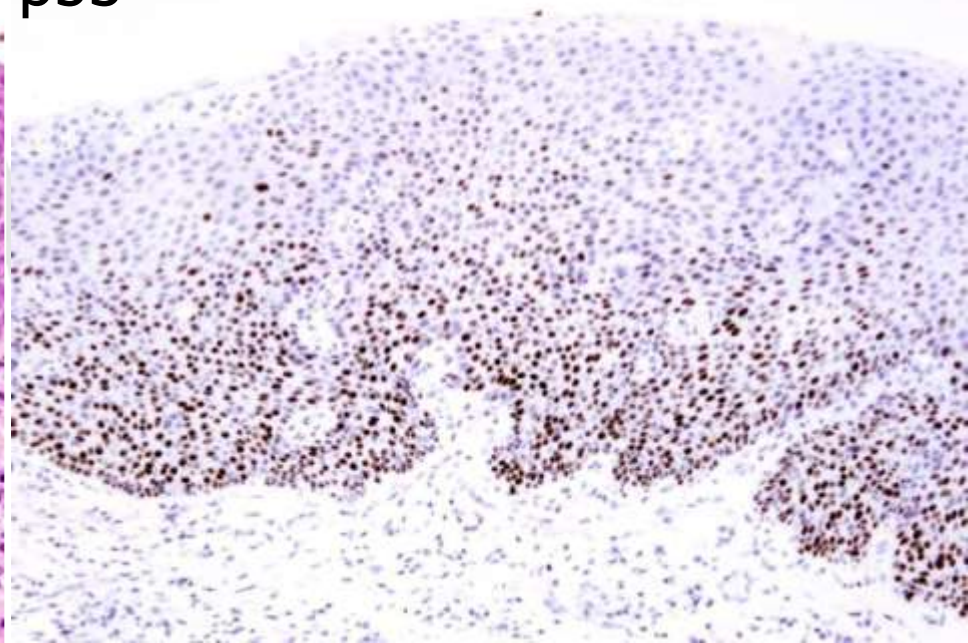




p16



p53



HPV (-) VIN with basaloid features

- 110 cases of HPV negative vSCC
 - 51 cases of differentiated VIN
 - 4/51 (7.8%) with basaloid features

	Age	Associated lesion	Invasive carcinoma	Grade
Case 1	60	Lichen sclerosus Squamous cell hyperplasia	Basaloid	3
Case 2	62	No	Keratinizing	3
Case 3	76	Squamous cell hyperplasia	Keratinizing	3
Case 4	45	Squamous cell hyperplasia	Keratinizing	2

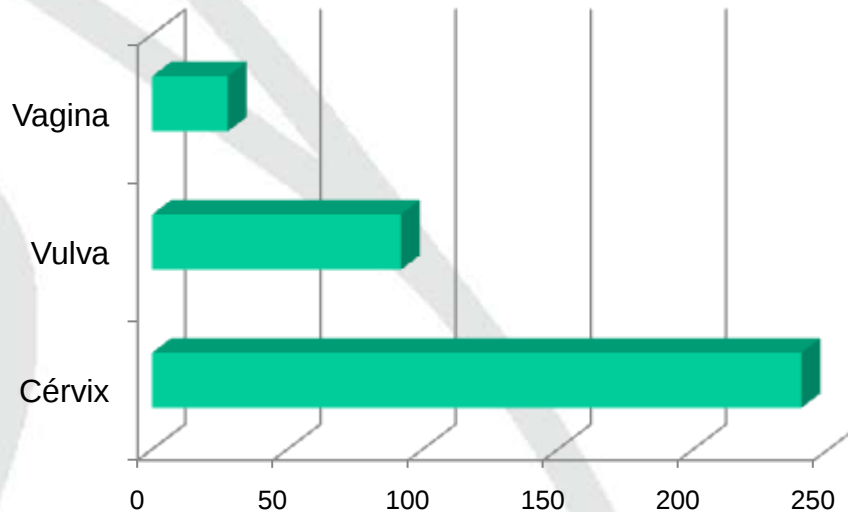
Ordi J, et al. *Am J Surg Pathol* 2009; 33:1659-1665





Carcinomas of the Vagina

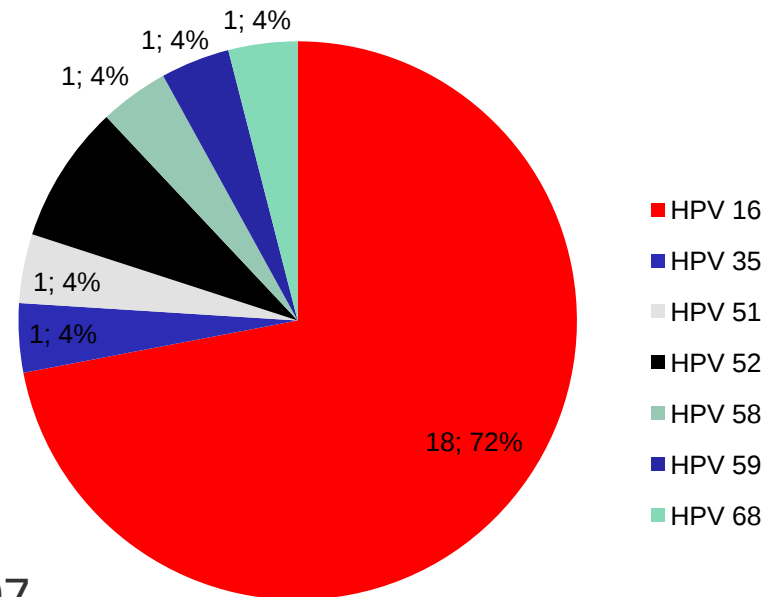
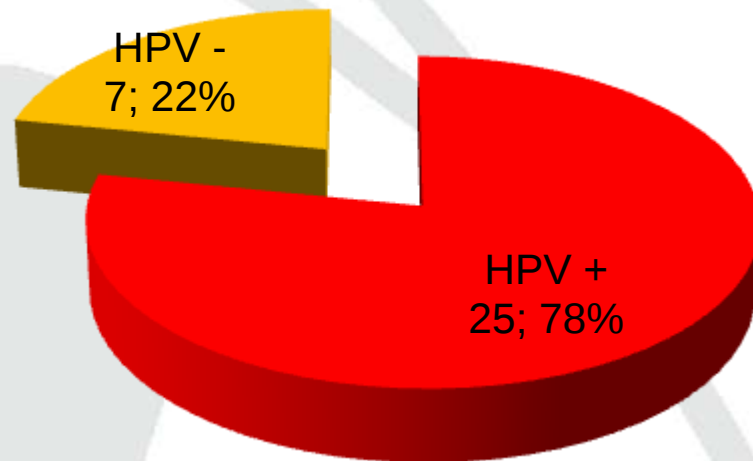
- Very low frequency (1-2% GYN neoplasms)



- Squamous cell carcinoma (SCC) >80%
- Two different etiopathogenic types

SCCs of the vagina: HPV

- 32 invasive SCC of HCP / HVH



Fuste V, et al. *Histopathology* 2010; 57: 907



SCCs of the vagina: HPV

		High-risk human papillomavirus				
		Positive (n=25)		Negative (n=7)		p value
Histologic type						0.006
	Keratinizing	4	(16.0 %)	6	(85.7 %)	
	Non-keratinizing	14	(56.0%)	1	(14.3%)	
	Basaloid	4	(16.0 %)	0	(0 %)	
	Warty	3	(12.0 %)	0	(0 %)	
Immunohistochemistry						
	p16 ^{INK4A} positivity	24	(96.0 %)	1	(14.3 %)	<0.001
	p53 positivity	3	(12.0 %)	4	(64.5 %)	0.025

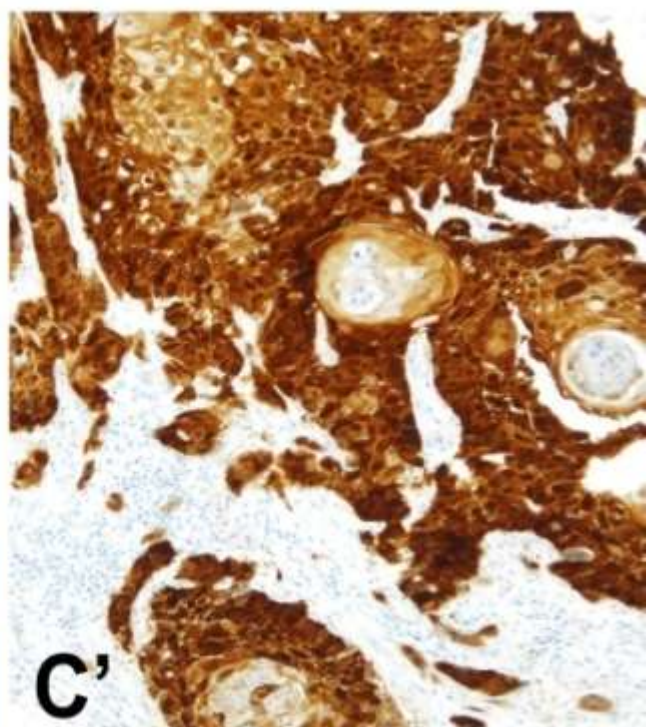
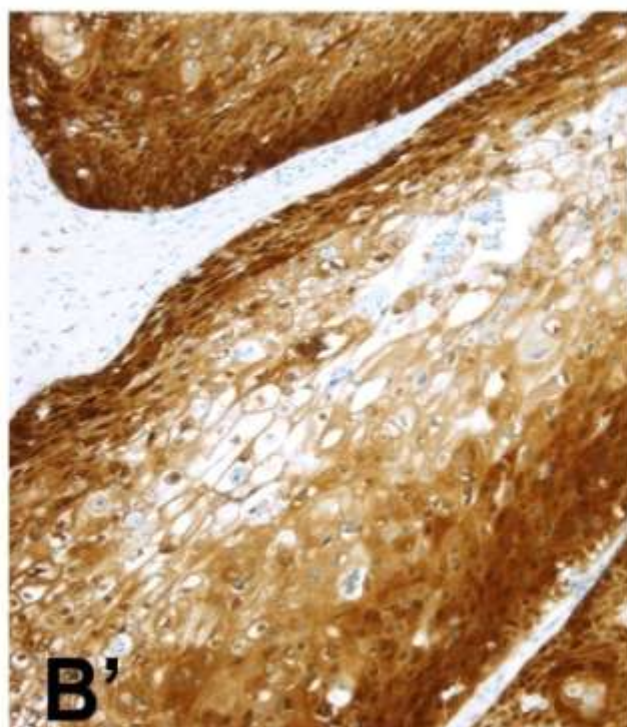
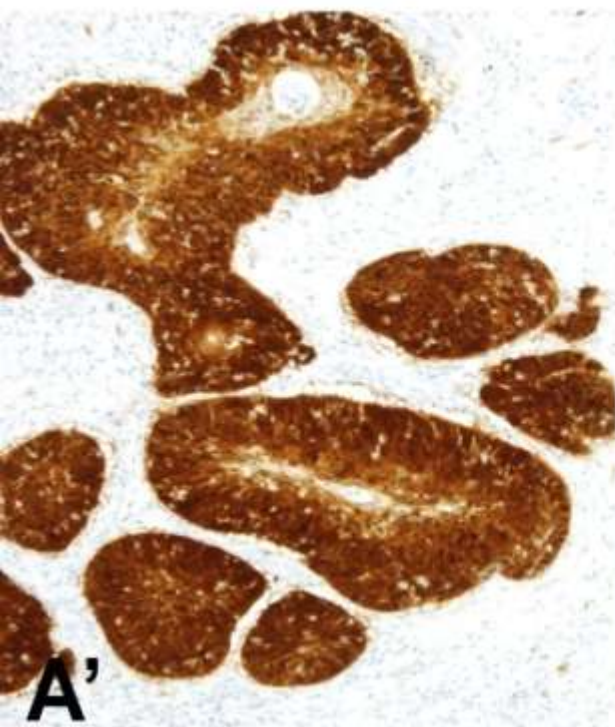
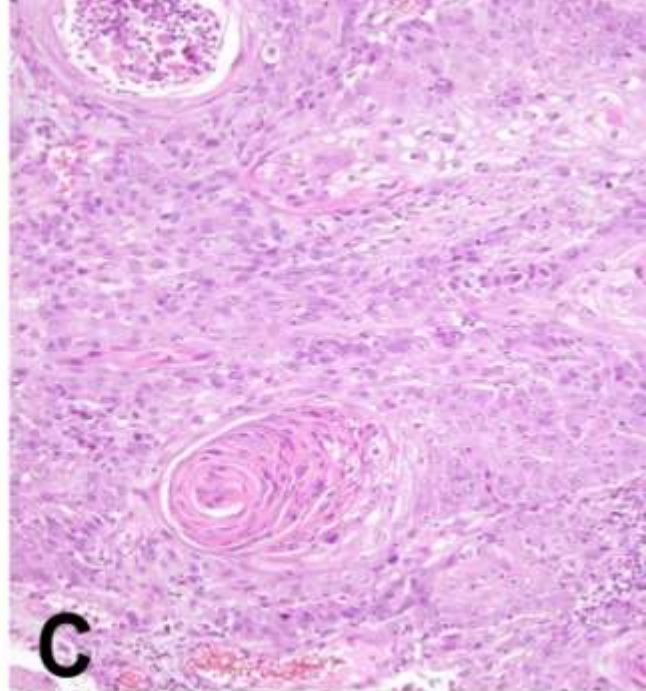
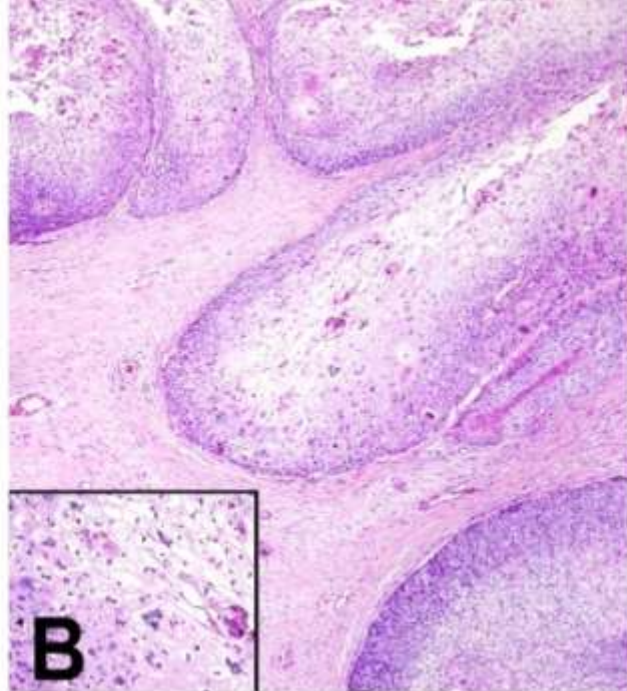
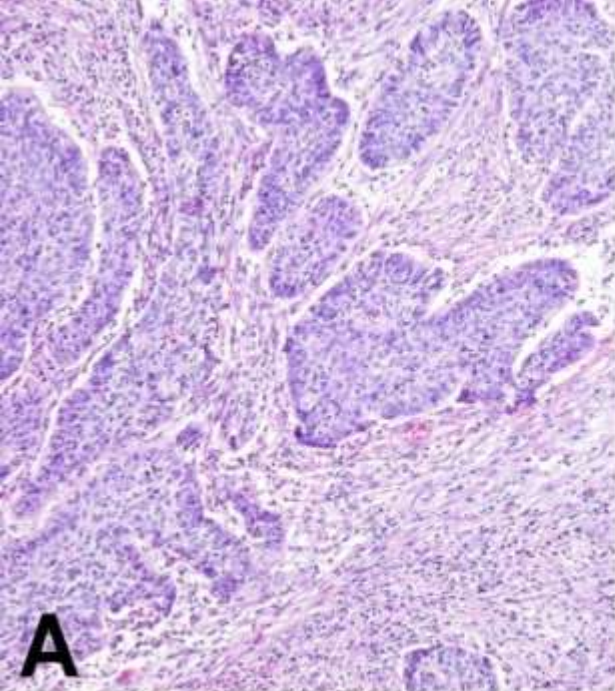
Fuste V, et al. *Histopathology* 2010; 57: 907

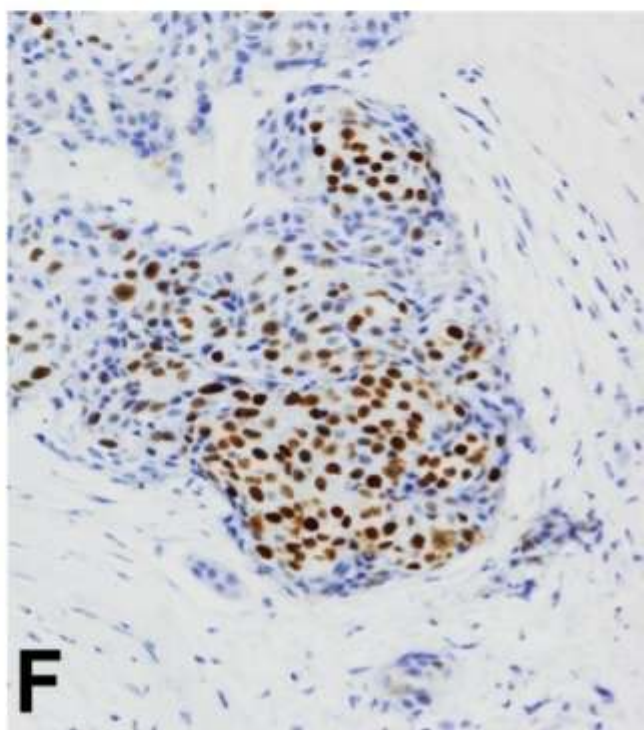
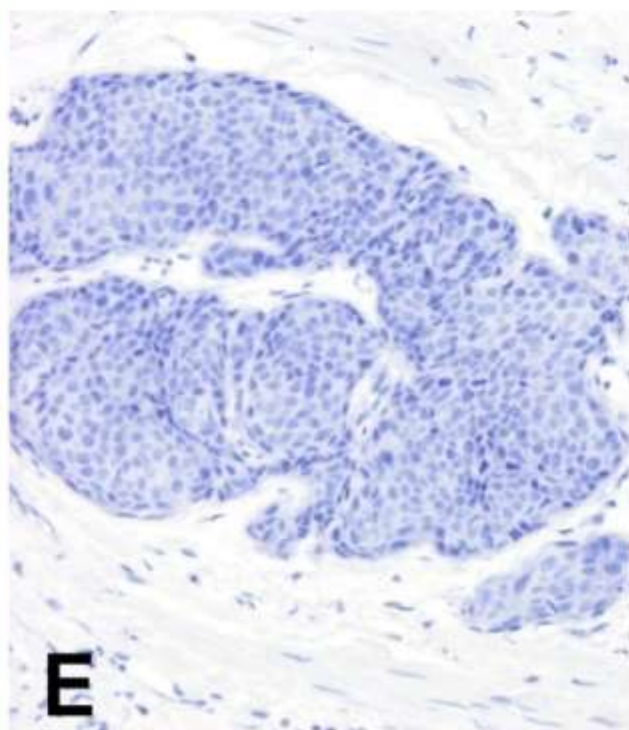
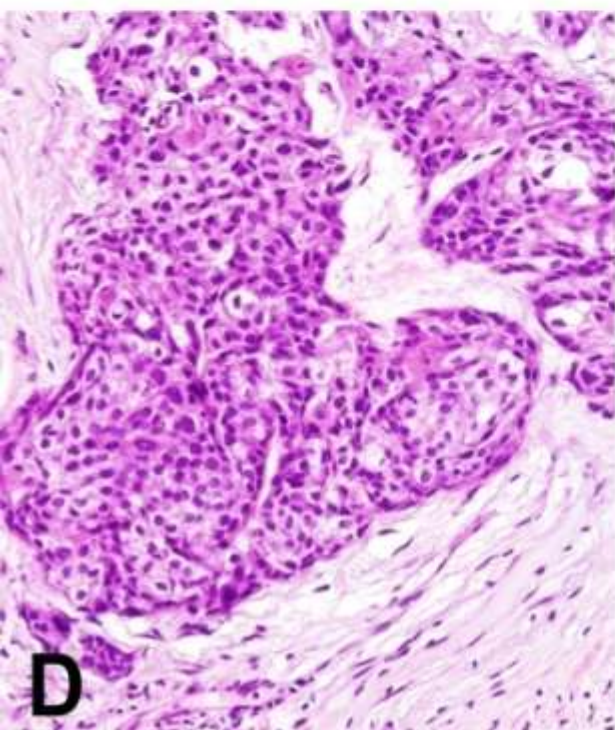
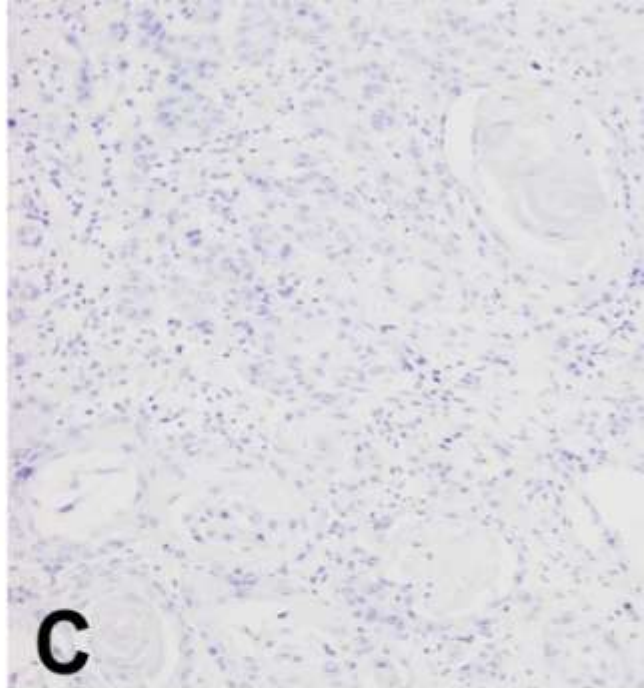
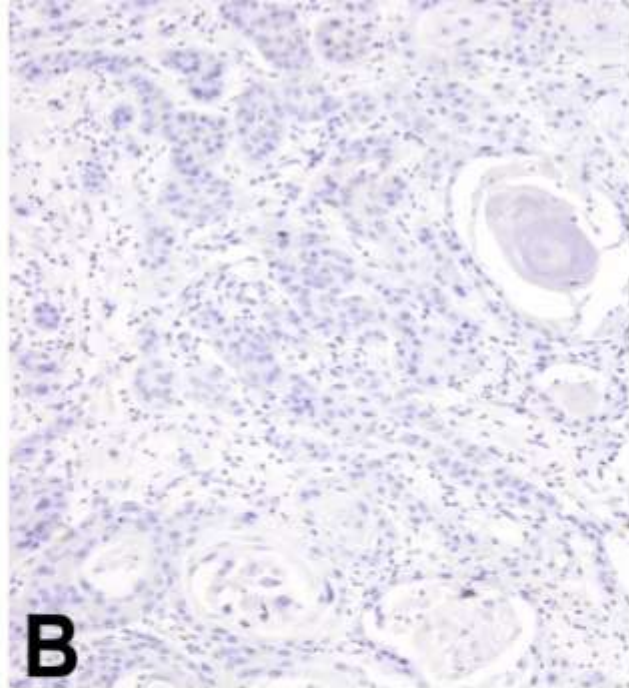
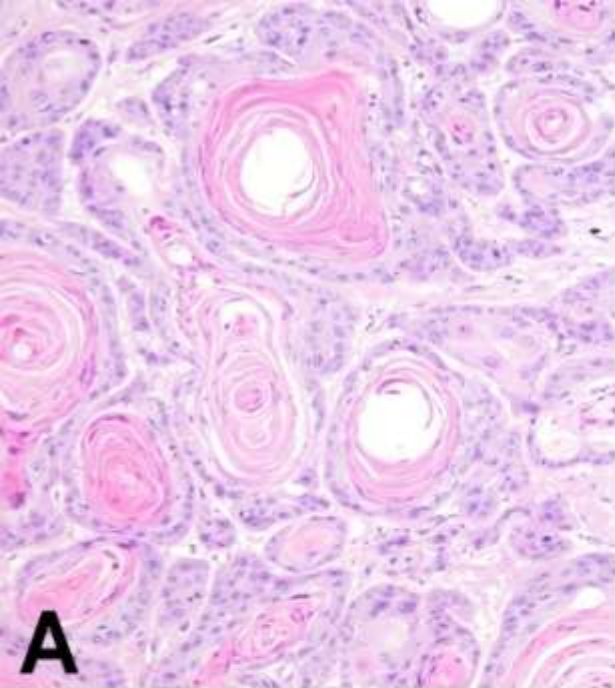


SCCs of the vagina: HPV

	p16 ^{INK4A} diffuse	p53 (-)	Non-keratinizing/ basaloid/warty histology
Sensitivity	96.0%	88.0%	95.5%
Specificity	85.7%	57.1%	60.0%
Positive predictive value	96.0%	88.0%	84.0%
Negative predictive value	85.7%	57.1%	85.7%

Fuste V, et al. *Histopathology* 2010; 57: 907







SCCs of the vagina: HPV

	High-risk human papillomavirus		p value
	Positive (n=25)	Negative (n=7)	
Age	62.6 ± 13.8	74.0 ± 8.5	0.049
History of cervical lesion	14 (56.0%)	0 (0%)	0.010

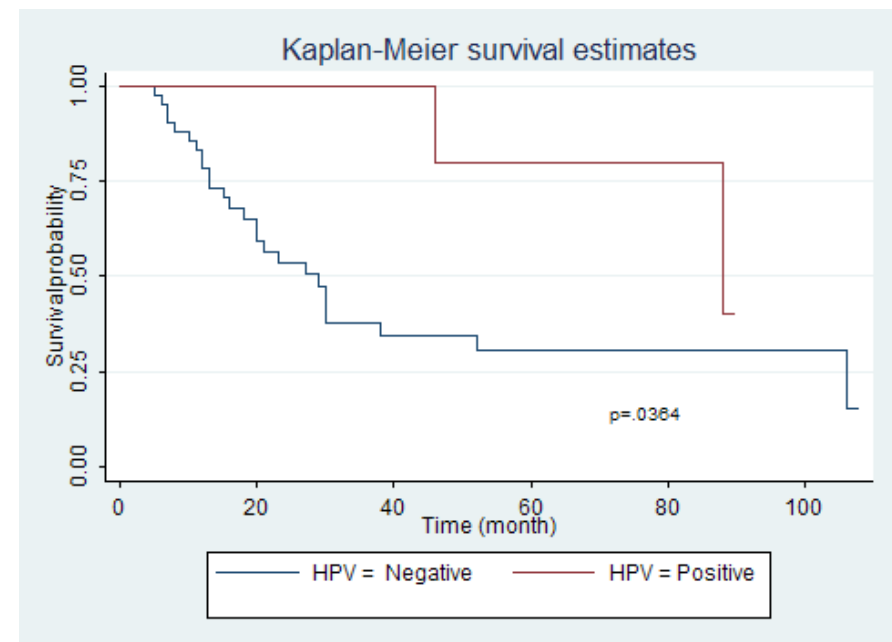
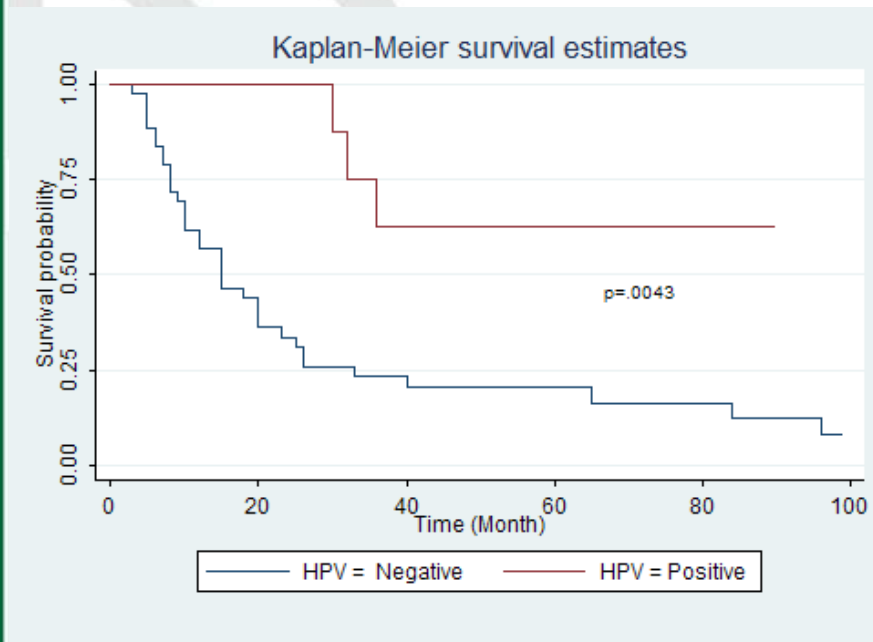
Fuste V, et al. *Histopathology* 2010; 57: 907

Carcinomas de Vulva y Vagina: VPH y pronóstico





Head & neck SCC: HPV & survival



Alos L, et al. *Cancer* 2009;
115:2701-2709



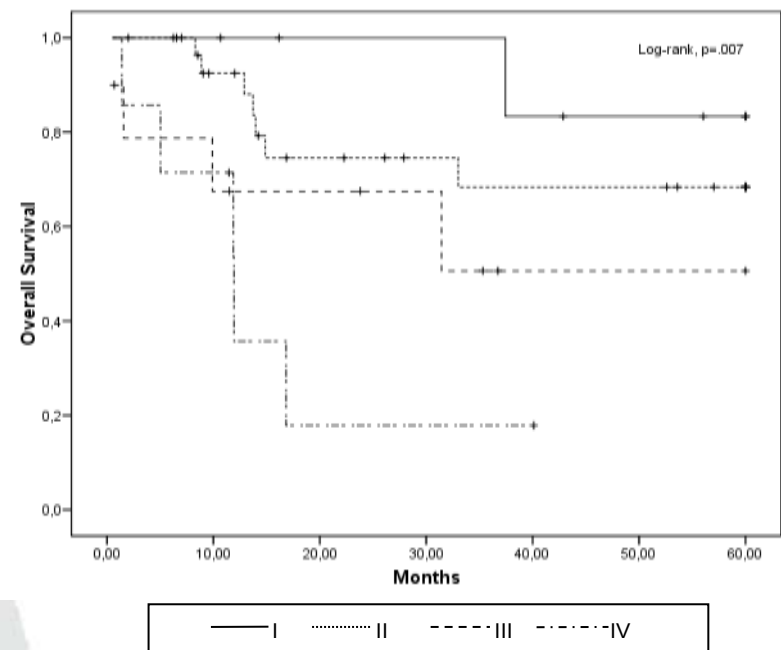
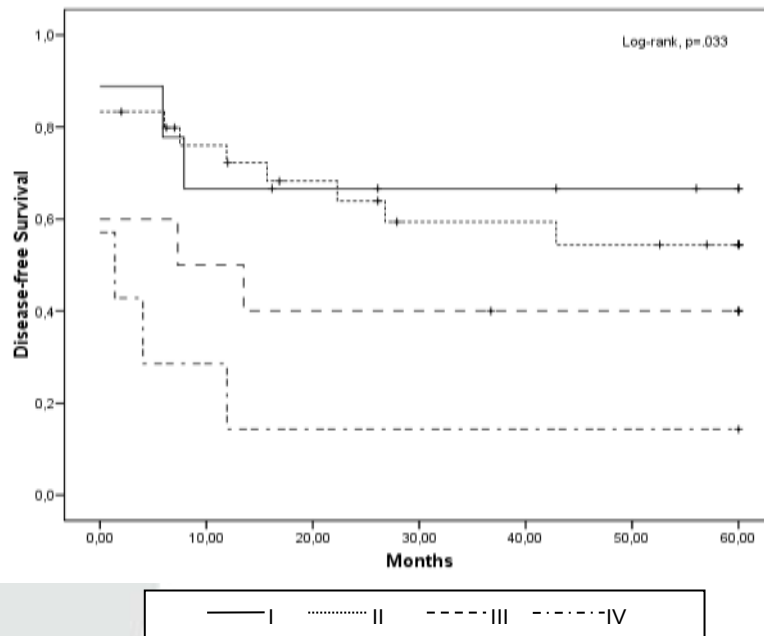
Ca. Vagina: Estadío y Pronóstico

	HPV-negative (n=17)		HPV-positive (n=40)		p-value
	n	(%)	n	(%)	
Age $\geq$ 68 years	10	(58.8)	19	(47.5)	.565*
FIGO stage					.854 [#]
I	3	(17.6)	7	(17.5)	
II	9	(52.9)	21	(52.5)	
III	4	(23.5)	6	(15.0)	
IV	1	(5.9)	6	(15.0)	
Tumor size $\geq$ 20 mm	7	(100)	20	(80.0)	.117*

Alonso I, et al. *in preparation* 2011



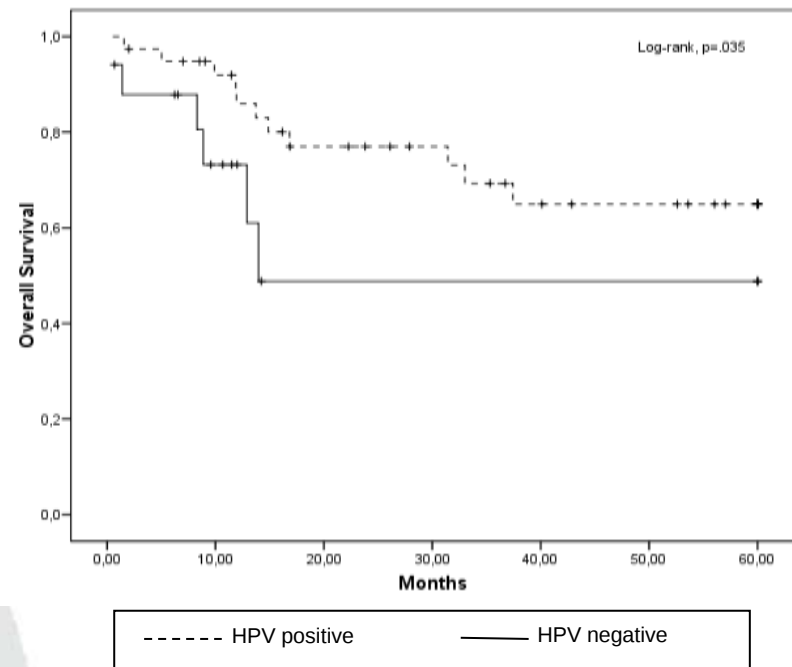
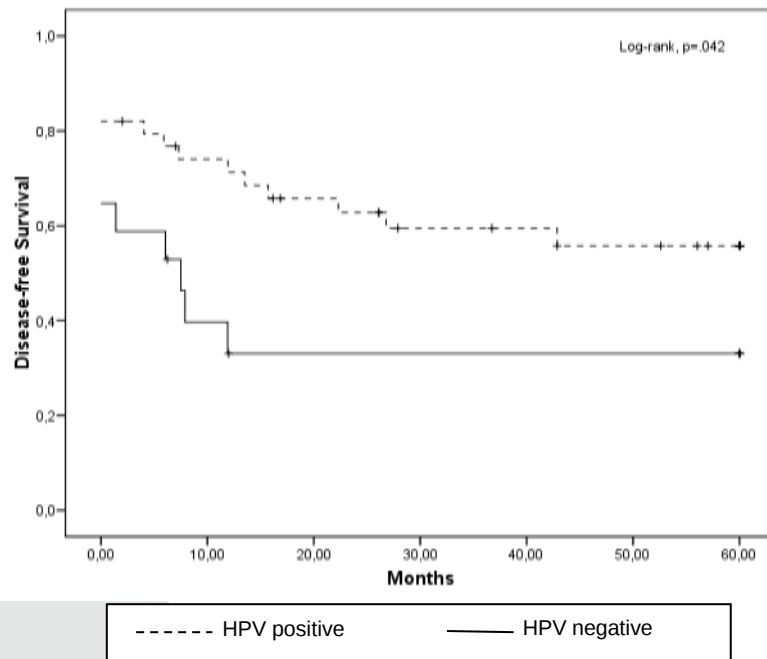
Ca. Vagina: Estadío y Pronóstico



Alonso I, et al. *in preparation* 2011



Ca. Vagina: VPH y Pronóstico



Alonso I, et al. *in preparation* 2011



Ca. Vagina: Estadío y Pronóstico

Disease Free Survival			
Variable	HR	95% CI	p-value
HPV positivity	0.45	(0.22-0.92)	.029
Age $\geq$ 68 years	1.85	(0.89-3.85)	.098
HPV positivity	0.49	(0.24-1.00)	.050
FIGO stage III-IV	2.33	(1.17-4.65)	.017

Overall survival			
Variable	HR	95% CI	p-value
HPV positivity	0.35	(0.13 to 0.94)	.038
Age $\geq$ 68 years	1.36	(0.51 to 3.59)	.539
HPV positivity	0.36	(0.14 to 0.93)	.035
FIGO stage III-IV	3.88	(1.49 to 10.10)	.005

Alonso I, et al. *in preparation* 2011



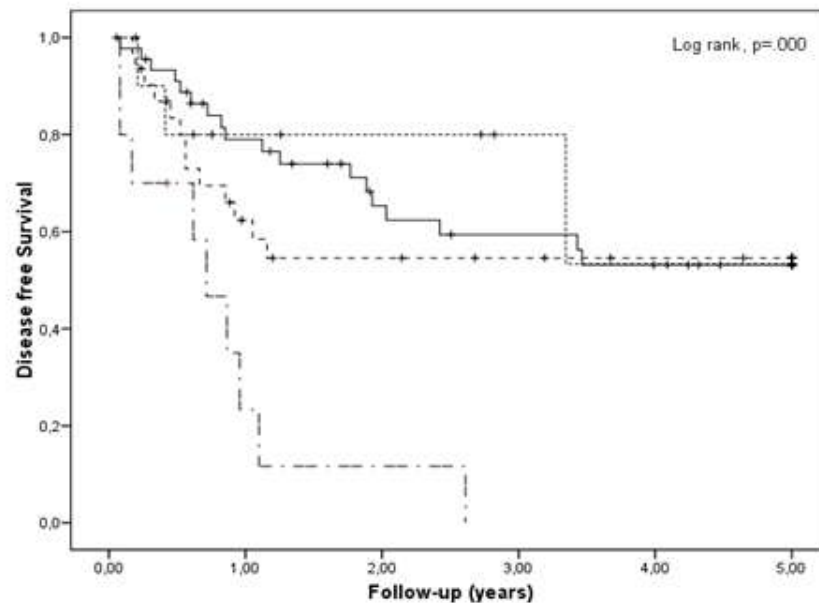
Vulvar SCCs: Clinical data

	Non-HPV n = 79	HPV n = 19	p
Age (x ± SD)	77,2 ± 11,2	64,0 ± 22,1	0,003*
Tumor size (mm) (x ± SD)	33,1 ± 19,4	35,3 ± 22,8	0,595*
Ulceration			
No	23 (31,9)	6 (37,5)	0,77***
Yes	49 (68,05)	10 (62,5)	
Stage FIGO	n (%)	n (%)	0,18**
I	39 (49,4)	6 (31,6)	
II	7 (8,9)	4 (21,1)	
III	27 (34,8)	5 (26,3)	
IV	6 (7,6)	4 (21,1)	

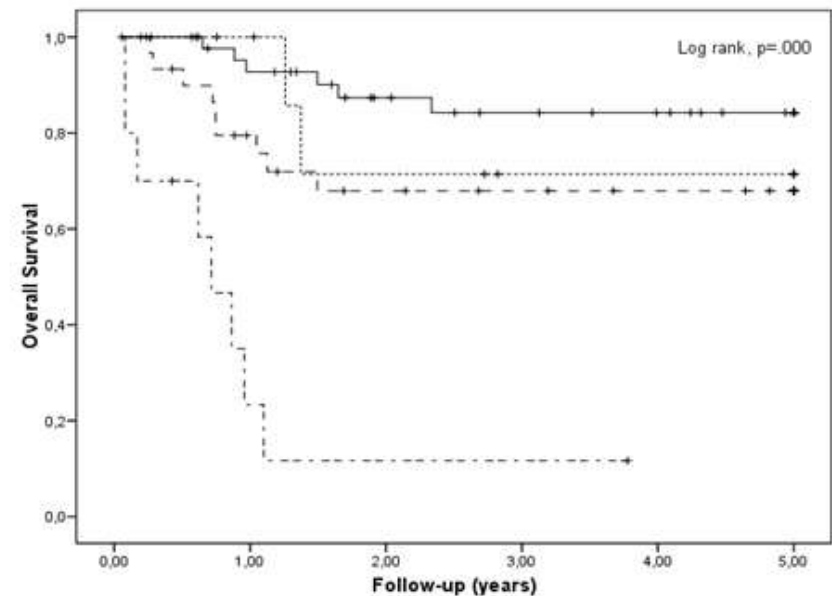
Alonso I et al. *Obstet Gynecol* 2011 (submitted)



Ca. Vulva: Estadío y Pronóstico



— I II --- III -.-.- IV

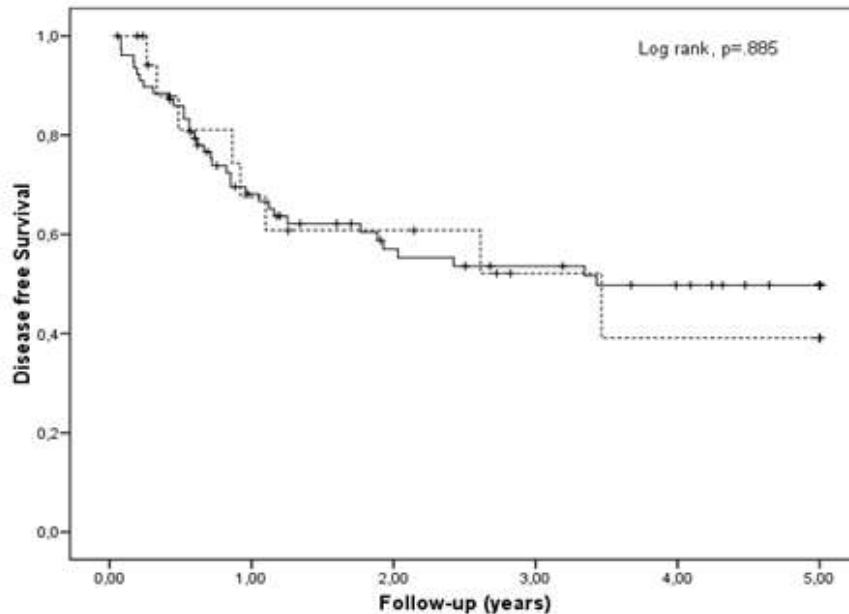


— I II --- III -.-.- IV

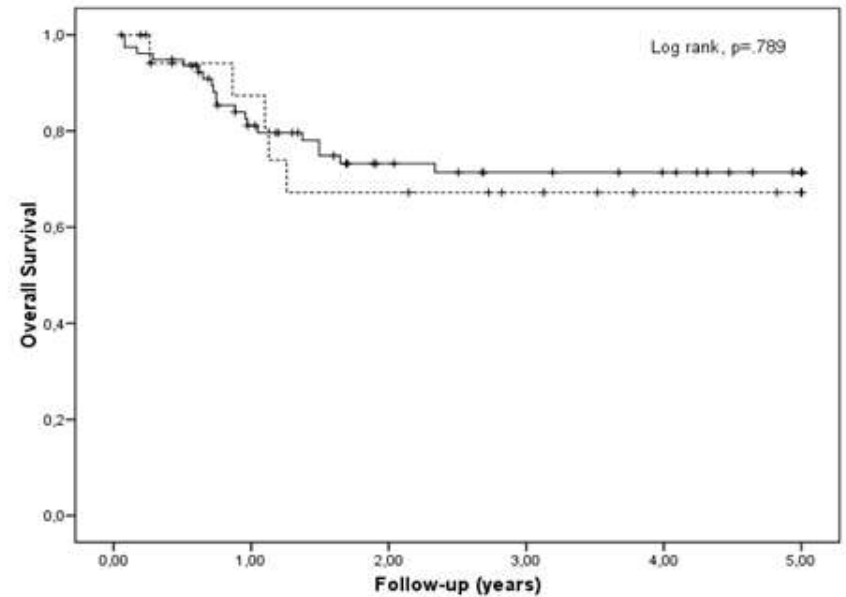
Alonso I, et al. *Gynecol Oncol* 2011 (in press)



Ca. Vulva: VPH y Pronóstico



--- HPV positive — HPV negative



--- HPV positive — HPV negative

Alonso I, et al. *Gynecol Oncol* 2011 (in press)



Vulvar SCC: logistic regression

	OR	95% CI	p-value
Overall Sv			
RDT (Yes vs no)	1.63	(0.58 to 4.63)	0.353
p16 (+ vs -)	1.08	(0.31 to 3.78)	0.900
HPV (+ vs -)	0.76	(0.19 to 3.01)	0.701
u-VIN vs d-VIN	0.97	(0.17 to 5.59)	0.970
Disease-free Sv			
RDT (Yes vs no)	1.63	(0.58 to 4.63)	0.353
p16 (+ vs -)	1.08	(0.31 to 3.78)	0.900
HPV (+ vs -)	0.76	(0.19 to 3.01)	0.701
u-VIN vs d-VIN	1.07	(0.28 to 4.06)	0.919

Alonso I, et al. *Gynecol Oncol* 2011 (in press)

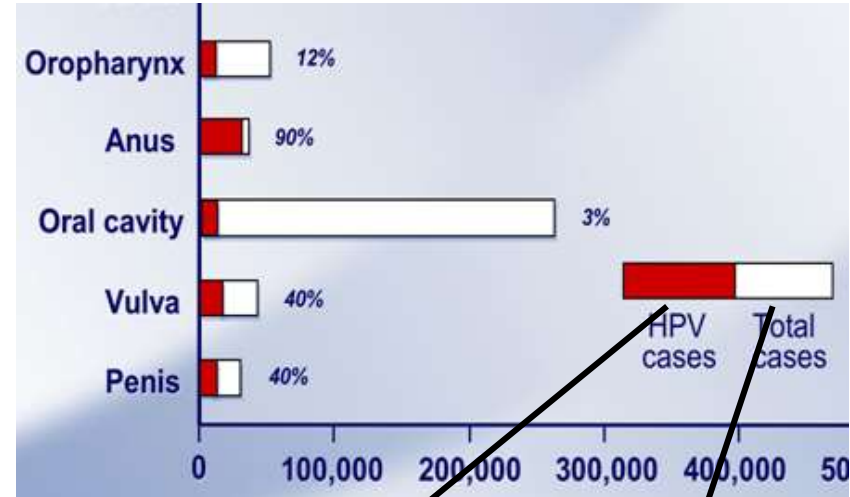


“Take home” messages

- Approximately **4/5** carcinomas of the **vagina** are related to **HPV**
- Approximately **1/5 to 1/3** of carcinomas of the **vulva** are related to **HPV** infection
- **HPV16** is the most prevalent type in all locations (60-70%)

"Take home" messages

- **p16^{INK4a} overexpression** has a **sensitivity and a specificity close to 100%** to identify HPV positive tumors of the head and neck, the vulva and the vagina and may thus be used as a **biomarker of HPV infection**



P16 (+)

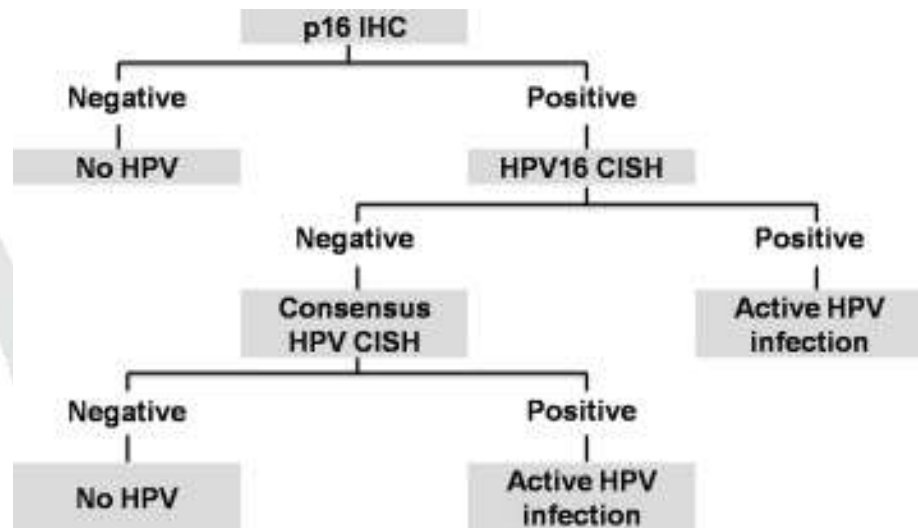
P53 (-)

P16 (-)

P53 (+)

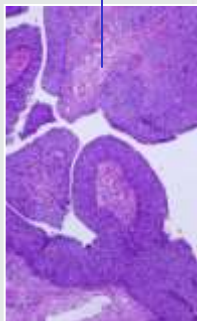
“Take home” messages

- **HPV positive carcinomas of the vagina have a better prognosis** than HPV negative tumors
- HPV positive and negative carcinomas of the **vulva** have a **similar prognosis**
- p16 and/or HPV testing should be included in the evaluation of vaginal carcinomas because it has prognostic and treatment significance





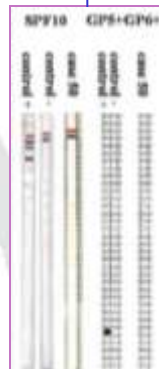
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