

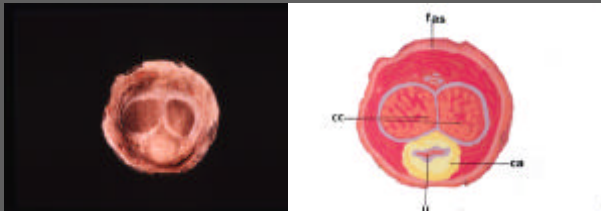
# Penile Carcinoma: From Anatomy to Molecular Biology

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And  
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## Anatomy



## Penis-Cross Section



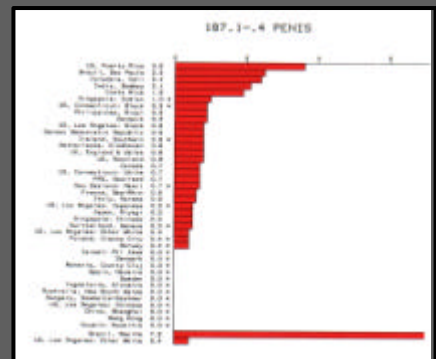
## Anatomy



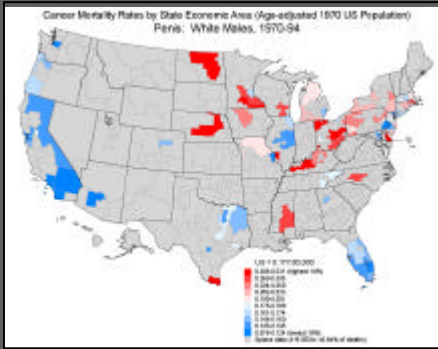
## Demographics

- ☞ Sporadic .familial
- ☞ Age: 7th decade
  - Verruciform, basaloid and low grade papillary carcinomas appear a decade before SCC,NOS
  - Young individuals as isolated cases or in clusters
- ☞ Race: no preference
  - Secondary tumors more frequent in AA

## Geographic Distribution Patterns



## Geographic Distribution Patterns



# Causes

## Causes

### Major causes

- ☞ Circumcision
- ☞ HPV
- ☞ Tobacco
- ☞ BXO
- ☞ PUVA

### Minor causes

- ☞ Hailey-Hailey
- ☞ Lichen planus
- ☞ Burns
- ☞ Asbestos
- ☞ Sinus tracts
- ☞ Hypospadias
- ☞ Mineral oil injection
- ☞ Sexual activity
- ☞ Zoon's plasmacellular balanitis

Not associated: Herpes virus, Epstein Barr virus, Syphilis

## Circumcision

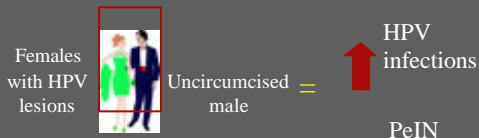
- ☞ The risk for PeCA was 3.2 times greater among men who were never circumcised than the risk in men circumcised at birth
- ☞ 88% of Kenyan patients with PeCA were uncircumcised and 12% had late circumcision

Type	# of cases	Circumcision	Late circumcision
PeCA	89	2.3	
PeIN	118	15.7	
HPV		0/29	3 of 32

- ☞ Late circumcision does not seem to have the same preventive effect.
  - Often performed because of early penile lesions or penile diseases associated to the development of PeCA. Bissada found 15 patients that developed PeCA post adult circumcision in circumcision scars
- ☞ Penile cancers do occur in circumcised males

## Circumcision and HPV

- ☞ Circumcision also has a protective effect against HPV infection, urinary tract infections and HIV.



- ☞ The foreskin provides a permissive microenvironment for infectious organisms and for the progression of HPV lesions.
- ☞ Penile cancers do occur in circumcised males

## HPV

- ☞ Invasive PeCA: HPV in 40-60%
- ☞ PeIN: HPV in 90-100%
- ☞ Condylomas and low grade PeIN: HPV 6 & 11
- ☞ High grade PeIN and PeCA: HPV 16 and 18
- ☞ HPV also found in normal mucosa (to the eye)
- ☞ HPV in PeCA is associated with histologic subtypes

# HPV in PeCA

Author	Country	Technique	# of PeCA	HPV +ve (%)	HPV 16 (%)	HPV 18 (%)	HPV 45 (%)	HPV 33/39 (%)	Other HPV (%)	PCR +ve (%)
12	Spain	Southern	35	100	25					
13	Spain	Spain	35	100						
14	Spain	Spain	35	40	11					
15	Spain	Spain	35	11						
16	Spain	Spain	35	11						
17	Spain	Spain	35	11						
18	Spain	Spain	35	11						
19	Spain	Spain	35	11						
20	Spain	Spain	35	11						
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100	Spain	Spain	35	11						

# HPV DNA detection in penile condyloma, dysplasia and carcinoma.

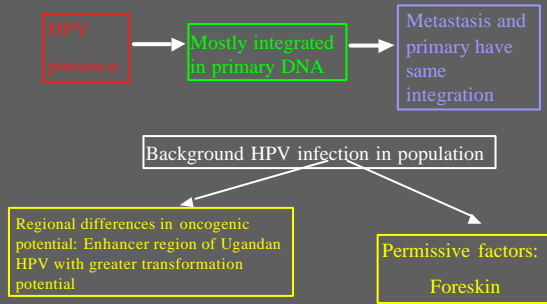
Gregoire et al.: HPV associated with SCC in areas showing basaloid and/or warty changes. HPV was found in a very low percentage of typical SCC of the penis (1.1%). Stepwise logistic regression analysis revealed that only tumor histopathology was a significant predictor of an HPV association.

DIAGNOSIS	n	HPV POSITIVE		SINGLE HPV TYPE LOW RISK		SINGLE HPV TYPE HIGH RISK		MULTIPLE HPV TYPES HIGH RISK		MULTIPLE HPV TYPES LOW&HIGH RISK	
		n	%	n	%	n	%	n	%	n	%
condyloma	12	12	100.0	11	91.7	1	8.3	0	0	0	0
dysplasia	30	27	90.0	5	18.5	16	59.3	4	14.8	2	7.4
verrucous scc	106	37	34.9	0	0	23	62.1	4	10.8	4	10.8
keratinizing scc	12	4	33.3	1	25.0	2	50.0	0	0	0	0
basaloid scc	15	12	80.0	0	0	11	91.7	1	8.3	0	0
warty scc	5	5	100.0	0	0	4	80.0	0	0	1	20.0
metastatic scc	1	1	100.0	0	0	1	100.0	0	0	0	0
<b>all cancer cases</b>	<b>142</b>	<b>60</b>	<b>42.2</b>	<b>1</b>	<b>1.6</b>	<b>42</b>	<b>70.0</b>	<b>5</b>	<b>8.3</b>	<b>5</b>	<b>8.3</b>

# HPV Regional Differences

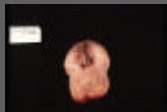
HPV PHYLOGENETIC TYPES*	PENILE CARCINOMA PARAGUAY		PENILE CARCINOMA USA	
	n	%	n	%
ANY HPV POSITIVE	20	37.0	40	45.4
A10: HPV 6,11,74	3	13.0	4	8.5
A9: HPV 16,31,33,35,52	1	5.0	32	68.0
A7: HPV 18,39,45,68,70	4	17.3	6	12.7
A5: HPV 51,69	1	4.3	1	2.1
Z OTHER HPV's	3	13.0	4	8.5

# HPV- Oncogenic Mechanisms



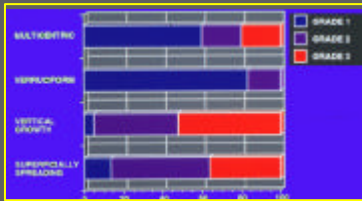
# Causes

- Tobacco
  - Case control study: Association with smoking, chewing and use of snuff
  - Odds ratio of developing PeCA for smokers: 2.8
  - 80% PeCA patients are heavy smokers
- PUVA
  - Dose dependent correlation
  - 14 patients followed for 12 yr. developed 30 genital CA
  - Incidence of PeCA 286x general population and 16.3 times lower levels of exposure
  - Risk of genital tumors with UVB is 4.6 higher than controls
- BXO
  - Anecdotal reports
  - 5.8% patients with BXO developed PeCA (lag time 17 yr..)
- Radiation
  - Secondary post radiation PeCA
  - Malignant progression post radiation
- Chronic Irritation

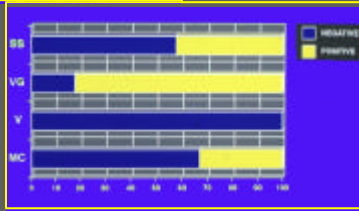


# Growth Patterns



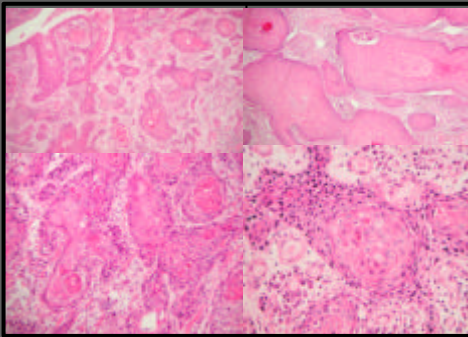


## Growth Patterns

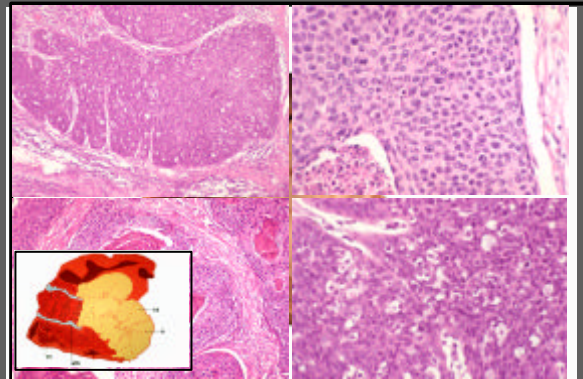


# Histologic Subtypes

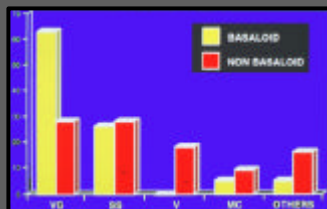
## SCC, NOS (not otherwise specified)



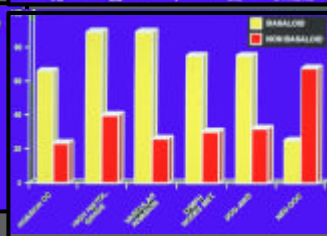
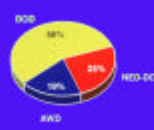
## Basaloid Carcinoma



## Basaloid Penile Carcinoma

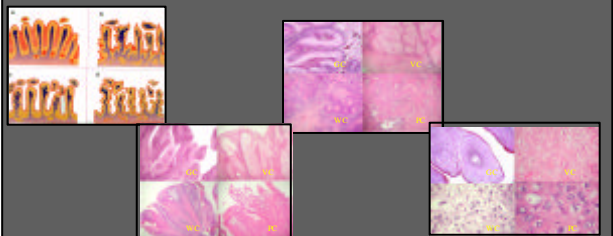


### BASALOID CARCINOMAS-FOLLOW UP



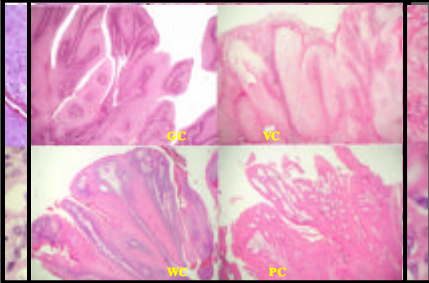
## Verruciform Tumors

	Warty Carcinoma	Giant Condyloma	Verrucous Carcinoma	Papillary Carcinoma, NOS
Papillae	Long & undulating, Condylomatous, complex	Arborizing, non undulating	Straight	Variable, complex
Fibrovascular cores	Prominent	Prominent	Rare	Present
Keratinic cysts	Prominent and diffuse	Present at surface	Absent	Absent
Base	Rounded or irregular	Regular, broad and pushing	Regular, broad and pushing	Irregular and jagged
Grade	1B	1	1	1B
HPV	HPV 16	HPV 6 and 11	Absent	Absent
Metastasis	Yes	No	No	Yes

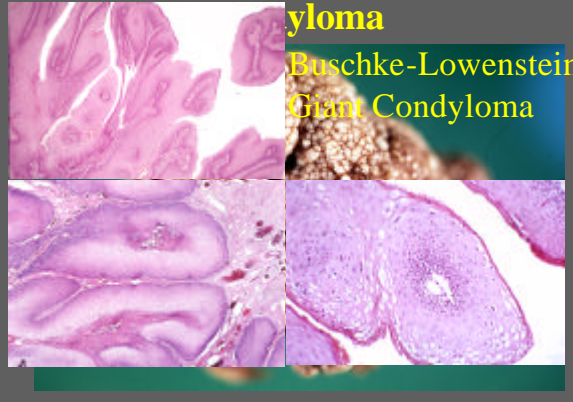


# Verruciform Tumors

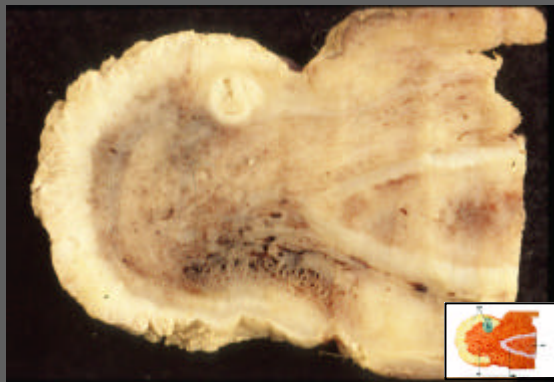
	Warty Carcinoma	Giant Condyloma	Verrucous Carcinoma	Papillary Carcinoma (VZG)
Papillae	Long & undulating	Condyломatous, complex	Arborescing, non undulating	Straight
Cytopathologic changes	None	None	None	None
Koilocytic atypia	Prominent and diffuse	Present at surface	Absent	Absent
Base	Rounded or irregular	Regular, broad and pushing	Regular, broad and pushing	Irregular and jagged
Grade	III	I	I	III
HPV	HPV 16	HPV 6 and 11	Absent	Absent
Metastasis	Yes	No	No	Yes



# Buschke-Lowenstein Giant Condyloma



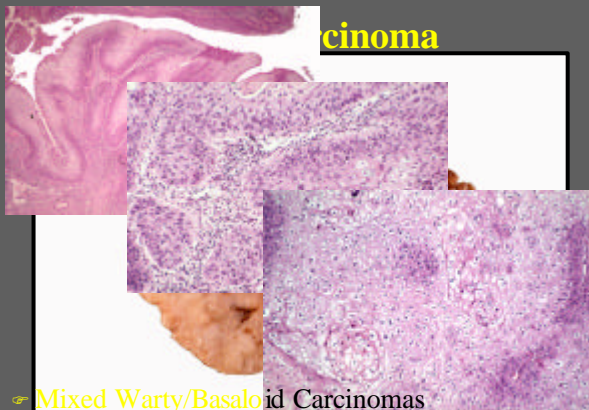
# Verrucous Carcinoma



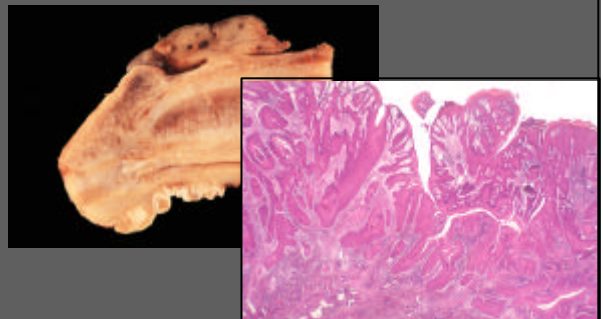
# Verrucous Carcinoma

- ◆ Glassy cytoplasm
- ◆ Keratohyaline granules
- Nuclei:
  - ◆ Low nuclear grade
  - ◆ Centrally located vesicular
  - ◆ Absence or paucity of koilocytes
- Cellular connections
  - ◆ Intercellular edema
  - ◆ Well formed cellular bridges
- Architecture:
  - ◆ Rare fibrovascular cores
  - ◆ Pushing border

# Carcinoma

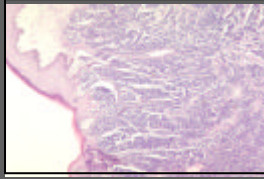


# Papillary carcinoma



## Rare Variants

- ☞ Small cell
- ☞ Adenosquamous
- ☞ Sarcomatoid



## Foreskin Carcinoma

- ☞ Associated to Lichen sclerosus
- ☞ Low grade
- ☞ More superficial



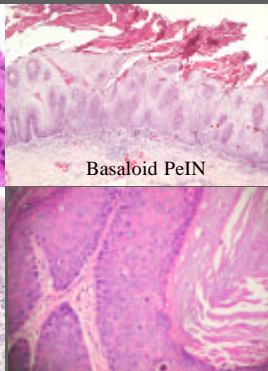
## Penile Intra-epithelial Neoplasia

- \*Low grade PeIN 33 yrs
- \*High grade PeIN 3-7 yrs later
- \*Subtypes

Warty PeIN

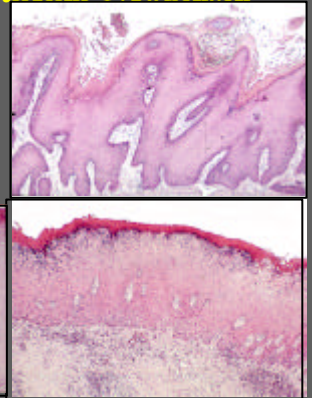
Basaloid PeIN

PeIN, NOS



## Penile Intra-epithelial Neoplasia

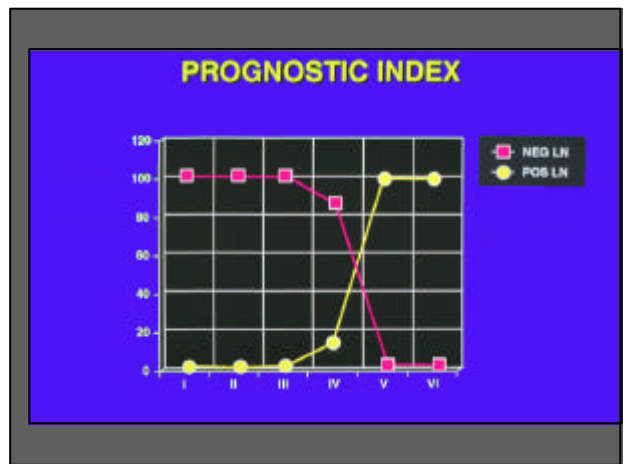
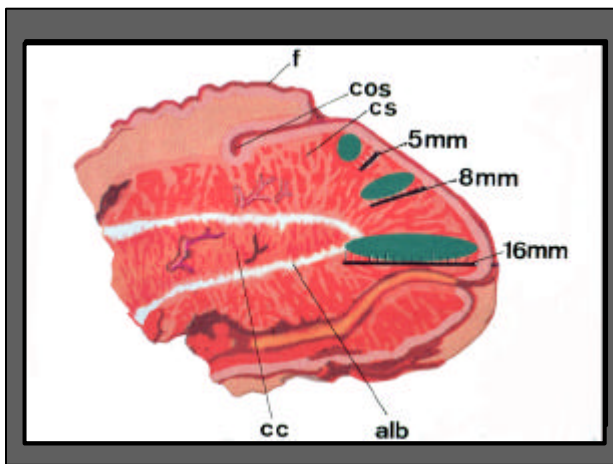
- ☞ Hyperplastic-hypertrophic PeIN
- ☞ Micaceous PeIN
- ☞ Pseudoepitheliomatous PeIN



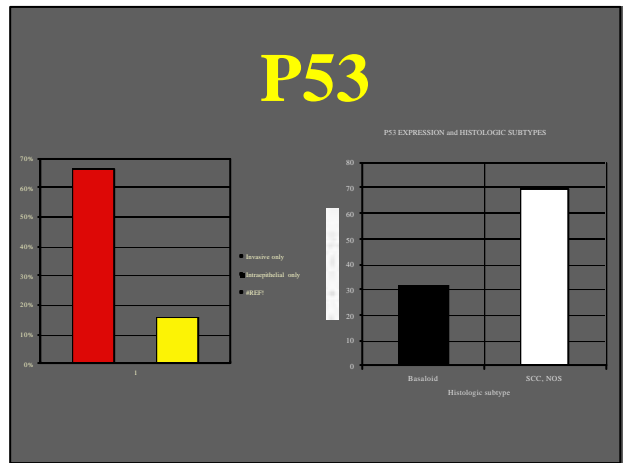
## Prognostic Index

### Prognostic factors

- ☞ Primary Tumor Site
- ☞ Anatomic site
- ☞ Morphologic Patterns
- ☞ Histologic subtypes
- ☞ Histologic grade
- ☞ Anatomic level & depth of infiltration in mm.
- ☞ Mitosis index
- ☞ Vascular invasion



# Molecular Changes



- ### Molecular Anatomy
- ☞ P21
    - 40 % of PeCA have p21
  - ☞ DNA ploidy
    - Prognostic significance questionable
    - Small nuclear size-bad prognosis (basaloid ?)
  - ☞ Ki-67
    - Growing edge of Verrucous carcinoma
  - ☞ Telomerase
    - 85 % of PeCA/ 80 % of normal epithelium and corpora
  - ☞ Cytogenetics
  - ☞ C-RAS
    - Found only in second metastasis of one case- Progression ?
  - ☞ ABO
    - Lost in most PeCA
  - ☞ SCRA
    - 54 % of PeCA
    - Lost most frequently (91%) in metastatic PeCA
  - ☞ Glucose transporter -1
    - Present in proliferating areas of tumor

- ☞ Penis-Cervix
  - ☞ Penis-Vulvar/anal cancer
  - ☞ Male-Female HPV transmission
  - ☞ Estrogen/progesterone receptors
  - ☞ Immune response
- Marital Clusters**  
**Micro-environmental**  
**Relationships**
- \*Some males more prone to HPV transmission with cervical cancer (29 cases)
- man developed cervical cancer



# Micro-environmental Relationships

## Penile carcinoma-Cervix carcinoma

- Anecdotal reports of concurrent cancers
- Puerto Rican couples: no correlation

Male w/  
PeCA



Risk of female developing preinvasive or invasive cervical cancer: 1.05/1.75

## Penile carcinoma-Vulvar carcinoma

- Histologic and demographic similarities-most similar cancers
- Same relation to HPV in invasive (basaloid/warty) and in situ lesions
- Anecdotal reports of concurrent cancers
- However no established link

# Micro-environmental Relationships

## Penile carcinoma-Anal canal carcinoma

- More common in women and homosexual men
- Similar to cervix
- Strong relation to HPV

## Penile carcinoma-Perianal skin carcinoma

- More common in heterosexual men
- Similar to vulva and penis
- Not related to HPV

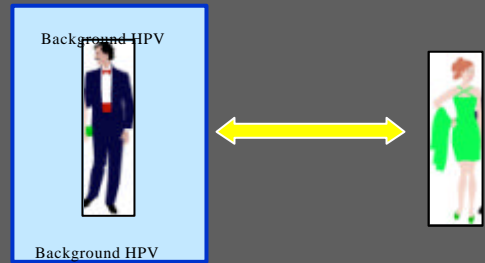
# HPV Male/Female

- Sexual transmission:
- Increased incidence of lesions
- Straight transmission:
  - 6/11 - condyloma
  - 16/18 - CIN

HPV Study	# of sites	With Cervical lesions: % of male partners with HPM lesions	With Penile Cancer: % of female partners with HPM lesions
Alvará	411	-	-
Chelak	6	-	833 (90)
Kotanda	167	29.94%	-
Minoz	210	25.7% (18.9 for control odds ratio of .2)	-
Castrosgu	816	Higher than controls	-
Selvey	35	82.9% (2935)	-
	50	50% (25 x 3 in control)	-
Barrao	186 CIN 294 condyloma	64.4%	-
Amund	1000	9-10%	-
Maymon	63	24%	-

# HPV Relationship Male-Female

Case control studies

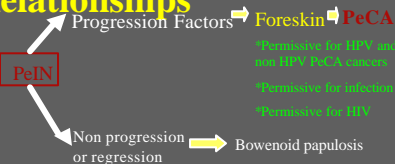


Differs according to populations  
Colombia 5x Spain

# Micro-environmental Relationships



Male  
HPV  
reservoir

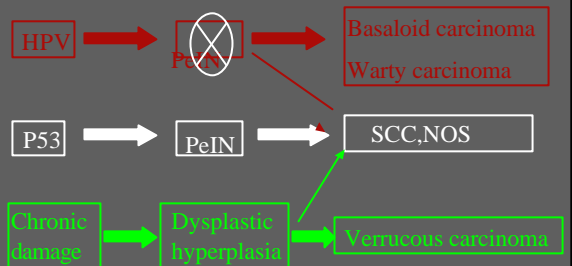


## ER/PR

- HPV has progesterone response elements
- Cervix tendency to HPV progression
- Penis and PeCA lack ER/PR

## Immune response

# Penile Carcinoma



# Penile Carcinoma

