Cutaneous HPV: a possible cause of skin cancer?

Joint Graduate Seminar

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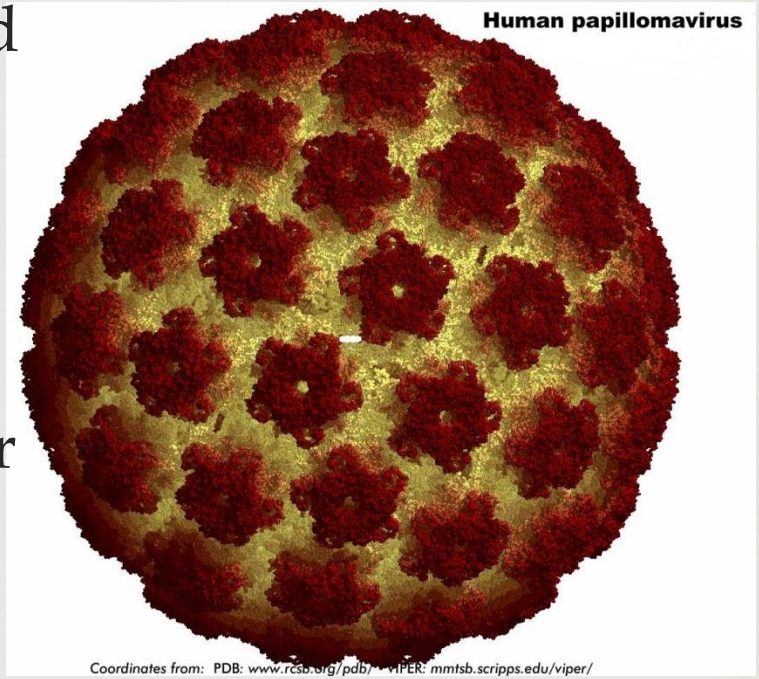
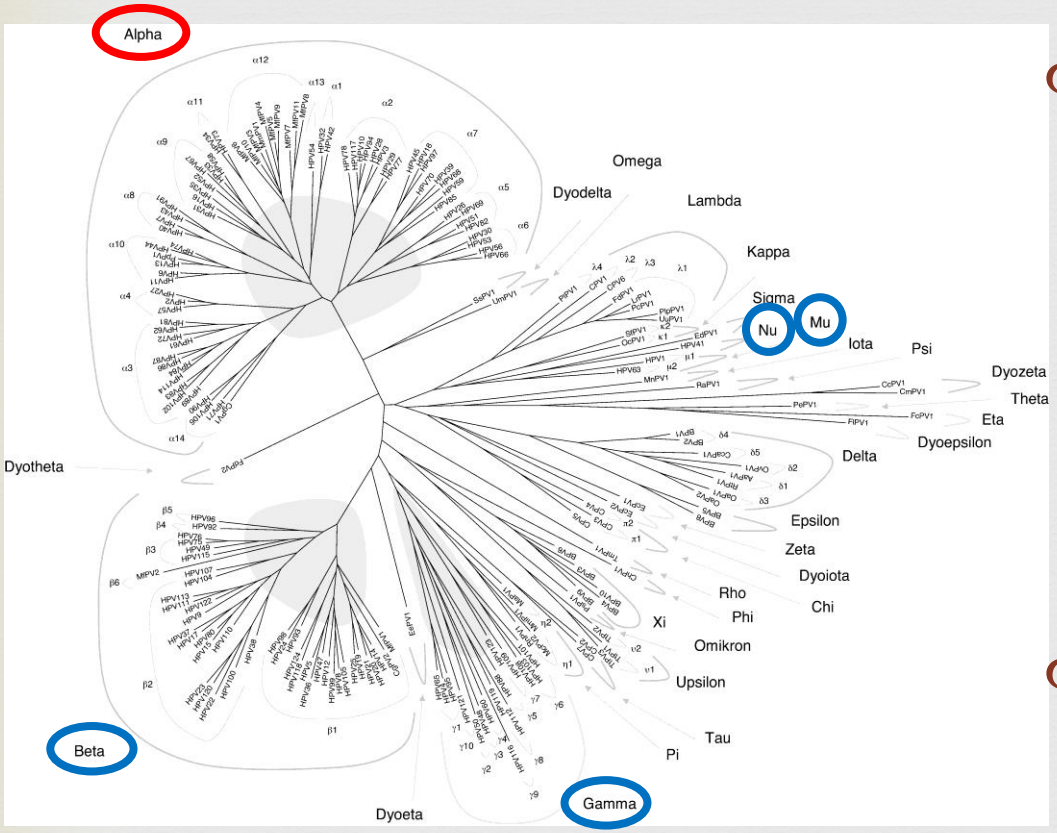
Human Papillomavirus (HPV)

- Non-enveloped, double-stranded DNA virus
- *Papillomaviridae* family
- More than 150 HPV types
- Infect keratinocytes of the skin or mucous membranes
- Primary cause of cervical cancer



Classification of HPV



- Mucosal HPVs:
  - Within α-PV genus
  - Low-risk types
    - Genital warts
  - High-risk types
    - Cervical and anogenital cancers, some cancers of head and neck
- Cutaneous HPVs:
  - β, γ, μ, and ν genera

<Bernard et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* (2010) 401: 70-79.>

Epidemiology of Cutaneous HPV

- Ubiquitous, usually without clinical symptoms.
- Skin warts occur most commonly in children and young adults.
- Transmitted by skin-to-skin contact.
- "Latent" infection, incubation period about 2-6 months.
- HPV 5, 8, and 23 are most frequently detected.

Disease associated with cutaneous HPV infection

- Common warts
  - exophytic, multiple, irregular, rough nodules
  - on fingers, hands, elbows and knees
  - HPV 2, 4, 7; occasionally other types in immunosuppressed (e.g. HPV 75-77)

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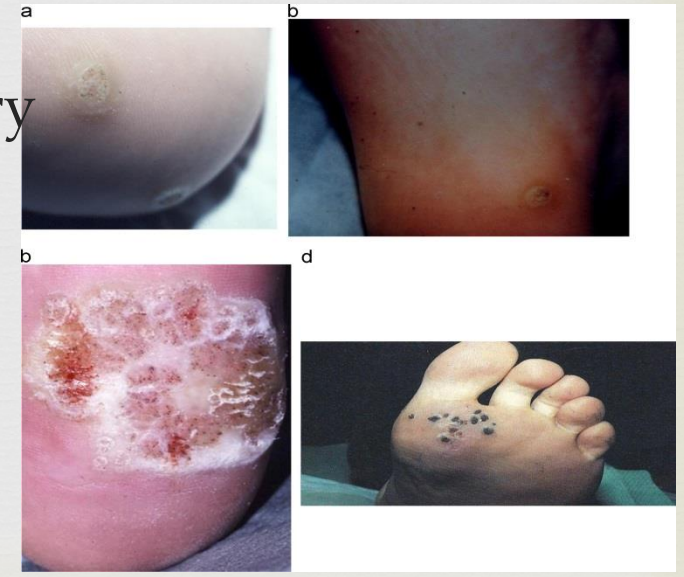
- Flat plane warts
  - small and less rough, presenting as flat-topped papules, flesh coloured or lightly pigmented
  - on the face and back of the hands
  - HPV 3, 10, occasionally HPV 26-29 and 41

- Plantar warts
  - a rim of keratin surrounding a softer keratotic plug, with scattered capillary points which bleed on paring down
  - on weight-bearing areas or pressure points of the feet
  - HPV 1, 2 and 4



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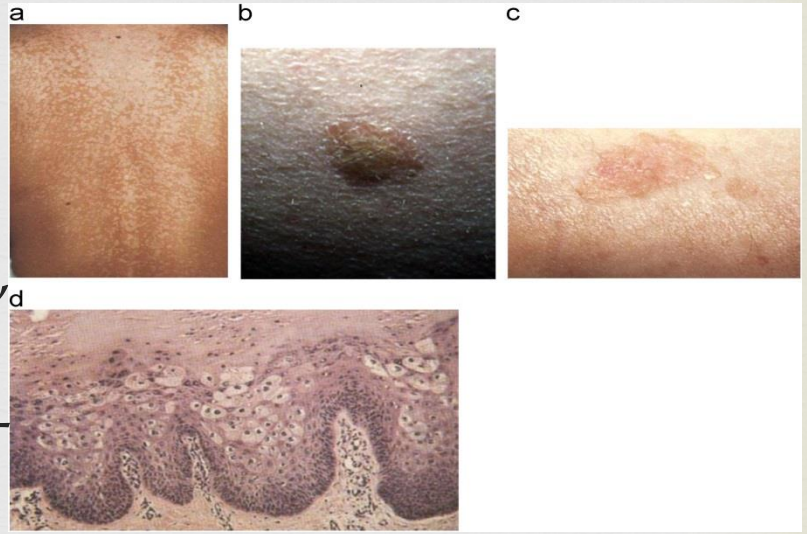
- Epidermodysplasia verruciformis (EV)
  - a rare autosomal recessive condition associated with extensive warts and skin cancer.
  - Plane wars
    - HPV 3, 10
  - Pityriasis-like plaques
    - HPV 5, 8; less commonly 9, 12, 14, 15, 17, 19-25, 36-39, 47 and 49
  - Squamous cell carcinomas of sun-exposed skin
    - HPV 5, 8; less commonly 14, 17, 20 and 47



- EV-HPV types
  - a sub-set of about 20 β-HPV types found in EV patients.

Oncogenic?

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Oncogenicity of Cutaneous HPV

- Mechanism contributes to cutaneous HPV-associated cancer development is unclear.
- Most studied EV-HPV types:
  - HPV 5 (β-1), 8 (β-1), and 38 (β-2)
  - IARC determined HPV 5 and 8 as possible carcinogens (group 2B)
- Oncogenes:
  - E6 and E7

Table 1. Association of E6 and E7 proteins encoded by high-risk α, low-risk α, and β HPVs with cellular proteins.

	E7	E6		
	pRB bdg/deg	p53 deg	p300 bdg/deg	BAK deg
High-risk α HPVs (eg. HPV 16)	+/+	+	+/-	+
Low-risk α HPVs (eg. HPV 6)	+/-	-	+/?	+
β HPVs (eg. HPV 5)	+/-	-	+/+	+

* "bdg" denotes "binding" and "deg" denotes "degradation"

Skin Cancer

- The most common form of cancer in the US
  - more than 1 out of every 3 new cancers are skin cancers
- Main risk factor
  - exposure to sunlight (UV radiation)
- Types of skin cancer
  - Melanoma
  - Non-melanoma skin cancer
    - Basal cell skin cancer (BCC)
    - Squamous cell skin cancer (SCC)

Melanoma

- The most dangerous form of skin cancer
  - Causes the majority (75%) of deaths related to skin cancer
  - Kills ~9,000 people in the US annually
- Often resemble moles; some develop from moles
- Other risk factors
  - Dysplastic nevus
  - More than 50 common moles

Basal Cell Cancer

- The most common form of skin cancer
  - ~2.8 million cases are diagnosed annually in the US
- Rarely lethal but often disfiguring
- Other risk factors
  - Old scars, burns, ulcers, or areas of inflammation on the skin
  - Exposure to arsenic at work
  - Radiation therapy

Squamous Cell Cancer

- The second most common form of skin cancer
  - ~700,000 cases are diagnosed each year in the US
  - The incidence increased up to **200%** over the past three decades in the US
- Other risk factors are same as BCC, besides
  - **HPV infection**

Is Cutaneous HPV A Possible Cause of Skin Cancer?

Cutaneous HPV & Skin Cancer

- Initial evidence:
  - Identification of HPV 5 and 8 from EV patients;
  - Etiologic role of specific HPVs in cervical cancer.
- Epidemiologic evidence
- Plausible biological roles

Epidemiologic Evidence

Is HPV Involved in the Development of SCC in **Immunocompetent** Individuals?

Study	Cases	Controls	Correlation	Finding
Karagas (2010)	663 SCCs 898 BCCs	805	Positive in SCC but not BCC	SCC cases, but not BCC cases, showed a higher prevalence of each of the individual β-HPVs tested compared with controls. The odds ratios for SCC were greater with more β types positive
Asgari (2008)	85	95	Positive and negative	No difference in HPV detection between various HPV species in case versus control tissue. HPV DNA from β-2 HPV was more likely to be identified in tumors than in adjacent healthy tissue in cases
Patel (2008)	101	101 BCCs	Positive	SCC lesions were significantly more likely to be infected with β-1 HPV (includes types 5 and 8) than BCC samples
Forslund (2007)	82	92	Positive and negative	Similar HPV detection rates in SCC and benign lesions. β-2 HPV predominated in SCC; β-1 were primarily found in benign lesions
Feltkamp (2003)	161	333	Positive	SCC relative risk was significantly greater in those seropositive for HPV 8 and 38

Is HPV Involved in the Development of SCC in **Immunosuppressed** Individuals?

Study	Cases	Controls	Correlation	Finding
Proby (2011)	210	394	Positive with concordance	β-HPV DNA was highly prevalent (>94%), with multiple types frequently detected in both groups. Individuals with β-HPV DNA and antibodies present for the same HPV type (concordant DNA and antibodies) were at significantly greater risk of SCC, even if each measure did not independently show an association
Berkhout (2000)	81	31	Positive	HPV DNA was more common in SCC than normal skin

Negative Evidence

Study	Cases	Controls	Immune status	Correlation	Finding
DeRisi (2011)	67	0	Not reported	Negative	Transcriptome sequencing did not identify β-HPV expression in any of the skin tumors
Andersson (2008)	72 SCCs 160 BCCs	121	Immuno-competent	Negative	Seroprevalence was the same in patients with SCC versus controls but higher in SCC patients versus BCC patients
Struijk (2006)	64	57	Not reported	Negative	Cutaneous HPV E6 seropositivity did not associate with an increased risk of SCC
Boxman (2000)	25 SCCs 51 BCCs	76	Immuno-competent	Negative	EV-HPV did not associate with a significantly greater risk of SCC or BCC

Plausible Biological Roles

- As a cofactor in only a subset of SCCs
- As an initiating factor only – “hit and run” mechanism
- As a bystander, with no role in UV-induced SCC

Conclusions

Cons

- Not all SCCs are infected with HPV.
- Low HPV viral loads and minimal gene expression are detected in tumor tissue.

Pros

- HPV may be involved in only a subset of SCCs or in high-risk populations.
- HPV may promote cutaneous oncogenesis through the “hit and run” phenomenon.

Conclusions

- In summary, more data are needed to confirm or contradict the role of cutaneous HPV in skin cancer in the general population and particularly in those who are immunosuppressed.

The end.