NCPTS

HPV and Cervical Cancer

Clinical aspects of Human Papillomavirus Infection

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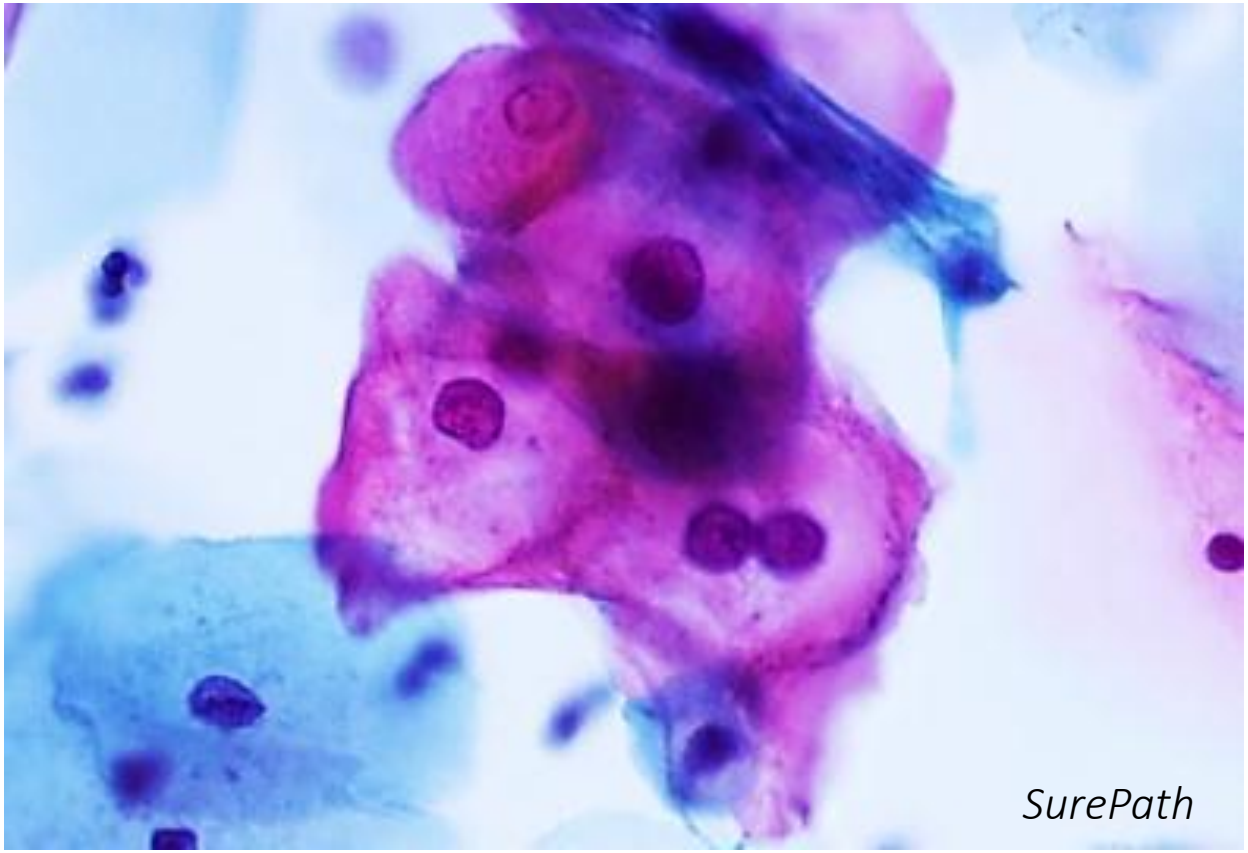
NCPTS Training Team
August/September 2017



Cytological evidence of HPV infection:
What is going on at a clinical, cellular and molecular level?

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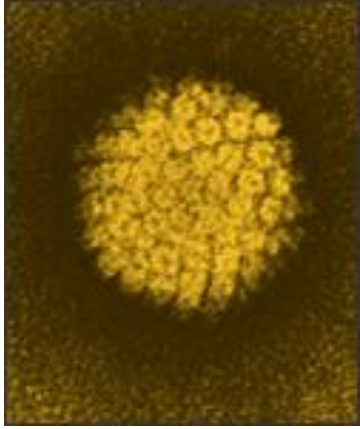
Cytological evidence of HPV infection:
What is going on at a clinical, cellular and molecular level?

HPV Infections of the genital tract



HPV viruses infect a range of different sites in humans. Different subtypes (genotypes) of the virus cause different manifestations of infection.

HPV subtypes are divided into cutaneous or **mucosal types:** at least 40 subtypes of HPV infect the genital tract/oropharynx

- genital warts are usually caused by low-risk HPV types
- high-risk HPV infections are usually asymptomatic but cause cancer in a very small proportion of those infected

Persistent hrHPV infection causes almost all cancers of the cervix as well as most cancers of the vagina, vulva, penis and anus.

Topics

1. Prevalence of HPV infection: How common is it?
2. Acquiring HPV: How do you get it?
3. Developing lesions: What happens if you have an HPV infection?
4. Clearing an HPV infection: Getting rid of it.
5. HPV and Cancer

1. Prevalence: Women

HPV infection: **Common Sexually transmitted Usually transient**

Worldwide [1] : 157,879 women with normal cytology:

(any type) HPV positive = 10.4% (CI 10.2-10.7)

By region: Africa = 22.1%

Central America and Mexico = 20.4%

North America = 11.3%

Europe = 8.1%

Asia = 8.0%

Estimated that 291 million women worldwide are carriers of HPV DNA: 32% infected with HPV 16 or 18 or both. Range of subtypes is the same as those with lesions, but proportions with HPV 16 and 18 are lower

Artistic trial (UK) [2] : 20,697 women 20-64 years in the English screening programme, (normal or abnormal cytology)

hrHPV +ve = 15.6% HPV 16 = 3.3% 18 = 1.1 % Other hrHPV = 11.2%

Refs:

1. Worldwide prevalence and genotype distribution of cervical HPV in women with normal cytology: a meta-analysis. de Sanjose S et al *Lancet Infect Dis* 2007 Jul;7(7):453-9
2. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. Kitchener HC et al *British Journal of Cancer* 2006 95, 56-61

HPV Prevalence: Age variation

– Prevalence is high in women under 30 years of age. After age 30, the prevalence of HPV infection declines rapidly

- Point prevalence in sexually active young women of about 25%
- ARTISTIC (UK) Data: 20-24 years = 40% hrHPV +ve
  35-39 years = 12%
  50+ years = 7% or less
- 80% of sexually active adults are likely to be infected at some point during their life.

"Greatest behavioural risk for acquisition of mucosal HPV is sexual contact, specifically the greater number of lifetime sexual partners"

Carter et al. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2011;51:103-08

HPV: Commonly acquired

Anogenital infection is common in people who have recently become sexually active.

- UK Study [1] : 242 women with one sexual partner: risk of acquiring an HPV infection was about 45% after three years
- USA [2] : 603 university students in Washington State followed. At 2 years, cumulative incidence of first-time HPV infection was 32.3%. Smoking, oral contraceptive use and a new male partner were predictive of incident infection
- hrHPV infection occurs in about 50% of women within 6 months after sexual debut (Kitchener, UK)

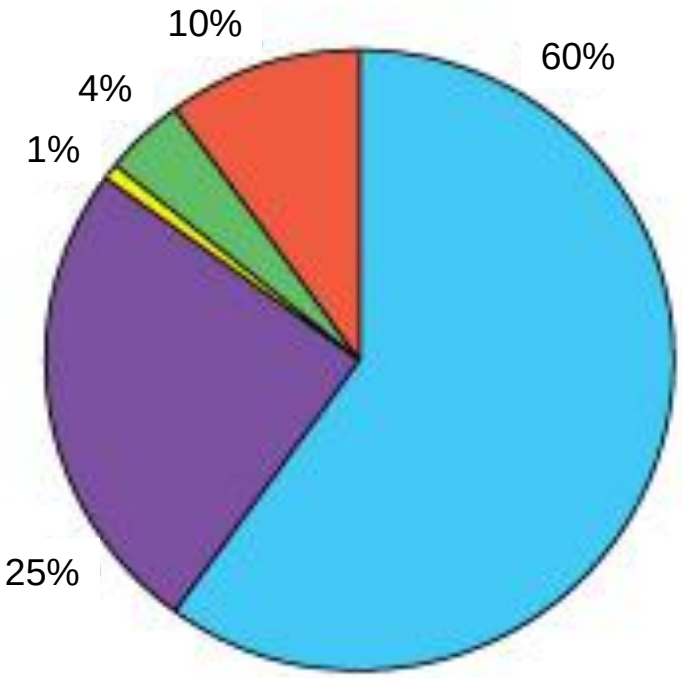
1. High incidence of cervical human papillomavirus infection in women during their first sexual relationship. Collins A et al *BJOG* Jan 2002, Vol 109,pp96-98
2. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Winer RL et al Am J Epidemiology 2003 Feb 1;157(3):218-26
3. Report to the National Steering Committee (UK). Professor HC Kitchener, Chair Advisory Committee for Cervical Screening June 2015

Prevalence: Men

- Prevalence of anogenital HPV probably higher than for women

- Men who have Sex with Men (MSM) have high rates of anogenital HPV

- *Refs:*
- *Giuliano AR et al Incidence and clearance of genital human papillomavirus infection in Men (HIM): a cohort study. The Lancet 2011;377(9769):932-40*
- *Goldstone S et al. Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men. Journal of Infectious Diseases,2011 Jan 1;203(1):66-74*



Visible genital warts

Subclinical HPV
Detected by cytology/colposcopy

Subclinical HPV
Detected by molecular HPV Tests

Prior infection

No prior or current infection

Adapted from Koutsky et al
Am J Med: 102 (5a) 1997

Estimated prevalence of genital HPV infection among men and women 1-49 years of age in the US (1994)

Note: "Subclinical" means not visible to the naked eye

Acknowledgement: The New Zealand HPV project ***www.hpv.org.nz***

Type-specific oncogenic human papillomavirus infection in high grade cervical disease in New Zealand

Leonardo Simonella, Hazel Lewis, Megan Smith, Harold Neal, Collette Bromhead and Karen Canfell

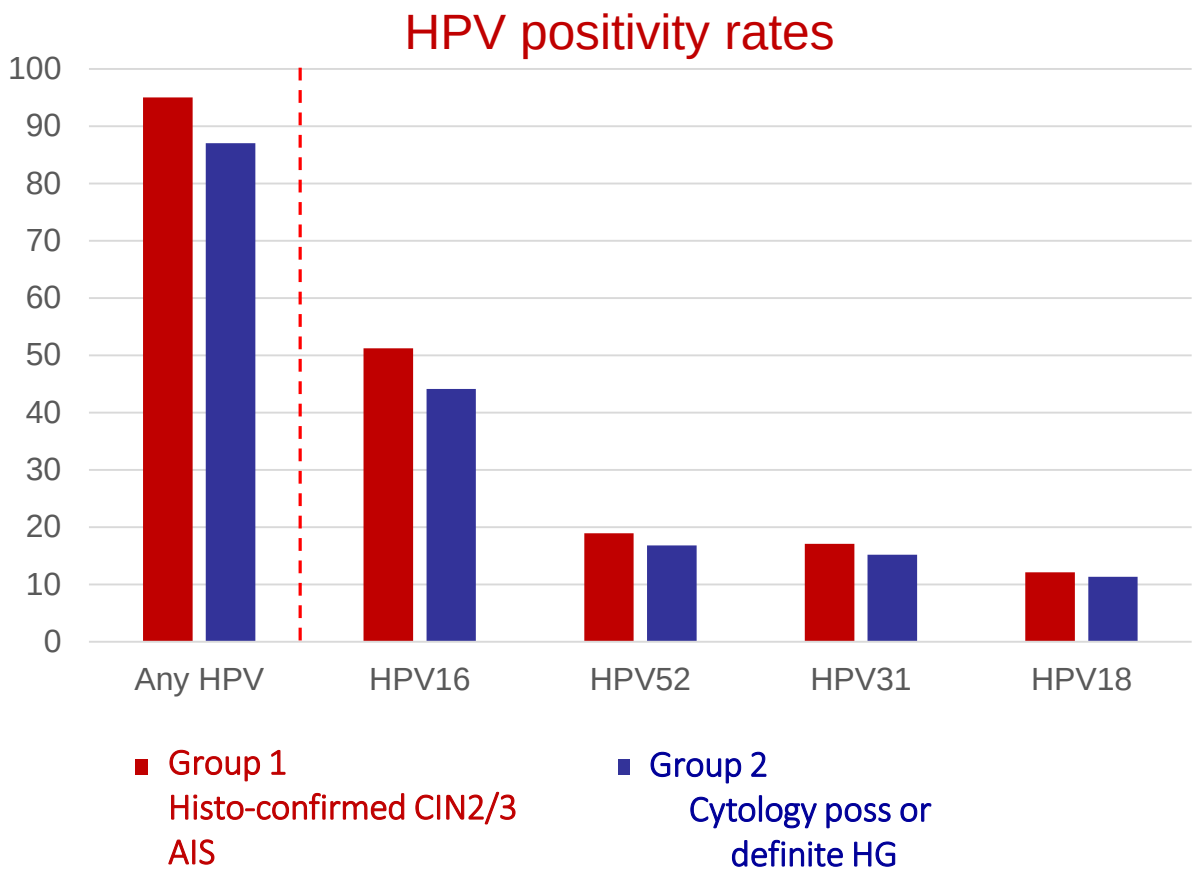
BMC Infectious Diseases 2013, 13:114

Aim: to measure the pre-vaccination prevalence of hrHPV in 20-69 yrs women with high-grade squamous and glandular lesions

594 women 20-69 years from NCSP-Register 2009-2011

LBC specimens were genotyped for 37 HPV subtypes

Results



Group 1: Histology confirmed

356 women = CIN2/3

6 women = AIS/glandular dysplasia

Any hrHPV infection: 95%

HPV 16/18: 60%

Most common types: **16** (51.2%)

52 (18.8%)

31 (17.1%)

18 (12.1%)

Group 2: Poss/definite HG cyto

594 Women

Any hrHPV infection: 87%

HPV 16/18: 53%

Most common types: **16** (44.1%)

52 (16.8%)

31 (15.2%)

33 (11.8%)

18 (11.3%)

HPV 16/18 rates were highest in women 20-29 years of age (women with confirmed CIN3)

International comparison

- The prevalence of HPV 16 in CIN2/3 was broadly consistent with that in Australia and Europe but higher than that reported for North America, Asia and South/Central America.
- The prevalence of HPV 18 in CIN2/3 was broadly consistent with Australia and North America but higher as that reported for Asia, Europe and South/Central America.

- The prevalence of HPV 52 was higher than that reported from other regions

2. Acquiring HPV: How do you get it?

- Almost always sexually transmitted
- Probability of transmission is very high: greater than 50% following unprotected sexual intercourse with a person with a productive anogenital infection
- Greatest behavioural risk of HPV infection is sexual contact
  - HPV infection rates increase in proportion to the number of lifetime sexual partners
  - can get low-risk HPV transmitted to the vulva/vagina via fingers, tampons. Transmission by non-penetrative sexual intercourse is described
  - vertical transmission in Juvenile Respiratory Papillomatosis
  - condoms may reduce risk but are not fully protective

What happens next?

- Acute infection generally occurs 6-12 weeks after exposure but the latency period is very variable
  - Warts often appear after 3-6 months but can be much later
  - HPV can be detected by molecular techniques before the acute infection is apparent by cytology/colposcopy
- Women who have been sexually inactive for many years can suddenly develop genital warts or cervical abnormalities
  - Important that women know that developing warts or cervical lesions many years into a long-term sexual relationship does not necessarily imply other recent sexual contacts

3. Developing lesions

After acquiring an HPV infection what can happen next?

1. **Asymptomatic** infection with no cytologic/histologic lesion, which resolves

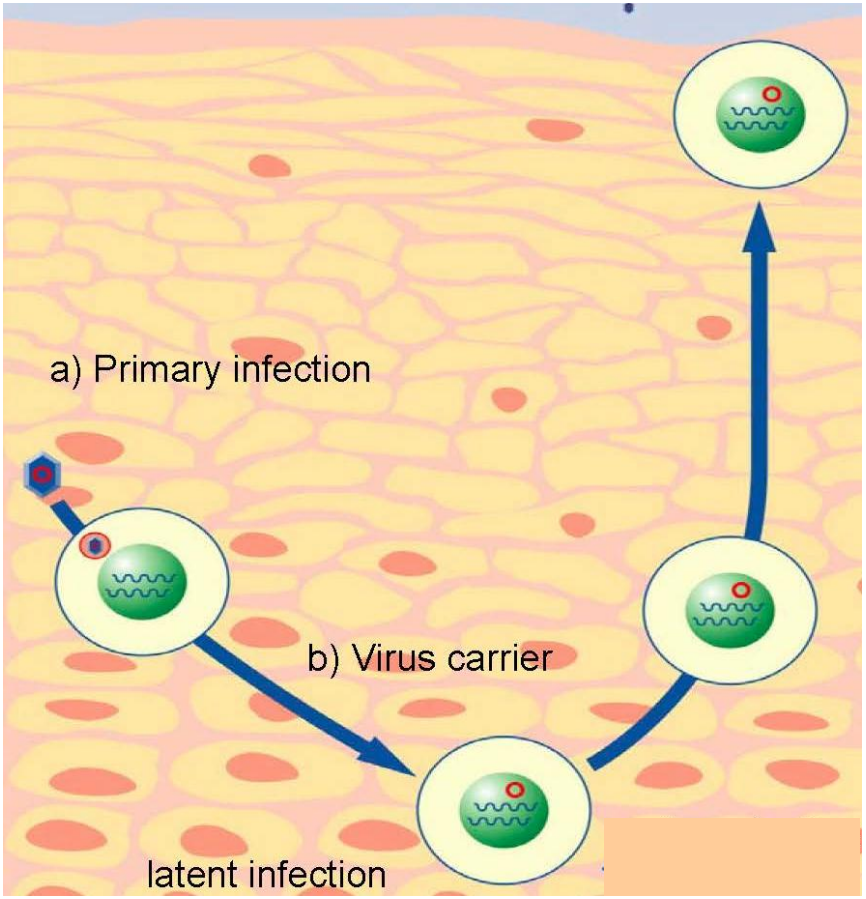
2. **Asymptomatic** infection with a low-grade lesion detectable by cytology/histology

3. **Asymptomatic** infection with a high-grade lesion detectable by cytology/histology. May progress if persists and become **symptomatic if invasive**.

4. **Symptomatic** warts: usually low-risk HPV

Whether hrHPV Testing is positive will depend on the HPV subtype and the viral load

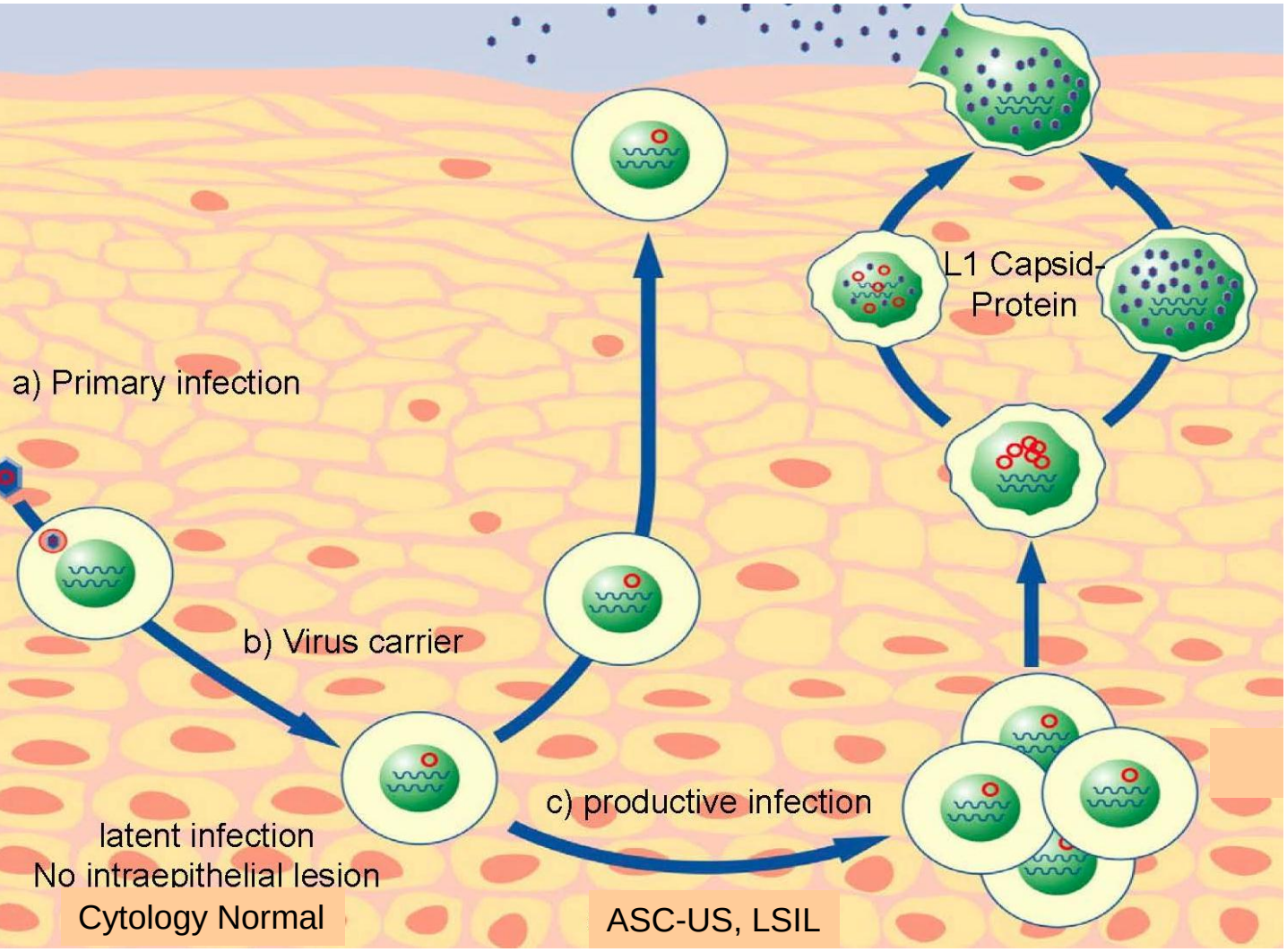
What is happening in the epithelium?



low viral load; no cytologic abnormality

- HPV infects epithelial cells
- the virus enters through microabrasions in the epithelium which allow it to be deposited on the basement membrane where it binds
- vial particles enter basal cells over the next 2-4 hours
- as soon as they are taken up, the envelope protein is decomposed and the viral DNA enters the cell nucleus where it exists as episomes within the nucleus but separate from the host DNA

What if a productive viral infection develops?



high viral load; low-grade cytologic/histologic abnormality

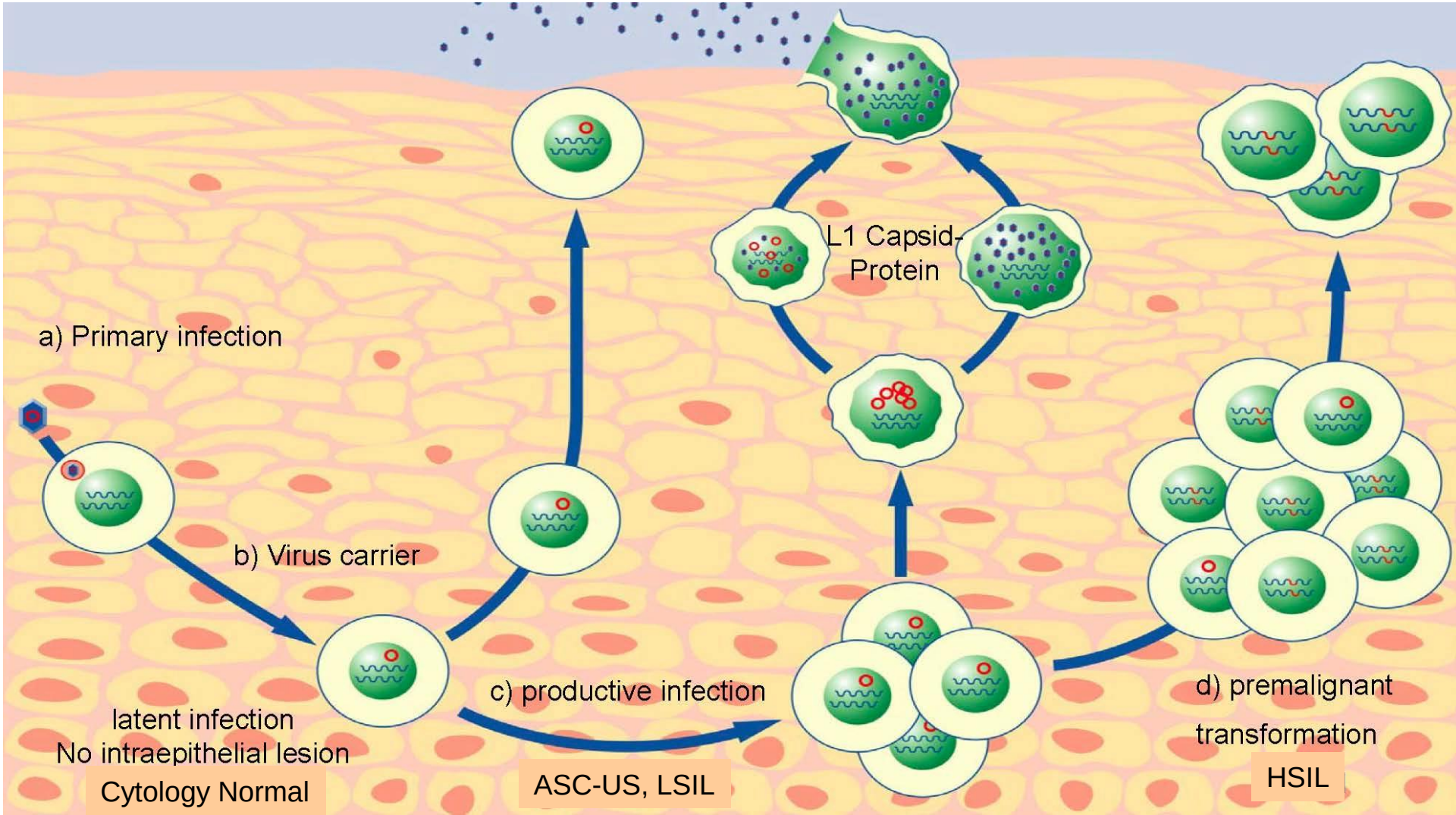
Episomal HPV DNA remains in the nucleus

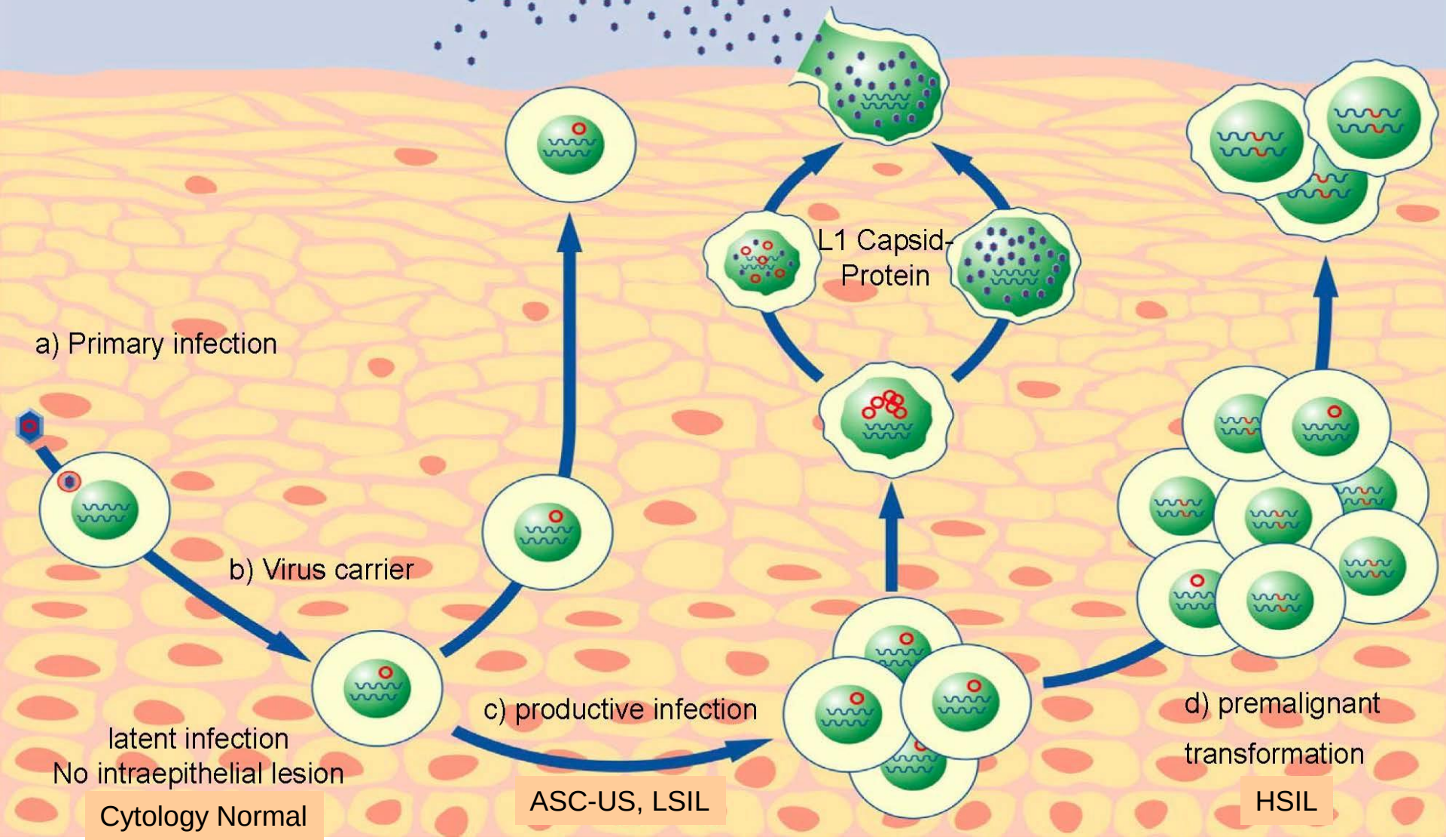
- Viral assembly occurs in the maturing squamous cell resulting in release of viral particles

-Takes three weeks (time for basal cell-superficial cell maturation)

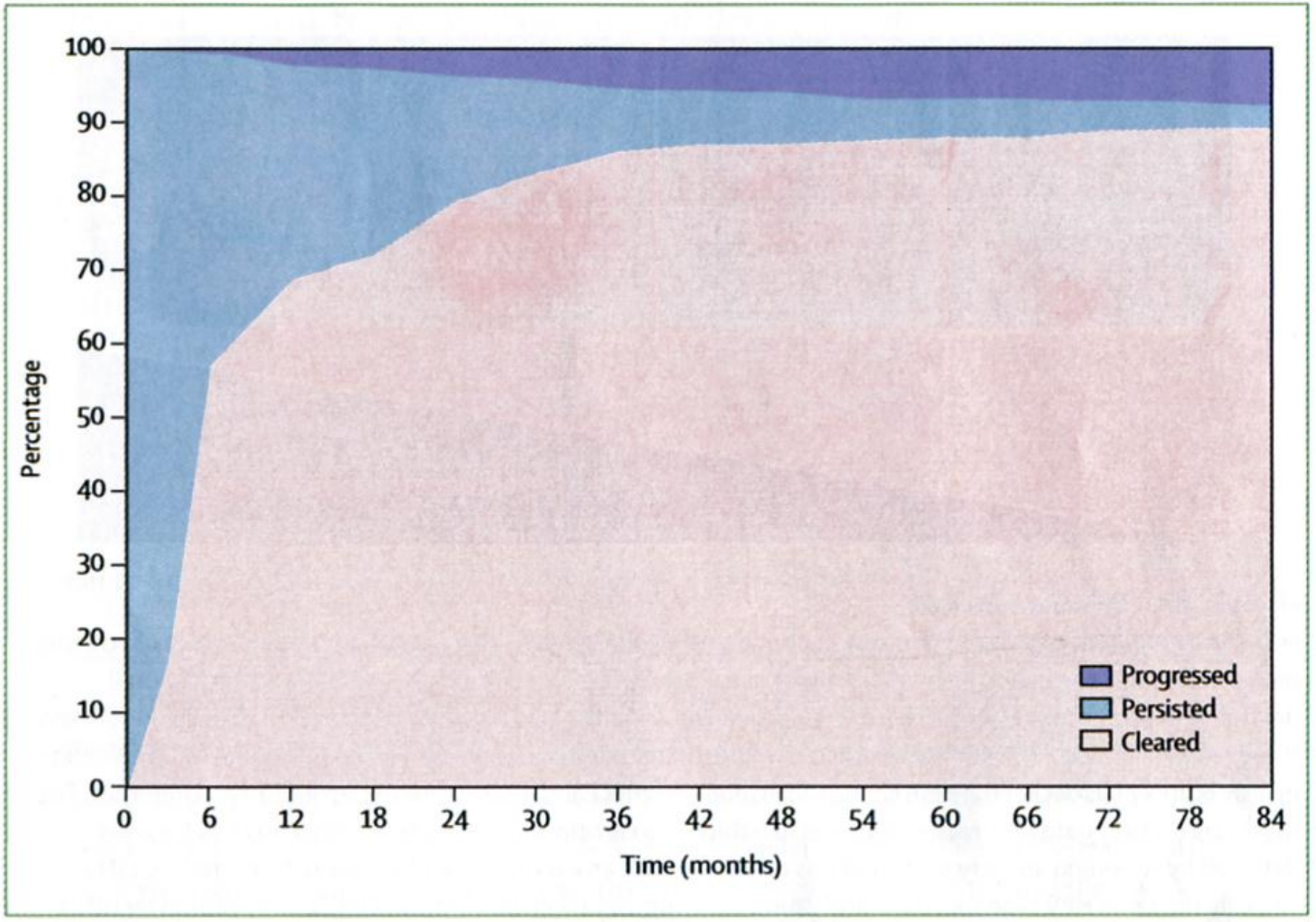
What about high-grade lesions?

- HPV DNA becomes linear and integrates into host DNA
- results in cellular effects leading to uncontrolled cell proliferation





"Human Papillomavirus and Related Diseases From Bench to Bedside A Diagnostic and Preventive Perspective"
Ed: Davy Vanden Broeck, ISBN 978-953-51-1072-9, Published: April 30, 2013 © The Author(s).
Chpt 4:HPV L1 Detection as a Prognostic Marker for Management of HPV High Risk Positive Abnormal Pap Smears (Ralf Hilfrich)



Typical pattern of clearance, persistence and progression of high-risk HPV infections with time

Progression

- Old idea of CIN1 → CIN2 → CIN3 now regarded as an oversimplification: many CIN3 lesions probably arise de novo
- Factors associated with progression: ongoing HPV exposure, hrHPV genotype, HPV viral load, immune status
- Smoking is an independent risk cofactor which may increase progression rates

HPV subtypes and pre-invasive lesions

Genital warts: 90% = HPV 6 and 11

LSIL: 10% = HPV 6 and 11

Up to 35% = 16 and 18: more likely to progress to HSIL

Remainder = a mix of other high-risk and low-risk viral types

HSIL: majority have 16, 18. Also 52,31,33 in NZ

remainder = mainly other hrHPV subtypes

4. Clearing the virus: becoming HPV negative

- Resolution = the virus is eradicated or suppressed to non-detectable levels
- Most HPV infections are rapidly cleared by cell-mediated immune mechanisms, usually in 6-12 months.
  - 80-90% become HPV negative on HPV testing by 2 years.
  - 98% of infections resolve spontaneously in 3-5 years
  - hrHPV subtypes take longer to clear. Type-specific viral persistence may be seen in around 30% of women with hrHPV subtypes after 2 years.
- The 2% of women in whom high-risk HPV infection persists after 5 years, are the group at significant risk for developing cervical cancer. Persistent HPV infection is associated with increasing risk of high-grade disease.

What role does immunity play?

- HPV life cycle is within squamous cells so is hidden from host immune systems
  - no blood-borne viraemic phase
  - infected epithelial cells undergo natural death, without invoking an inflammatory response
  - if an immune response does occur after natural infection, there are LI neutralising and binding antibodies at the basement membrane which prevent the virus binding.
  - IgG and IgA antibodies throughout the epithelium bind to the HPV before it is able to infect cells

Clearing the virus: resulting immunity

Clearance leaves a woman partly or fully immune to that particular genotype

- after acute infection with hrHPV with HPV 16, only about 50% or women will seroconvert i.e. many women do not have antibodies to HPV 16 or 18 despite having had an infection
- an insufficient immune response leaves these women at risk of future infection with the same HPV subtype
- immunisation helps a lot here because the antibody titres induced by the vaccines are considerably higher than those achieved by natural infection

No screening test is perfect

There is a very small number of high-grade lesions/cancers that will be hrHPV test negative.

Some will be HPV-related:

- a subtype of HPV that is rarely oncogenic so is not in the hrHPV test
- low viral load
- loss of LI target (viral capsid protein) as invasion develops

Other rare types of cervical cancer than are not due to HPV.

- most are aggressive rapidly developing cancers
- we rarely detect these by screening asymptomatic women

5. HPV and Cervical Cancer

- HPV infection is necessary but not sufficient in causing cervical cancer
- Cancer is a rare outcome of hrHPV infection. Women worldwide:
  - Estimated prevalence of genital HPV infection = 326 million
  - Annual incidence of new cases of cervical cancer = 530,000
- Progression to cancer is generally slow
  - Modal age of first hrHPV infection between 15 and 25 years.
  - Modal age of invasive cervical cancer is 35-50 years (in unscreened women, some differences geographically)

HPV subtypes and cancer

- HPV 6 and 11 rarely cause cervical cancer
- HPV 16 + 18 cause about 70% of invasive cervical cancer cases
  - HPV 16 is the most common and highest risk subtype with the highest progression rate. Present in 55% of SCC

    48% endocx AdenoCa
  - HPV 18 present in 12% of SCC, 36% endocx AdenoCa
  - HPV 45, 31, 33 in 4-5% for invasive cancer, any type
- HPV 16 is strongly associated with anal and throat cancer.

Worldwide prevalence

- Same HPV subtypes cause cervical cancer with little regional variation
  - No population-based genetic predisposition
  - Risk is directly related to amount and time of HPV exposure
  - Are some identified cofactors such as smoking

- We don't know (yet) why some women with HPV infections don't clear the virus and progress to invasive cancer. Likely to be related to host immunity in some way.

Type distribution of human papillomavirus among adult women diagnosed with invasive cervical cancer (stage 1b or higher) in New Zealand

Peter Sykes, Kusuma Gopala, Ai Ling Tan, Diane Kenwright, Simone Petrich, Arico Molijn, and Jing Chen

BMC Infectious Diseases 2014,14:374

- Women ≥18 years of age with ICC FIGO stage 1b or higher diagnosed 2004 - 2010 from five NZ hospitals
- Stored paraffin embedded cervical specimens were used with HPV genotyping performed on malignant tissue

Results: HPV Positivity

Invasive cancer cases n=227

Squamous cell carcinoma (SCC) = 70% (n=159)

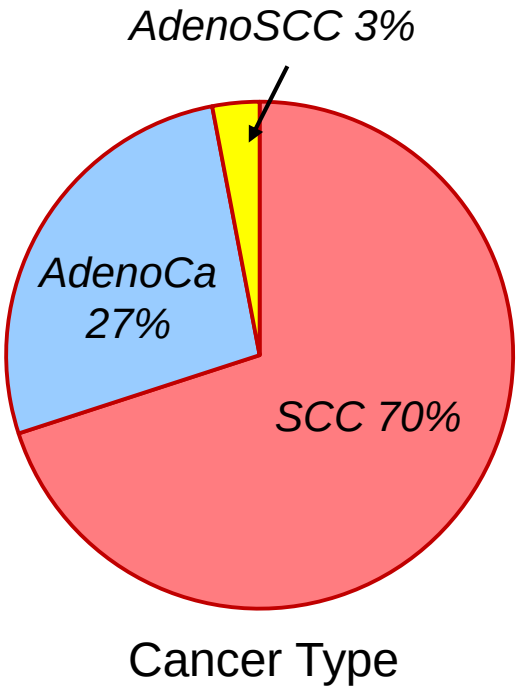
Adenocarcinoma (ADC) = 27% (n=61)

Adenosquamous carcinoma (ASC) = 3% (n=7)

HPV was detected in 88.5%

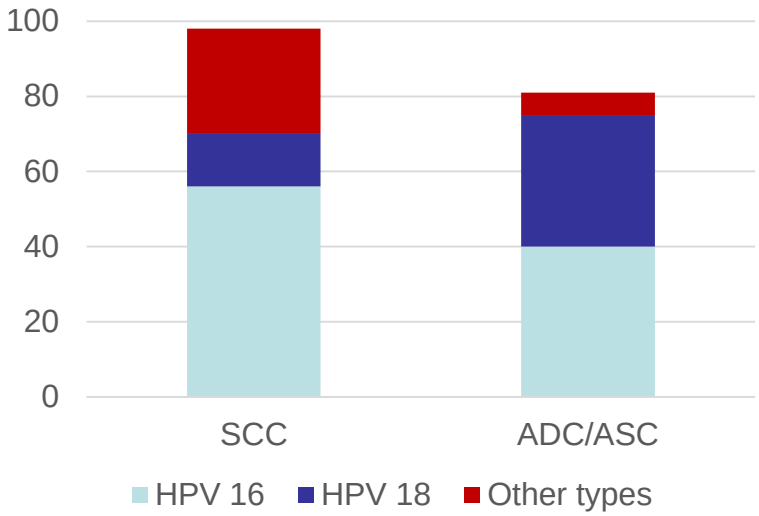
SCC = 93.1%

ADC/ASC = 77.9%

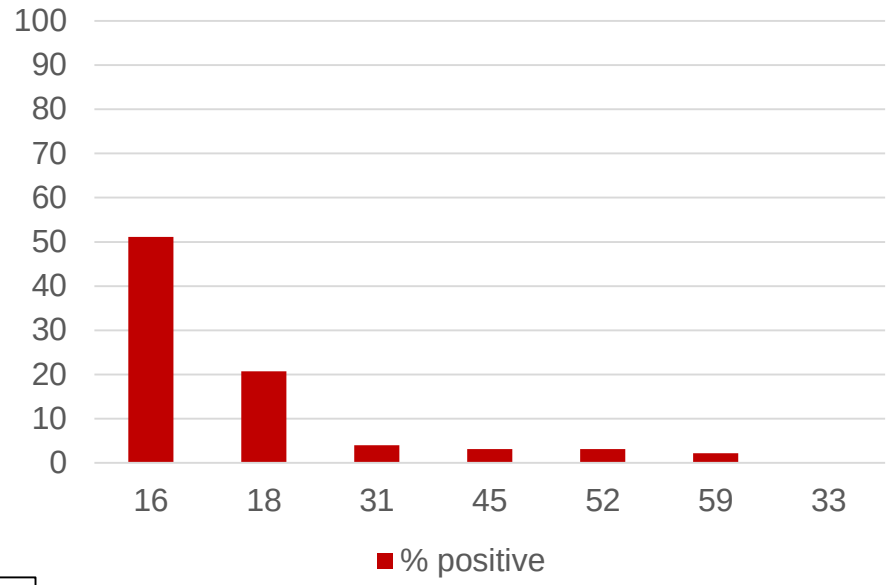


Results: HPV subtypes

Invasive cancers by type



All cancers: genotypes



For the 227 ICC cases, HPV 16 and 18 were the most frequent

HPV 16 = 51% : 56% SCC
40% ADC/ASC

HPV 18 = 21% : 15% SCC
35% ADC/ASC

For the 201 HPV positive cases

HPV 16 + 18 = 81.1%

Frequent non-16/18 types: 31, 45, 52, 59,33

Two low-risk HPV types (11,70) both SCC

Multiple subtypes

5.5% had multiple subtypes present (Both SCC and ADC/ASC)

Results: Ethnicity

- 15% of the women (n=34) with invasive cervical carcinoma were of Maori ethnicity
- There was no significant association between ethnicity and either HPV detection rate or histological cancer type or stage of disease at diagnosis
- Subtype prevalence was similar:
  - HPV 16: 58.8% Maori 49.7% non-Maori
  - HPV 18: 11.8% Maori 22.3% non-Maori
  - Minor variations in non-16/18 subtype distribution

International Comparison

HPV infection and subtype distribution rates are comparable with other international studies

Main Points

- HPV infection is sexually transmitted, common and usually asymptomatic and transient. High prevalence under 30 years
- Clearance can mean eradication of viral DNA or suppression to undetectable levels: latent infection can be reactivated years later
- Immunity following natural infection is variable whereas immunisation achieves high antibody titres
- Cancer is a rare outcome of infection
- The profile of HPV subtypes in invasive cancers differs from that of pre-invasive lesions and is more consistent worldwide