PREINVASIVE DISEASE OF THE LOWER GENITAL TRACT

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ASCOT CLINIC, ADHB
Cervical cancer is caused by the human Papillomavirus, with 99.7% of cervical cancers containing Papillomavirus DNA\textsuperscript{1,2}.

HPV 200 types
HR 16, 18
LR 6, 11

IARC\textsuperscript{1}
ASSOCIATION BETWEEN HPV DNA AND RISK OF S.C. CANCER CERVIX

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>RR/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>435</td>
</tr>
<tr>
<td>HPV 18</td>
<td>248</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure</th>
<th>RR/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV / Liver cancer</td>
<td>50</td>
</tr>
<tr>
<td>Smoking / Lung cancer</td>
<td>10</td>
</tr>
</tbody>
</table>
RISK OF ACQUIRING HPV AFTER FIRST INTERCOURSE

Cumulative Risk of Cervical HPV Infection in Female Adolescents With Only 1 Sexual Partner (UK, 1988-1992)

N=242

Study of Female College Students (US, 1990-2000)

N=603

Adapted from Collins, et al.

Adapted from Winer, et al.
Prevalence of HPV infection by age - Females

Prevalence of HPV in US females (n=1921) as assessed by self collected vaginal swab specimens

Prevalence of HPV infection by age - Males

Males aged 18–44 years in Tucson, Arizona (N = 290).
Transient Infection

HPV infection

Persistent infection

Low Grade Dysplasia CIN 1

High Grade Dysplasia CIN 2/3

Invasive Cancer

0-2 years

2-5 years

4-5 years

9-15 years
Carcinogenic mechanism: HPV Persistence

- Persistent infection: Detection of same HPV type two or more times over 2 years
- Persistence of hr HPV is crucial for the development of cervical precancer and cancer.

Co factors
- High parity
- Immune suppression (transplants, meds, HIV)
- Smoking
- Genetics
Carcinogenic mechanism: HPV persistence

- **HPV 16** is the most carcinogenic: 12% risk of inducing CIN 3 or invasive disease after 3 years of persistent infection.
- Most common subtype in cervical, vulvar and oropharyngeal cancers.
- **HPV 18** is 2nd most common subtype in cervical and glandular lesions.
Natural History of Cervical Carcinogenesis

Normal Cervix → HPV-Infected Cervix via Infection → Clearance

HPV=human papillomavirus.
Estimated Annual Incidence of HPV Cervical Infection/Dysplasia

- Virtually all cases of cervical cancer come from high-grade dysplasia

<table>
<thead>
<tr>
<th>Cervical Infection</th>
<th>Worldwide (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysplasia</strong></td>
<td></td>
</tr>
<tr>
<td>• HPV infection without detectable cytological abnormalities</td>
<td>300</td>
</tr>
<tr>
<td>• Low grade dyplasia</td>
<td>30</td>
</tr>
<tr>
<td>• High grade dyplasia</td>
<td>10</td>
</tr>
</tbody>
</table>
Cumulative Incidence of CIN 3+ in 20,512 Women: 10-year Follow-up

HC2=Hybrid Capture 2 HPV Test.
HPV AND CANCER PREVENTION

- **Primary Prevention**
  Vaccination

- **Secondary Prevention**
  Cytology
  HPV testing

- **Treatment of preinvasive disease**
HPV AND CANCER PREVENTION

- **Primary Prevention**
  1. **Prophylactic Vaccination**
  2. **Condom use** Consistent use reduced HPV infection by 70%
  3. **Male circumcision** decreases HPV infection in men and reduces women's exposure to HR HPV. Also decrease risk of HIV, herpes (males) BV, trichomoniasis (females)
  4. **Potential for microbicides** carrageenan (inexpensive safe gelling agent) tested for HIV but x1000 more effective in HPV
QUADRIVALENT HPV VACCINE

- Prophylactic vaccination is highly effective against\textsuperscript{1-5}
  - cervical intraepithelial neoplasia (CIN)
  - vulvar intraepithelial neoplasia (VIN)
  - vaginal intraepithelial neoplasia (VaIN)
  - adenocarcinoma in situ (AIS)
  - genital warts (GW)

- The quadrivalent HPV Vaccine prevents re-infection and disease related to the same vaccine HPV type\textsuperscript{6}

GARDASIL® - QUADRIVALENT HPV (TYPES 6, 11, 16, 18) L1 VLP VACCINE

- VLPs manufactured in *S. cerevisiae*
- Aluminum Adjuvant 225 µg per dose
- 0.5 mL injection volume given in a 0, 2, 6 (month) dosing regimen

<table>
<thead>
<tr>
<th>Type</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
</table>
| 16/18 | 70% of Cervical Cancer  
       | 60% of CIN 2/3  
       | 25% of CIN 1  | 70% of HPV-related Cancer  
       | Prevention of infection |
| 6/11  | 10 to 15% of CIN 1  
       | 90% of Genital Warts  | Prevention of infection  
       | 90% of Genital Warts |
**IMPACT ON SCREENING**

- 75% reduction of cervical cancer in 25 years
  - HPV 16 – 50-60%
  - HPV 18 – 20-30%
- Decrease in CIN 3
- ASCUS/LSIL continue with less CIN 3
- Decrease in cost-effectiveness of cervical cytology and colposcopy
Clinical Results with HPV Vaccines

Large phase 3 trials demonstrated that the quadrivalent vaccine is

- **99% effective** in preventing HPV 16/18 associated CIN2/3 and adenocarcinoma in situ
- **100% effective** in preventing HPV16/18 associated vulvar and vaginal intraepithelial dysplasia

New data also suggest that the vaccine prevents most cases of CIN and anogenital lesions **in women who have been previously been infected with at least one of the HPV types targeted** by this vaccine.
Impact of qHPV Vaccine on the Incidence of New HPV Disease – After Treatment for Cervical Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any disease</td>
<td>↓46%*</td>
<td>(22, 63)</td>
</tr>
<tr>
<td>Any cervical disease</td>
<td>↓48%*</td>
<td>(19, 68)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>↓65%*</td>
<td>(20, 86)</td>
</tr>
<tr>
<td>Any GW, VIN or VaIN or related disease</td>
<td>↓47%*</td>
<td>(4, 71)</td>
</tr>
<tr>
<td>Any 6/11/16/18 related disease</td>
<td>↓79%</td>
<td>(49, 93)</td>
</tr>
</tbody>
</table>

*Irrespective of HPV type
Gardasil protects for 10 years
Smallpox Vaccination Act 1840.
Free vaccination. Not compulsory.
Prophylactic HPV vaccines demonstrate high-level protection from HPV 6/11/16/18 infection and related preinvasive and invasive cervical, vaginal and vulvar lesions.

Pap screening to detect and treat lesions in women infected prior to vaccination or infected with HPV types not covered by the vaccine will continue.

- Fewer women will require cervical biopsies and treatments.
Cytopathology (1)

“Pap” Test

- Historical perspective
- Most widely used screening test
- Impact on cervical cancer
Improvements in screening coverage can further reduce the incidence of cervical cancer


Cytopathology (2)

Concerns

- False negatives
  - Sensitivity 58%* (lab dependent-78%)
  - Specificity 68%*
- ‘Unsatisfactory’ rates
- Sampling: Screening errors 2:1

HPV DNA TESTING

- Amenable to automation
- **Hybrid Capture** (Digene) nucleic acid hybridization assay with signal amplification detects 13 Hr HPV but does not type
- **PCR** techniques allow typing (Cervista, Roche)
- **CCCaST** confirms HPV testing more sensitive (95% vs 55%) but less specific than cytology (94% vs 97%) in detecting high grade CIN
TRIAGE OF hrHPV +ve WOMEN
AGE OF STARTING hr HPV TESTING

- Cytology is best triage of hrHPV+ve women needing immediate colposcopy. Using HPV alone will → increase in colposcopies and overtreatment
- Use of P16

- Start at 30 years as highest prevalence is 20-25 yrs and decreases by 35 yrs. Detecting clinically relevant lesions
**HPV TESTING**

HrHPV testing is currently recommended in the Guidelines in three clinical situations:

<table>
<thead>
<tr>
<th>Situation</th>
<th>Who usually initiates the HPV test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Women 30 years and older with ASC-US or low-grade changes, to help assess risk of progression</td>
<td>Laboratories (the HrHPV result is reported at the same time as the ASC-US/LSIL result) Smear takers are required to ensure that all women over 30 years are informed about HPV testing.</td>
</tr>
<tr>
<td>2. Women (all ages) treated for a high-grade lesion, to help assess whether the lesion has been completely resolved. Includes ‘historical testing’ for women on annual smears for previous high-grade lesions and with negative smears since, to assess whether they can return to routine 3 yearly screening - refer page 3.</td>
<td>The smear taker, after discussing with the woman.</td>
</tr>
<tr>
<td>3. Where colposcopy has shown discordant results from cytology, to help interpret these results.</td>
<td>Colposcopists</td>
</tr>
</tbody>
</table>

**Who should not be offered HrHPV testing as part of the NCSP?**

Women under 30 years (unless they have had a previous high-grade (HSIL/ASC-H) lesion). Note that where HrHPV testing is requested outside the Guidelines, women may be asked to pay for it.
HPV DNA TESTING (>30 yrs)

- **Hr HPV test** is 30% more sensitive than cytology in detecting CIN2 and 22% more sensitive than cytology in detecting CIN3. Specificity is 4-6% lower than cytology.
- **Combined test** CYTO and hr HPV no added value to single hrHPV test in detecting CIN 2 or CIN3.
- hrHPV –ve is better protection than cyto –ve; 50% lower CIN 3 detection rate in hrHPV-ve 1st round vs CYTO-ve 1st round. (2nd round testing) NO CANCERS in hrHPV –ve 1st round vs 8 in cytol-ve.
Low grade dysplasia granular, ill defined
HIGH GRADE DYSPLASIA MOSAICISM
High Grade Dysplasia Punctuation
HIGH GRADE DYSPLASIA
GLAND CUFFING
PUNCH BIOPSY OF CERVIX
LSIL Follow Up

Flowchart 2

Colposcopic Assessment

Satisfactory & normal

Satisfactory & abnormal

Unsatisfactory

Refer back to smear taker

Target biopsy

CIN1

CIN2 / 3

LSIL confirmed

Treatment

see special circumstances for pregnancy and under 20 yrs

Repeat colposcopy and cytology in 12 months

Repeat smear at 12 months

Routine 3-yearly screening

Any abnormal smears

Management may be individualised based on age, reproductive status and clinical risk.

Treatment is not usually indicated.
RISK OF CIN 2-3

2 year cumulative risk CIN2-3
- ALTS ASCUS smear =15%
  ASCUS+ HR HPV =27%
No difference in subsequent risk of CIN2-3 between women with no disease and CIN1 at initial colposcopy

- NCSP registrar data ASCUS smear = 16%
GLANDULAR LESIONS

- 15-20% of all invasive cancers
- Smears are less effective in preventing this
- Hr HPV is associated with 90% of ACIS and adenocarcinoma of the cervix
- Not uncommon to have both squamous and glandular lesions co-existing
TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

Modalities
- Ablation -- cryotherapy, CO2 laser
- Excision –LEEP/LLETZ(+LLETZ cone), cold knife cone biopsy, laser cone biopsy, hysterectomy

Cochrane database – no superior method (28 RCT)
Ablative Methods

- High primary cure rates with minimum morbidity (80% cryo, 95% laser ablation)

- When cancer occurred after ablative therapy, occurred within 12 months in 66% of cases and within 2 years in 90% -- triage error at initial assessment

- Experienced clinician
LEEP/LLETZ

- Most commonly used treatment modality in NZ

- Allows for excision of TZ, with no greater morbidity

- When performed by inexperienced operator, histological assessment can be difficult
LLETZ PROCEDURE

Beginning of Cut

CIN Lesion

End of Cut

Diathermy
COLD KNIFE CONE BIOPSY

- Tailor treatment to the individual woman
- Size of lesion
- Extent of lesion
- Severity of lesion
HYSTERECTOMY

- Rarely indicated for primary treatment for CIN. Used if there is **coexistent gynae pathology** warranting hysterectomy.

- Need **colposcopic assessment** first, excisional conization might need to be performed to exclude invasion.

- 2-3% high grade CIN, **disease extends beyond vaginal vault** ➔ **vaginal cuff** fashioned appropriately.
Post Rx TZ
CERVICAL STENOSIS
**SPONTANEOUS HPV CLEARANCE - EVIDENCE FOR NOT RX <25**

<table>
<thead>
<tr>
<th>CIN 1</th>
<th>Regression rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult women</td>
<td>70-80%</td>
</tr>
<tr>
<td>Adolescent/young women</td>
<td>90%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CIN2</th>
<th>progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>Older women</td>
<td>30-40%</td>
</tr>
</tbody>
</table>
"Could you hurry and find a cure for cancer? That would be so much easier than prevention."

ASBESTOS INDUSTRY

CHEMICAL AND PESTICIDE INDUSTRIES

FOOD AND DRUG INDUSTRIES

TOBACCO INTERESTS

POLLUTING INDUSTRIES

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### HPV and Cancer: A Broader Picture

<table>
<thead>
<tr>
<th>Cancer</th>
<th>% Associated With Certain HPV Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Vaginal</td>
<td>~50%</td>
</tr>
<tr>
<td>Vulvar</td>
<td>~50%</td>
</tr>
<tr>
<td>Penile</td>
<td>~50%</td>
</tr>
<tr>
<td>Anal</td>
<td>~85%</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>~20%</td>
</tr>
<tr>
<td>Larynx and aerodigestive tract</td>
<td>~10%</td>
</tr>
</tbody>
</table>
VIN
(Vulva Intraepithelial Neoplasia)
CLASSIFICATION OF VIN

- **VIN USUAL TYPE**
  - high grade VIN only
  - encompasses warty, basaloid and mixed HPV related

- **DIFFERENTIATED VIN**
  - Non HPV related

- **VIN NOS**
HPV Prevalence: VIN Warty/ Basaloid

HPV 16  80%  (CIN 3  50%)

Hillemans, Wang. Gynecol Oncol 2006; 100:276
IMPORTANCE OF VIN

- Symptoms that it causes
- The potential for progression to invasive cancers
SYMPTOMS

Absent in 20% of cases
MULTIPLE LOWER GENITAL TRACT NEOPLASIA (USUALLY CIN)

Occurs in 30-50% of cases of VIN
VIN

- Spontaneously regress
- Persist unchanged indefinitely
- Progress to invasive cancer
Heterogeneous clinical features VIN

- Unifocal or multifocal
- Flat or Papular
- Red, White, Pigmented
- May involve perianal or urethral skin
VIN 3. "Missed" (occult) Invasion on Vulvar Biopsy

- Chafe et al. Gynecol Oncol 1988; 31: 154
  - 18%
  - 16%
  - 23%
- Husseinzadeh et al. Gynecol Oncol 1999; 73: 119
  - 20%
INVASIVE POTENTIAL OF VIN IS BOTH UNCLEAR AND CONTENTIOUS

LITERATURE FAILS TO CLEARLY ACKNOWLEDGE THE EFFECT OF TREATMENT ON THE NATURAL HISTORY OF THE DISEASE
VIN 3

113

Treated
105

4 (3.8%)
Invasive vulvar cancer

Untreated
8

7 (87.5%)
1 spont. regression

Jones RW, Rowan DM
Obstet Gynecol 1994; 84:741
TREATMENT

- Control of symptoms
- Cancer risk

- Psychosexual sequelae
- "mutilation"
VIN MANAGEMENT

- Observation
- Surgery/Laser
- Medical
- Immunotherapy
EXCISIONAL THERAPY ALLOWS FOR HISTOLOGY

SHOULD BE GOLD STANDARD
LASER AND VIN

- Excellent results in young women with extensive multifocal disease
- Knowledge and skill of operator essential
Recurrences of VIN

- 30%+ of cases
  - either - persistent disease (incomplete treatment)
  - or - “new” disease (field effect”)
VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN)
HIGH GRADE VAIN

- Premalignant
- Incidence increasing, age of diagnosis decreased
- Rarity of vaginal cancer (1-2% of female genital tract cancers) suggest malignant potential is low
- In association with CIN3 (3%) or as primary lesion
- Involves upper 1/3 vagina in >70% of cases
DIAGNOSIS

- Colposcopy and biopsy

- **High Grade VAIN** has colposcopic appearance similar to **High Grade CIN**

- Exam after aqueous Iodine
TREATMENT

SURGICAL EXCISION

- Lesion
- Vault
- Partial /total vaginectomy

Access is difficult
Proximity to vital organs
30% can have occult cancers
TREATMENT

Radiotherapy
- Irradiate vagina using applicators
- Co morbidities/ difficult surgical access
- Morbidity
  Bowel symptoms-proctitis
  Bladder symptoms- cystitis
  Vaginal stenosis
TREATMENT

**Laser treatment**

- Superficial treatment to 2-3mm to depth of lamina propia
- Delayed healing and scarring occurs with over enthusiastic treatment$\rightarrow$ problems in follow up and sexual function
- Young patients , reliable follow up
TREATMENT : CHEMICAL

- **5-fluorouracil cream**
  - intravaginal 1/4 applicator
  - daily - > 2x per week

- **Overall cure rate**
  - Rome 45% (5/11)
  - 4 of those cured had previously received RT
  - Murta et al 63% (10/16)
TREATMENT: IMMUNOLOGICAL

- **5% imiquimod**
  - Studies usually small numbers, short follow-up, dubious end-points
  
  *Buck and Guth (2003), Haidopoulous et al (2005)*

*Imiquimod effect is “non-permanent”*

*May also have a role in difficult cases*
JUST...JUST STOP
Because the more you talk, the stupider you sound.