Role of HPV in Cervical Screening

Mr Nick Nicholas MD FRCOG
Lead Colposcopist
Figure 2: Population pyramid of United Kingdom

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 5</td>
<td>1900000</td>
<td>1809000</td>
</tr>
<tr>
<td>5-9</td>
<td>1768000</td>
<td>1683000</td>
</tr>
<tr>
<td>10-14</td>
<td>1844000</td>
<td>1746000</td>
</tr>
<tr>
<td>15-19</td>
<td>2039000</td>
<td>1924000</td>
</tr>
<tr>
<td>20-24</td>
<td>2142000</td>
<td>2042000</td>
</tr>
<tr>
<td>25-29</td>
<td>2066000</td>
<td>2019000</td>
</tr>
<tr>
<td>30-34</td>
<td>1927000</td>
<td>1936000</td>
</tr>
<tr>
<td>35-39</td>
<td>2102000</td>
<td>2124000</td>
</tr>
<tr>
<td>40-44</td>
<td>2295000</td>
<td>2339000</td>
</tr>
<tr>
<td>45-49</td>
<td>2274000</td>
<td>2328000</td>
</tr>
<tr>
<td>50-54</td>
<td>1959000</td>
<td>2011000</td>
</tr>
<tr>
<td>55-59</td>
<td>1763000</td>
<td>1820000</td>
</tr>
<tr>
<td>60-64</td>
<td>1839000</td>
<td>1932000</td>
</tr>
<tr>
<td>65-69</td>
<td>1414000</td>
<td>1523000</td>
</tr>
<tr>
<td>70-74</td>
<td>1153000</td>
<td>1308000</td>
</tr>
<tr>
<td>75-79</td>
<td>874000</td>
<td>1095000</td>
</tr>
<tr>
<td>80-84</td>
<td>588000</td>
<td>883000</td>
</tr>
<tr>
<td>85+</td>
<td>440000</td>
<td>990000</td>
</tr>
</tbody>
</table>

Population of United Kingdom by sex and age group
Figure 3: Population trends of four selected age groups in United Kingdom

Population in thousands. Data sources:
Figure 4: Incidence of cervical cancer compared to other cancers in women of all ages in United Kingdom

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Annual Crude Incidence Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>146.2</td>
</tr>
<tr>
<td>Colorectum</td>
<td>54.5</td>
</tr>
<tr>
<td>Lung</td>
<td>52.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>22.4</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>20.2</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>16.7</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>15.5</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12.6</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>10.4</td>
</tr>
<tr>
<td>Bladder</td>
<td>10.0</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>9.3</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>9.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>9.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>8.5</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6.2</td>
</tr>
<tr>
<td>Brain, nervous system</td>
<td>5.9</td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>5.2</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4.8</td>
</tr>
<tr>
<td>Liver</td>
<td>4.1</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>2.8</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2.2</td>
</tr>
<tr>
<td>Other pharynx</td>
<td>1.6</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.2</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>0.3</td>
</tr>
</tbody>
</table>
How often should you take a smear?

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frequency of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>First invitation</td>
</tr>
<tr>
<td>25–49</td>
<td>Three yearly</td>
</tr>
<tr>
<td>50–64</td>
<td>Five yearly</td>
</tr>
<tr>
<td>65+</td>
<td>Only screen those who have not been screened since age 50 or who have had recent abnormal tests</td>
</tr>
<tr>
<td>Risk Factors for Cervical Cancer</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td>• HPV infection</td>
<td></td>
</tr>
<tr>
<td>• Recent infection, persistent infection</td>
<td></td>
</tr>
<tr>
<td>• # of sexual partners</td>
<td></td>
</tr>
<tr>
<td>• Age of onset of sexual activity</td>
<td></td>
</tr>
<tr>
<td>• Smoking</td>
<td></td>
</tr>
<tr>
<td>• Dietary factors</td>
<td></td>
</tr>
<tr>
<td>• Lack of physician contact</td>
<td></td>
</tr>
<tr>
<td>• &gt;50% women who develop cervical cancer have never had pap smears or no pap in &gt; 5 years</td>
<td></td>
</tr>
<tr>
<td>• Race and ethnicity</td>
<td></td>
</tr>
<tr>
<td>• Socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>• Immunocompromised state</td>
<td></td>
</tr>
<tr>
<td>• Promotes persistent HPV infectious state</td>
<td></td>
</tr>
</tbody>
</table>
Human Papilloma Virus (HPV)

- There are over 100 subtypes of HPV. Most do not cause significant disease.
- The high risk HPV subtypes are 16, 18, 31 & 33 – types 16 & 18 are found in 70% of cervical cancers. Non oncogenic types are 6 & 11, which cause visible genital warts.
- Transient HPV is common especially in women under 35 years.
- It persists in 20-30% of women putting them at increased risk of developing cervical cancer.
- Women or their partners may have had HPV for many years without knowing it.
- There is no reliable treatment to clear the virus.
HPV and Cancer

- Cervix
- Anus
- Vagina
- Penis
- Vulva
- Oropharynx
- Oral Cavity

Percentage distribution for HPV associated cancers.
HPV Infection

- 75 - 80% of sexually active adults will acquire a genital tract HPV infection before the age of 50
- Can be detected in 99.7% of all cervical cancers
- 15 genotypes are considered oncogenic
- 2 most common: 16, 18 are found in >70% of all cervical cancers
- Increases risk of HG disease by 250x
- Causative factor in squamous cell cancers of multiple sites:
  - cervical, anal, vulvar, penile, oropharyngeal
- HPV 6 and 11 responsible for ~80% of genital warts

Walboomers JM. J pathol 1999 sept; 189(1): 12-9
An estimated 70% of sexually active people will be exposed to the virus at some point during their life\textsuperscript{2,3,4}

Infection is very common\textsuperscript{2,3,4}

The majority of Human Papillomavirus infections occurs early in adolescence or adulthood\textsuperscript{2,3,4}

\textsuperscript{1} Sanofi Pasteur MSD, data on file. \textsuperscript{2} Koutsky LA. Am J Med 1997 \textsuperscript{3} Koutsky LA et al. Epidemiology Rev 1988 \textsuperscript{4} Syrjänen K et al. Sex Transm Dis 1990
## Natural History of CIN

<table>
<thead>
<tr>
<th></th>
<th>Regress</th>
<th>Persist</th>
<th>Progress To CIN3</th>
<th>Progress to Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>57%</td>
<td>32%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43%</td>
<td>35%</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32%</td>
<td>56%</td>
<td>&gt;12%</td>
<td></td>
</tr>
</tbody>
</table>

THE GOOD NEWS

- Vast majority clear the virus or suppress it to levels not associated with CIN 2/3+, and for most women this occurs promptly.

- The duration of HPV positivity is shorter and the likelihood of clearance is higher in younger women.

- Only 1 in 10 to 1 in 30 HPV infections are associated with abnormal cervical cytology.
MORE GOOD NEWS

- Only 15% of women with negative cytology reports and positive HPV will have abnormal cytology within 5 years.
- The risk of cervical cancer in women who do not harbour oncogenic HPV is extremely low.
- The time course from CIN 3 to invasive cancer averages between 8.1 and 12.6 years.
Currently no “cure” for genital HPV infection, most cases are transient and clear themselves without medical intervention.

Approximately 80% of all HPV infections in women between the ages of 15 and 25 years are transient.

Repeated HPV DNA testing showed that 70 percent of the women cleared their HPV infections within one year through the natural immune process, and only 9% were still infected after 2 years.

Another study conducted in Sweden supported these findings, with a five-year clearance rate of 92 percent (Elfgren, et al., 2000).
HPV Infection

• Duration of incubation period unclear
• Immunologic clearance of HPV infection
  50% of patients at 15 months
  80% at 2 years
• Persistence of infection is the greatest risk of progression to cancer.
  • Older cross-sectional studies showed progression rate at 5-15 years
• Recent longitudinal studies suggest 7-20% of new infection showing progression to CIN 2 or 3 over 36 months.

Insigna RP, Infect Agent Cancer 2007; 2:15
Cytology vs. Cytology + HPV testing
- Cytology alone low sensitivity
- Cytology + HPV testing much higher sensitivity
- HPV testing especially helpful in patients > 30 years old
HPV Persistence

• Persistence of HR types of HPV is crucial for development of cervical precancer and cancer.

• Other associated factors:
  Age * (≥ 30 years)
  Infection with multiple HPV types
  Immune suppression

• Currently, no antivirals available to treat the underlying HPV infection

Molecular Pathology Model of Cervical Cancer

Wright and Schiffman, NEJM, 2003
HPV-Associated Malignant Disease 5% of ALL cancers
The cumulative incidence of cin3+ in 13,229 women over a ten year period by single HPV test result at enrolment.

- 70% of cancers
- 50% of pre-cancers
- Non-informative for 10 years…

- HPV16 POSITIVE
- HPV18 POSITIVE
- HPVPOSITIVE non HPV16/18
- HPV NEGATIVE

FOLLOW-UP TIME (MONTHS)

CUMULATIVE INCIDENCE RATE OF CIN3

0% 5% 10% 15% 20% 25%

0.0 4.5 15.0 27.0 39.0 51.0 63.0 75.0 87.0 99.0 111.0 119.5
TEN MOST FREQUENT HPV TYPES AMONG CERVICAL CANCER CASES WORLDWIDE BY HISTOLOGY

SQUAMOUS CELL CARCINOMA
- 16: 57.6%
- 18: 12.2%
- 58: 5.4%
- 33: 5.0%
- 45: 4.3%
- 31: 3.6%
- 52: 3.5%
- 35: 1.7%
- 39: 1.6%
- 51: 1.0%

ADENOCARCINOMA
- 18: 38.7%
- 16: 35.3%
- 45: 5.2%
- 33: 2.5%
- 31: 2.4%
- 58: 1.8%
- 52: 1.3%
- 59: 0.9%
- 51: 0.8%
- 35: 0.7%
Biopsy in Diagnosing Women with CIN 2 or Worse

- Colpo biopsy 208/364 (57.1%)
- Colpo biopsy + 2 o’clock 256/364 (70.3%)
- Colpo biopsy + 2, 4 o’clock 297/364 (81.6%)
- Colpo biopsy + 2, 4, 8 o’clock 329/364 (90.4%)
- Colpo biopsy + 2, 4, 8, 10 o’clock 344/364 (94.5%)
- Colpo biopsy + 2, 4, 8, 10 + ECC 3 64/364 (100%)

57.1% vs. 70.3% vs. 81.6% vs. 90.9% vs. 94.5% vs. 100%
Chi-Square = 326, df=5, P<.001

Conclusion of study

Regardless of colposcopic skill, performing 4 random biopsies plus Endo Cervical Curettage (ECC) increases the yield of CIN3+ per colposcopy !!!
Putting risk into perspective:

- Risk of cervical cancer if HPV 16 (+) positive compared to HPV 16 (-) is 434
- Risk of lung cancer in U.S. white male smoker compared to non-smoker is only 8
- *Risk of breast cancer with HRT in Women's Health Initiative only 1.3*
HPV-DNA Testing?

1. Primary screening for cervical neoplasia

2. In triage of minimally abnormal and inconclusive smears ie ASCUS / Borderline (5-7%)

3. As a test of cure
1. Use of HPV DNA test

As a primary screening
The NEW ENGLAND JOURNAL of MEDICINE

Canadian Cervical Cancer Screening Trial (CCCaST)

Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer

Marie-Hélène Mayrand, M.D., Eliane Duarte-Franco, M.D., Isabel Rodrigues, M.D., Stephen D. Walter, Ph.D.,
James Hanley, Ph.D., Alex Ferenczy, M.D., Sam Ratnam, Ph.D., François Coutlée, M.D.,
and Eduardo L. Franco, Dr.P.H., for the Canadian Cervical Cancer Screening Trial Study Group

- 10,456 women 30-69 yrs of age seeking screening in Montreal or St. Johns
- Had BOTH digene HPV Test & conventional cytology
- Women positive on either test had colposcopy

Comparison of HPV DNA to Pap

N Eng J Med, 2007: Canadian Cervical Cancer Screening Trial (CCCaST)

- Sensitivity HPV DNA: 94.6%
- Sensitivity Pap: 55.4%
- Specificity HPV DNA: 94.1%
- Specificity Pap: 96.8%

95% CI: 84.2-100 for HPV DNA, 95% CI: 33.6–77.2 for Pap, P=0.01
95% CI: 93.4-94.8 for HPV DNA, 95% CI: 96.3-97.3 for Pap, P<0.001

N Eng J Med 2007; 357: 1,579 - 88
The trial reported:

- No significant psychosocial impact of adding HPV testing to cervical cytology
- No clear evidence of effectiveness of HPV as a stand-alone test
- HPV of value as a triage with LBC
POSSIBLE ALGORITHM FOR THE USE OF HPV TESTING AS THE SOLE PRIMARY SCREENING MODALITY FOR WOMEN AGES 25-64, FOLLOWED BY PAP TRIAGE OF HPV POSITIVE WOMEN

WOMEN AGED 25 - 64 YEARS
HPV TEST

Negative
NORMAL 5 YEAR RECALL

Positive
CYTOLOGY

Normal or Borderline
HPV & CYTOLOGY at 6 – 12 months
NORMAL 5 YEAR RECALL

≥ Mild
COLPOSCOPY

Cytology Negative
HPV Negative

HPV Positive & Cytology < Mild
HPV Negative & Cytology Borderline

HPV & CYTOLOGY at 6 – 12 months
COLPOSCOPY
2. Use of HPV DNA test

Triage of Borderline/ASCUS smears
The trial compared 3 management strategies for ASCUS Pap smears:

- reflex HPV-DNA testing (the initial Pap sample is tested for HPV only if the results are ASCUS),
- immediate referral for colposcopy,
- and repeat Pap smears
ASCUS-LSIL Triage Study (ALTS)

- Reflex HPV testing - sensitivity of 96% for detecting HSIL and a negative predictive value of 98%.
- The 44% of women with ASCUS who tested negative for high-risk HPV were able to avoid colposcopy.
- A single repeat Pap smear within 4 to 6 months, with referral for colposcopy if abnormal, had a sensitivity of 85% and a similar colposcopy referral rate.
The colposcopy results showed that about 5 percent to 10 percent of women with ASCUS had precancer or cancer and that, of these women, 96.3 percent had a positive HPV test.

As a corollary, 99.5 percent of women with a negative HPV test did not have precancer or cancer.
LSIL (CIN 1): ALTS summary points

- CIN 3 is found in about 15%
- CIN 2 is found in about 10%
- CIN 2 may regress
- Colposcopy sensitivity for detection of CIN 3 is only 50-70%
- 83% tested positive for high-risk HPV
- The majority had repeat abnormal Pap

The ALTS Group. Management of women with LSIL. AJOG 2003
80% - 85% of LSIL (CIN 1) is HPV pos

10% - 15% is non-oncogenic HPV pos

Of the approximately 10% of LSIL HPV Negative

5% due to False Negative HPV test

5% due to a False Positive LSIL

Zuna R et al (ALTS) 2005
ASCUS

Immediate HR HPV

Colposcopy

Loss to follow up 10%

Screening Pap Cycle
HPV testing the pros and cons

- HPV testing is more reproducible and sensitive than cytology but only slightly less specific.
  - sensitivity 96% vs 53%; specificity 90% vs 96%

- BUT ....

- Detection of limited value in HPV positive women with transient infections and no or regressing lesions

- Need to prevent over-referral and colposcopy
Use of HPV DNA test

3. TEST OF CURE AFTER TREATMENT OF CERVICAL PRECANCER
**Risk of Invasive Cervical Cancer after treatment**

- Risk $\times 4-5$ times > general population
- Long-term Risk for 20 years
- Incidence of Cx Ca: SIMILAR between treatment methods

Soutter WP, de Barros Lopes, Fletcher, Monaghan, Dunkan, Paraskevaidis E, Kitchener HC. Lancet, 1997

Kalliala I, Anttila A, Pukkala E, Nieminen P. BMJ, 2005

Soutter WP, Sasieni P, Panoskaltsis T. Int J Cancer, 2006
HPV testing as an adjunct to cytology in the follow up of women treated for CIN

- 917 women recruited at 6 months of follow up,
- 778 (85%) and 707 (77.1%) being recruited at 12 and 24 months, respectively.
- At recruitment:
  - 700 women had high-grade CIN (grades 2 or 3) and 217 had CIN1.
- At 6 months:
  - 14.6% were HPV positive and 10.7% had non-negative cytology.
  - Of those with negative cytology, 9% were HPV positive.

Kitchener et al, BJOG June 2008 pg 1001-7
(HPV) testing in combination with cytology in the follow up of treated women

- Of the 744 women who were cytology negative/HPV negative at baseline:
  - Only 6 developed further abnormal smears
- 9 of 10 cases of CIN3 were in the HPV-positive women
- At 23 months, 1 cancer in woman with CGIN with clear resection margins, who had been cytology negative/HPV negative at both 6 and 12 months.

Women who are cytology negative and HPV negative at 6 months after treatment for CIN can safely be returned to 3-year recall.
Test of Cure Protocol
(Follow up of treated CIN)

- HPV testing following treatment for CIN.
- Women who are cytology negative and HPV negative proceed to a three year recall period – avoiding the need for 10 years of annual tests.
- Untreated CIN1 followed up at colposcopists discretion.
- Women who are cytology +ve or HPV +ve at 6 months post treatment are colposcoped.
Guidance on Explaining HPV Triage to Women

- We cannot know when an individual woman became infected.
- We cannot know from whom this infection was transmitted.
- High risk HPV does not cause genital warts and wart associated types do not cause CIN.
- HPV infection cannot be treated, only CIN.
- HPV vaccination will help prevent HPV infection/CIN in the future.
Explaining HPV

- A positive HPV test does not mean their current partner has been unfaithful.
- HPV is very common. Many women will acquire it when they become sexually active.
- Most women will clear an HPV infection, approx 90%.
Explaining HPV

- HPV is usually cleared by the immune system.

- Having HPV is not a marker for sexual behaviors, infidelity or timing of infection.
Explaining HPV

Cervical cancer should be considered a very rare complication of a very common virus.

Cervix cancer can be prevented
Vaccines
Misconception:
My daughter doesn’t need this vaccine now because she isn’t sexually active........

• Significant number of girls are sexually active by age 16 but not as many at age 12

• HPV is acquired soon after sexual debut

• This is a preventative vaccine and needs to be administered BEFORE possible acquisition of disease
Risk of Acquiring HPV After First Intercourse in Female Adolescents

Proportion of new cases with Warts per quarter

Vaccination program started July 2007

+1.8% P=0.03

-25.1, P=< 0.001
P for change<0.001

+1.0% P= 0.43

-4.7% P=0.34

Women<28

Women ≥28

HSV

Quarters since 2004

Fairley C K et al – Melbourne, Australia
Thank You
What is HPV Triage?

- All cervical samples with first BNC or mild dyskaryosis test result will be tested for HPV to distinguish between women who need referral to colposcopy and women who can be safely returned to routine recall.

- Women who test positive for HPV will be referred to colposcopy. Women who are HPV negative will be returned to routine recall.
Test of Cure Protocol
(Follow up of treated CIN)

- HPV testing will be used following treatment for CIN.
- Women who are cytology negative and HPV negative will proceed to a three year recall period – avoiding the need for 10 years of annual tests.
- Untreated CIN1 will be followed up at colposcopists discretion.
- Women who are cytology +ve or HPV +ve at 6 months post treatment will be colposcoped.
# Sentinel Site Study

<table>
<thead>
<tr>
<th>Cytology result (1st Occurrence)</th>
<th>Current Management</th>
<th>HPV Triage Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline</td>
<td>Repeat in 6 months</td>
<td>HPV –ve</td>
</tr>
<tr>
<td>Mild dyskaryosis</td>
<td>Colposcopy referral</td>
<td>HPV +ve</td>
</tr>
<tr>
<td></td>
<td>Routine recall</td>
<td>Colposcopy referral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cumulative risk of progression from HPV 16/18 infection to CIN3+ by age group

HPV in management of low grade abnormalities

- HPV+ve and ASCUS=LSIL biologically
- HPV-ve and ASCUS is relatively safe

<table>
<thead>
<tr>
<th>histology</th>
<th>ASCUS HPV-</th>
<th>ASCUS HPV+</th>
<th>LSI L all</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2&amp;3</td>
<td>3.1</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>CIN3</td>
<td>1.7</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

AJOG 2003