CIN3 et cancer du col HPV négatif

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Models for cervical cancer screening

21st century
Molecular model
HPV-alone screening

21st century
Hybrid model
HPV + Pap screening

CO-TESTING
was initiated only in the United States, without any clinical trial, in order to compensate the lack of performance of the Pap test

Countries Adopting HPV Testing
- Netherlands
- Australia
- New Zealand
- UK
- Belgium
- U.S.
- Turkey
- Italy
- Spain
- British Columbia and Ontario, Canada
- Mexico
- Rwanda

Many pilots and trials on-going e.g.
- Finland, Norway, Denmark
- Sweden, El Salvador, Colombia, Argentina, Bolivia

20th Century
Cytology Model
Pap test screening
Consequently, to maximize the detection of cervical cancer, co-testing was recommended as the primary screening method instead of HPV-testing alone.

Confusion arose from retrospective studies using paraffin-embedded cervical tissue or from historical data regarding the existence of HPV-negative CIN3 and cervical cancer.
Objectives

1. Possible reasons for a negative hrHPV test result in a CIN3 or invasive cancer
2. Recognized (true) HPV-negative cervical cancers
3. Co-testing versus hrHPV-only primary screening

HPV-negative CIN3 and cervical cancer in Switzerland: any evidence of impact on screening policies?

Vassilakos Pierre, Tran Phuong Lien, Sahli Rolan, Low Nicola, Petignat Patrick
What is the rate of HPV-negative CIN3 and cervical cancer in Switzerland?
Objective:
Baseline distribution of HPV types in women aged 17-81 years diagnosed with cervical intraepithelial neoplasia and worse (CIN3+) in a representative sample of Swiss women.

Methods:
• Cross-sectional study consisting of retrospectively analysed samples from 2014 and samples from prospectively analysed patients from 2015.
• Ten laboratories from six cantons and three language regions participated in the study.
• HPV typing on formaldehyde fixed-paraffin embedded specimens.
• Each laboratory conducted DNA extraction and HPV typing according to their standard practice. Negative and non-evaluable specimens were retested at the WHO Global HPV Reference Laboratory in Sweden.
Results:
hrHPV-positivity rate amongst all evaluable samples was 99.3% (95% CI 98.5–99.8%, 745/750)

Conclusions from the CIN3+ Swiss study:
hrHPV-negativity in CIN3 and cervical cancers is rare and largely attributable to technical artifacts such as poor DNA quality and/or low viral load.

However, hrHPV is not detected in some CIN3 and certain types of carcinomas
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Possible reasons for a negative hrHPV test result in a CIN3 or invasive cancer

Reasons related to specimens
• Inadequate cellularity in the specimen
• Insufficient specimen collected from clinically overt cancer with necrosis
• Interfering substances (e.g., lubricants) in the specimen
• Low copy number

Reasons related to HPV tests
• Assay does not test for a specific rare high-risk HPV sub type
• Limitation of analytic sensitivity

The Sensitivity of HC2 is 5,000 copies of HPV DNA
The Sensitivity of PCR can be <10 copies of HPV DNA
To minimize **analytic** deficiencies, clinicians are advised to use sufficiently sensitive and clinically validated hrHPV tests in qualified laboratories accredited by authorized accreditation bodies and in compliance with international standards.
Possible reasons for a negative hrHPV test result in a CIN3 or invasive cancer

Pitfalls in the diagnosis of CIN3

Transitional Cell Metaplasia

Basicmedical Key
Fastest Basicmedical Insight Engine

IARC,
HPV-negative CIN3 should be verified using immunostaining with p16
24 years

- Pap test: HSIL
- HPV test: negative
- Biopsy: CIN 2-3
- Repeated HPV test: negative

P16: negative

Final diagnosis: Metaplasia
HPV-negative CIN3

“Approximately two thirds of CIN3 HPV-negative may be explained by false-positive histopathology diagnoses and/or infection with non-high-risk HPV types and therefore can be considered almost meaningless. However, even very good HPV tests may miss CIN3 associated with high-risk HPV types in 1–3% of cases”.

Karl Ulrich Petry, J. et al
Possible reasons for a negative hrHPV test result in a CIN3 or invasive cancer

**Misclassification of endometrial adenocarcinoma**

- Nearly 60% of the HPV-negative cases could not be distinguished histologically from endometrial primary adenocarcinomas, suggesting that these tumors may not be of cervical origin.

*Hopenhayn C, et al.*
Prevalence of human papillomavirus types in invasive cervical cancers from 7 US cancer registries before vaccine introduction.
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Recognized (true) HPV-negative cervical cancers

Endocervical adenocarcinoma:
1. Gastric type (including minimal deviation type)
2. Clear-cell carcinoma
3. Mesonephric carcinoma

HPV association
Squamous cell carcinoma
Endocervical adenocarcinoma, usual type
Mucinous adenocarcinoma:
   - NOS type
   - Intestinal type
   - Signet ring cell type
Villoglandular adenocarcinoma

HPV association controversial
Endometrioid adenocarcinoma
Serous adenocarcinoma
NB. Spread from the endometrium, ovaries, or peritoneum should be excluded

Recognized (true) HPV-negative cervical cancers
Endocervical adenocarcinoma:
1. Gastric type (including minimal deviation type)
2. Clear-cell carcinoma
3. Mesonephric carcinoma
Recognized (true) HPV-negative endocervical cancers

Mucinous adenocarcinoma: gastric type may be associated with Peutz–Jeghers syndrome

Pyloric Glands of Stomach

Pyloric Mucin: HIK 1083, MUC6

NHSCSP Publication No 10 September 2012

Courtesy Kay Park MD
Recognized (true) HPV-negative endocervical cancers

Mucinous adenocarcinoma: minimal deviation variant

may be associated with Peutz–Jeghers syndrome
Recognized (true) HPV-negative endocervical cancers

Recognized (true) HPV-negative endocervical cancers

Mesonephric carcinoma

Maniar, K, Wei, J, Glob. libr. women's med., (ISSN: 1756-2228) 2016; DOI 10.3843/GLOWM.10230
Is Pap screening preventing HPV-negative adenocarcinomas?
Despite cytology screening programs, adenocarcinoma incidence is still rising

Adenocarcinoma incidence rates have increased in Europe:

- ~0.5% per annum in Denmark, Sweden, and Switzerland
- ≥3% per annum in Finland, Slovakia, and Slovenia

Wang et al 2004
Less than 5% of all endocervical adenocarcinomas are true HPV-negative tumors and therefore not prevented by HPV testing.

*NB Incidence of endocervical adenocarcinomas: ~ 1/100’000*

It is unclear if Pap test would detect HPV-negative adenocarcinomas and if detection is clinically meaningful.
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Does HPV-alone screening invite risk into women's lives?
HPV testing alone is nearly as sensitive as HPV & Pap

CIN2+

<table>
<thead>
<tr>
<th>Study</th>
<th>HPV alone best</th>
<th>HPV &amp; cytology best</th>
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</thead>
<tbody>
<tr>
<td>Ronco, 2006</td>
<td>1.03 (0.74, 1.42)</td>
<td></td>
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<tr>
<td>Mayrand, 2007</td>
<td>1.05 (0.57, 1.93)</td>
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<tr>
<td>Kitchener, 2009</td>
<td>1.07 (0.94, 1.22)</td>
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<tr>
<td>Naucler, 2007</td>
<td>1.06 (0.81, 1.37)</td>
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<tr>
<td>Rijkaart, 2012</td>
<td>1.06 (0.89, 1.26)</td>
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</tbody>
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Overall (95% CI) 1.06 (0.97, 1.16)

Arbyn et al., Vaccine 2012
CIN3+ Risk Following a Negative Test

Joint European Cohort Study
(24’000 women -various age ranges)

Dillner et al. BMJ 2008
3-year adjusted cumulative incidence of CIN 3+ in women ≥25 years stratified by baseline screening test result.*

Maaike G Dijkstra et al, 2016

14 year follow-up of a population based randomised cohort from the POBASCAM randomised trial

doi: 10.1136/bmj.i4924 | BMJ 2016;355:i4924
Cumulative risks of cancer among women aged 30-64 at Kaiser Permanente Northern California by enrollment Pap and HPV test result, 2003-2012.

Adapted from Gage, JC et al. JNCI 2014.
“The risks following an HPV-negative and cotest negative test are definitely lower than those following a negative Pap test. Adding a Pap test to hrHPV testing (cotesting) confers only a very slight marginal gain (0.003 %) in reassurance against cancer (lower cancer risk).”

Adapted from Gage, JC et al. JNCI 2014
Complexity of guidelines and expensiveness are the enemies of participation in screening programs
PAP negative
HPV positive
PAP > ASC-US

Any HPV result
PAP  ASC-US
HPV positive
PAP  ASC-US
HPV negative

PAP negative
HPV negative

Repeat BOTH Cytology and HPV DNA test at 12 months

HPV genotyping 16/18

HPV 16/18 negative
(Other HR positive)

PAP ASC-US
HPV negative

PAP ASC-US
HPV positive

PAP > ASC-US
Any HPV result

PAP negative
HPV negative

Colposcopy
Screening
at 5 yrs

Colposcopy
Screening
at 3-5 yrs

Colposcopy

Manage as above
for PAP ASC-US or >ASC-US

With Genotyping HPV 16 & 18

Screening
at 3-5 yrs

Manage as above
for PAP ASC-US or >ASC-US

Screening
at 5 yrs

Colposcopy

HPV 16/18 positive

Repeat BOTH Cytology and HPV DNA test at 12 months

Both negative

PAP negative
HPV positive

PAP abnormal
Any HPV result

EXPENSIVENESS and ALGORITHMIC COMPLEXITY OF COTESTING
HR HPV DNA TESTING
Women 30-65 yrs

- positive
  - HPV 16 or 18 positive
  - HPV 16 and 18 negative (other HR positive)
    - ≥ASC-US
      - Colposcopy
    - Negative
      - CYTOLOGY
  - 3 to 5 years follow-up

- negative
CONCLUSION

- hrHPV DNA testing like other cancer screening tests cannot detect all cases of prevalent or incipient cervical cancer.
- Most missed cases are a small subset of adenocarcinomas that are not linked to HPV.
- The evidence base demonstrated that a validated hrHPV test is sufficiently accurate for clinical use and could reduce the complexities of interpretation and management of co-test results as well as resource expenditure inherent in screening with two tests.
Thank you very much for your attention!