Impact of the Introduction of HPV/Cytological Co-Testing on the Detection of High-Grade Cervical Dysplasia (CIN II+) in Women Aged 35 and Older: A Study from two German Colposcopy Units

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Background

- Cervical cancer remains a major global health burden, despite screening and vaccination strategies [6]
- Persistent infection with high-risk HPV is the central cause of cervical carcinogenesis [5]

In 2020, Germany restructured its national screening program:
- **Women ≥35 years: HPV + Cytology co-testing (every 3 years)** [1]
- Women <35: cytology-based screening only (every year)

Previously:
- Screening was cytology-based and opportunistic [4]
- HPV testing used only after abnormal cytology
- Cytology alone is often observer subjective and has limited sensitivity[2]

Rationale for HPV integration:
- Higher sensitivity for detecting CIN II+ lesions
- Enables earlier detection and longer screening intervals[3]

Clinical challenge:
- Increased sensitivity may come at the cost of:
  - Overdiagnosis
  - Unnecessary colposcopies

Methodology

Study Design & Setting
- Retrospective multicenter cohort study (two certified colposcopy wards (Munich & Erlangen)
- **Study Period**: **Jan 2020 – Dec 2024**
- **Real world implementation** of Germany's updated screening program

Study Population
- n = 5,413 women referred for colposcopy after abnormal screening results
- Stratified by screening-relevant age groups to filter for our main group of interest: **≥35 year olds (received HPV/cytology simultaneous co-testing)**
  - n = 4,570

Inclusion & Exclusion
- **Inclusion:**
  - Participation in national screening program
  - Received an abnormal Co-test result
- **Exclusion**
  - Missing/unclear histological result
  - Incomplete follow-up data
- **Final n = 3,839**

Colposcopy & Procedure
- **Colposcopy procedure:**
  - Visual inspection using **acetic acid and iodine staining**
  - **Targeted punch biopsies** of suspicious lesions
- **Additional diagnostics:**
  - Cytology at time of colposcopy
  - **Liquid-based cytology (LBC) (immunohistochemical analysis** (Ki-67, L1 capsid protein)
  - **HPV test** where indicated, including subtype differentiation (HPV16, HPV18, others)

Histology
- **Histological assessment from:**
  - **Punch biopsies** (colposcopy-directed)
  - **LEEP/LOOP (conization)** where indicated

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Results

Figure 1: Histological Outcomes
- **Key Take-Away:** High Frequency of clinically relevant Biopsies found in colposcopy/conization (CIN II+, which include CIN II, CIN III, Adenocarcinoma in Situ, Adenocarcinoma, Squamous Cell Carcinoma).

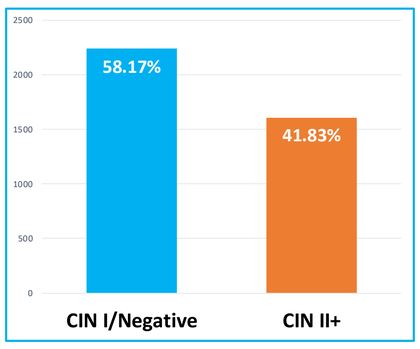


Figure 2: Cytological Group Frequencies (Referral Cytology from Co-test)
- **Key Take-Away:** Higher frequency of of Low-grade cytological results referred for colposcopy(blue), vs high grade cytologies (orange). Unclear/Borderline groups (green)

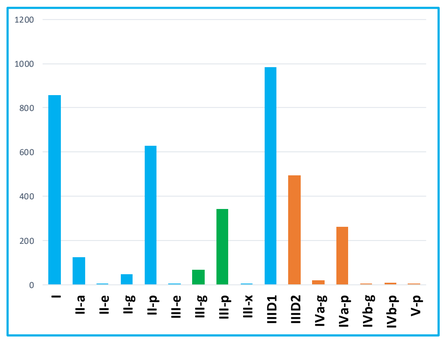


Figure 3:

Frequency of Cytological Groups in Referral with CIN II+ Results in Colposcopy/Conization (All HPV positive)
- **Key Take-Away:** A substantial proportion of CIN II+ lesions occurred in patients with low-grade or unclear cytology; 1069 of the 1606 CIN II+ cases (66.56%) fell into these categories

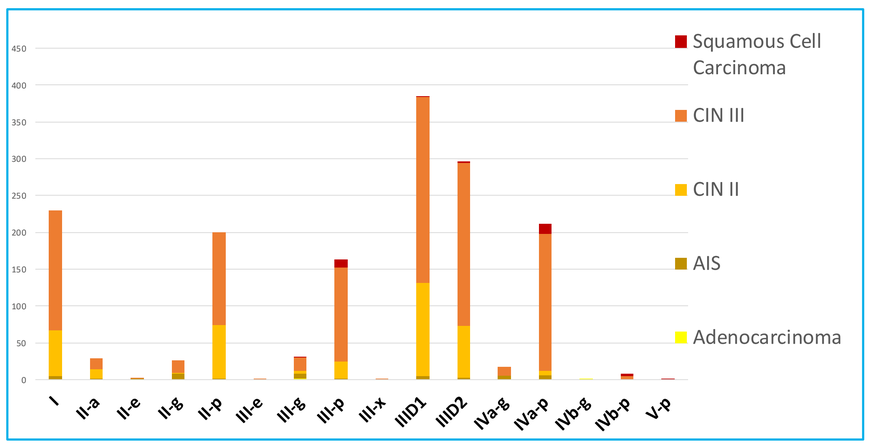
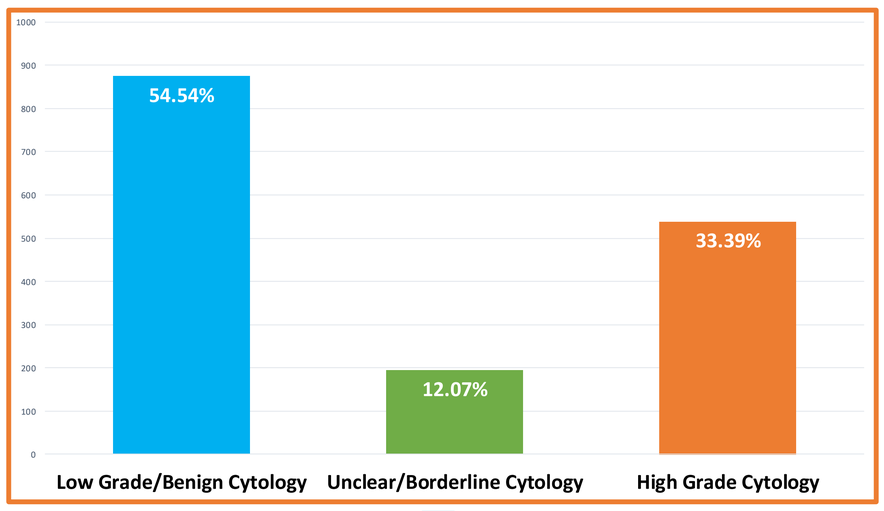


Figure 4 (Main Finding):

Breakdown of High Grade vs Low Grade/Borderline Cytological Results in Referral for CIN II+ Results in Colposcopy/Conization (All HPV positive)
- **Key Take-Away:** Most CIN II+ lesions were **not** associated with high-grade cytology, but in fact occurred in low-grade and unclear groups



66.61% of all HPV positive CIN II+ were referred with low grade/benign/unclear cytological groups in screening

Discussion

HPV Co-Testing Increases Sensitivity

Detection of CIN II+ is strongly associated with HPV positivity. While 74.7% of all referred women were HPV-positive, this rose to **98–99% among CIN II+ cases**, underscoring the central role of HPV in cervical carcinogenesis.

Clinically relevant lesions occur in low-risk cytology

The majority of CIN II+ lesions were **not associated with high-grade cytology**, but occurred in patients with **low-grade or unclear findings (66.6%)**. This underscores the difficulties with cytology based screening, as the sensitivity is limited.

Impact of Co-Testing

Integrating HPV testing into primary screening enables **earlier detection** and **shortens colposcopy referral intervals**, supporting its role as a more sensitive screening strategy, with cytology serving as a triage tool.

Clinical Trade-Off

Increased sensitivity may lead to **overdiagnosis and higher referral rates**, resulting in greater diagnostic burden and potential patient harm. It should be noted that patiens were excluded from the final patient collective, in part due to no biopsy having been taken, which was the case for some non-susipciious lesions. As such, a proportion of likely negative histological results are not included in the study, strengthening the possibility of HPV testing contributing to possible overdiagnosis.

Limitations

This study is based on a preselected, colposcopy-referred cohort with a high prevalence of HPV positivity, limiting generalizability to the broader screening population. The retrospective design precludes direct comparison with the previous screening algorithm. Additionally, biopsy decisions, although performed by experienced clinicians, may be partially operator-dependent.

Conclusion

HPV/Pap co-testing substantially improves the detection of CIN II+ lesions, particularly in women with low-grade cytology, where most clinically relevant disease would otherwise remain undetected. While this increases screening sensitivity, it may also lead to higher diagnostic burden, highlighting the need for optimized triage strategies.

References

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