Utility of gene methylation analysis, cytological examination, and HPV-16/18 genotyping in triage of high-risk human papilloma virus-positive women

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Cervical Cancer in China

• In China, cervical cancer remains the seventh-leading cause of death from cancer among females and there were almost 62,000 new cases and 30,000 deaths due to cervical cancer in 2012 (Stewart BW, 2014).

• In certain developed cities, such as Beijing and Shanghai, the incidence of cervical cancer has dropped significantly owing to the wide promotion of cervical cancer prevention information and opportunistic screening in hospitals.

• In urban areas of China, awareness of cervical cancer screening is still deficient.
Current Situation of Cervical Cancer in China

- The huge number of hrHPV(+) patients referred for colposcopic examination.
- Not enough expert cytologists for daily screening.
- High numbers of non-HPV16/18 high risk+ ASCUS patients.
- New biomarkers expected for the hrHPV(+) triage.

NEW BIOMARKERS
What is Methylation?

**NORMAL**

- **ENHANCER**
- **PROMOTER**
- **GENE**

- mRNA

  • Regulation cell growth
  • Repair DNA
  • Cell death

**CANCER**

- **PROMOTER**

  • Methylation

**SILENCE**

- Silencer break down
  - • Uncontrolled cell growth
  - • Resistance to cell death

- Chromosome
- Histone
- Histone tails
- DNA
Methylated PAX1 Gene is the Biomarker for Cervical Cancer
The Interim Clinical Guidance for Cervical Cancer in 2015

- (Primary screening for hrHPV
- HPV16/18+ for colposcopy
- HPV high risk+ and HPV16/18- go for Cytology
- Cytology results >=ASCUS go for colposcopy
- Normal cytology results follow-up at 12 months
Aim

- Propose a new strategy to effectively manage hrHPV(+) : Interim Clinical Guidance.
- Reduce colposcopic examination referred rate.
- Reduce unnecessary anxiety in hrHPV(+) women.
Study and Analysis

- CYTOLOGY
- HPV31/33
- HPV31/33/52/58
- Methylated PAX1/ZNF582

Paired box 1 (PAX1) & zinc finger protein 582 (ZNF582) were studied and published in Taiwan & Xiangya Hospital groups.
Characteristics of subjects and colposcopic biopsy results

hrHPV(+) n=312

34% ≥ CIN3 undetected by HPV16/18(+)

HPV16/18(+) n=139

Colposcopy

HPV16/18(-) n=173

STUDY
- Cytology
- HPV31/33
- HPV31/33/52/58
- PAX1/ZNF582

Normal n=19
CIN1 n=5
CIN2 n=12
CIN3 n=36
CIS n=11
SCC/AC n=56

Normal n=81
CIN1 n=13
CIN2 n=27
CIN3 n=35
CIS n=4
SCC/AC n=13
The positive percentage of different individual or combined tests in the pathologic categories

- Pap smears had very high positive rates in each category.
- HPV 31/33 showed a lower (~30%) positive rate for CIN3+.
- HPV-52/58 was ~50-60% positive rate for CIN3+ but still high percentage in ≤CIN2.
- HPV-31/33/52/58 genotype was associated with an 84.6% positive rate for CIN3+ but still high percentage (~60%) in ≤CIN2.
- Methylated PAX1/ZNF582 achieved 100% positivity for histology results indicating cancer with lower percentage in ≤CIN2 than others.
Conclusion and Suggestion

Proposed cervical cancer screening strategy using the hrHPV assay as primary screening tool and testing for HPV-16/18 and methylation of PAX1/ZNF582 as reflex triage tests.
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Thank you for your attention

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