



**Cochrane Gynaecological
Cancer Review Group**

Subgroup Cervical Cancer Prevention

**Organization: Dr. Marc Arbyn, Belgian Cancer Centre, Brussels, Belgium
Thursday, May 14, 2009, 12:30–15:00, room Gripen, Malmö Exhibition &
Convention Center, Malmö.**

http://www.malmomassan.se/public/english/anlaggningen/eng_oversikt_anlaggning.html

Fourth Cochrane Workshop on Systematic Reviews on Prevention of
Cervical Cancer, Malmö, May 14, 2009

Background:

Clinicians and decision makers need regularly updated reviews, given the continuously increasing amount of new information on innovative cervical cancer prevention methods. Nowadays, this is certainly the case, since we are in an era where primary prevention of cervical cancer by vaccinating against human papillomaviruses became a realistic option. Systematic reviews and meta-analyses allow synthesizing our current knowledge on a particular new method compared with a conventional one. Health technology assessment often precedes decisions on application or reimbursement of new technologies. However, authors of meta-analyses often come to discordant conclusions and this confuses the clinicians and stakeholders. Therefore, it looks useful to bring experts from different professional backgrounds with particular interest in synthesizing the current knowledge of cervical cancer prevention methods together, in order to identify priorities for new reviews and to improve methods and quality of future reviews. The Cochrane Colloquium represents the most appropriate environment to realize this objective.

A First Cochrane Workshop on Systematic Reviews on Prevention of Cervical Cancer was organized in 2006, at the 14th Cochrane Colloquium, held in Dublin, Ireland (October 25th). At this meeting, it was agreed that a subgroup - dedicated to cervical cancer prevention - should be set up and integrated within the existing Gynaecological Cancer Cochrane Review Collaboration (Bath, UK, <http://www.cochrane-gyncan.org/>).

A Second Cochrane Workshop on Systematic Reviews on Prevention of Cervical Cancer was held on Nov 7, 2007, at the occasion of the 24th International Papillomavirus Conference in Beijing, China. At the Beijing Workshop, it was unanimously agreed to set up an international team of experts in systematic reviews, involving the principal investigators of the main trials, to meta-analyze data from all randomized and major non-randomized studies comparing cytology with HPV-based primary screening. Besides HPV-based primary screening, other topics of cervical cancer prevention proposed to be developed or updated in future meta-analyses are: alternative cytology-based cervical

cancer screening (liquid-based and automated cytology); triage of minor cytological lesions; follow-up after treatment of high-grade cervical neoplasia; cervical cancer screening in developing countries; clinical applications of detection of over-expressed p16, a cyclin-dependent kinase inhibitor; detection of transcripts (mRNA) of HPV genes; and last but not least, prophylactic vaccination against HPV associated disease.

A Third Cochrane Workshop on Systematic Reviews on Prevention of Cervical Cancer was organised at the occasion of the 16th Cochrane Colloquium in Freiburg, Germany, on Oct 4, 2008. At this meeting, diagnostic studies to be included in Cochrane reviews were discussed. Diagnostic studies, deviating from the standard “STARD” guidelines, such as randomised controlled trials or cross-sectional studies with incomplete verification with a gold standard, could be considered for inclusion in a diagnostic Cochrane Review, in the future. Neither absolute sensitivity nor absolute specificity can be derived from these incomplete studies, unless a random sample of screen test negative subjects is submitted to gold standard verification. However, relative sensitivity and relative positive predictive values are outcomes from such incomplete studies, which do not suffer from verification bias. Another topic of discussion concerned improved gold standards, which are needed, given the poor accuracy of the conventional colposcopy targeted biopsy.

Objectives:

- To bring experts together who are involved in systematic reviews of studies on:
 - evaluation of new methods used in screening, triage and management of screen positives (liquid based cytology, automated screening, HPV DNA and RNA detection, spectroscopy);
 - treatment of cervical cancer precursors, follow-up after treatment, adverse effects of treatment;
 - prevention of cervical cancer in developing countries;
 - HPV vaccination (prophylactic, therapeutic);
 - participation of the target population.
- To present and discuss recent systematic reviews and meta-analyses.
- To define priorities for future meta-analytical work.
- To train young scientists in methods of systematic reviews and meta-analysis.
- To assist in the development of statistical methods and study design, quality of reporting.
- To spread guidelines for good practice and quality of design, conduct and reporting of studies and pooling of the results of these studies:
 - CONSORT guidelines: reporting of randomized trials (Moher, JAMA 2001);
 - QUORUM guideline: pooling of randomized trials (Moher, Lancet, 1999);
 - MOOSE guideline: pooling of observational studies (Stroup, JAMA 2000);
 - STARD guideline: reporting of diagnostic studies (Bossuyt, BMJ 2003);
 - QUADAS guideline: assessment of quality of diagnostic studies (Whiting, BMC Med Res Methodol 2003);

- STROBE guidelines: reporting of observational studies (von Elm, BMJ 2007).
- To debate on how to develop further this special subgroup within the current Gynaecological Cancer Cochrane Review Collaboration.

Experts, present at the first Workshop identified that two priority topics require urgent meta-analytical work:

- Primary screening for cervical cancer precursors using hrHPV testing, cytology or both.
- Prophylactic vaccination with HPV type-specific VLPs containing L1 protein (immunogenicity, protection against incident, persistent infection, cytological and histological cervical lesions, other HPV related disease, stratified age, HPV type (vaccine and other types), duration of follow-up).

Other important identified issues are: triage of HPV-positive women who are cytologically negative; triage of low-grade intra-epithelial lesions; clinical utility of HPV genotyping (DNA, RNA) and molecular markers; variation of sensitivity and specificity of screening and triage options by age; evaluation of protective effect of screening using population-based case-control studies including linkage with screening and cancer registries and cervical cytology biobanks.

Provisional Programme of the Malmö Workshop

1. Welcome and introduction: *J. Dillner & T. Broker* (12:30-12:40)
2. Performance of cervical cancer screening methods: a logic framework for evidence assessment: *M. Arbyn* (12:40-12:55)
3. How to improve the accuracy of the gold standard to ascertain presence of cervical cancer precursors?: *N. Wentzensen* (12:55-13:10)
4. Primary HPV-based screening: how to triage HPV positive women?
 - A: with cytology: *J. Cuzick* (13:10-13:25)
 - B: with p16: *G. Ronco* (13:25-13:40)
 - C: with repeat HPV testing: *J. Koshiol* (13:40-13:55)
 - D: comparison of several options: *P. Naucler* (13:55-14:05)
5. Study designs needed to assess the factors that determine obstetrical outcomes after treatment of CIN: *M. Kyrgiou* (14:05-14:20)
6. Discussion: *M. Steben & E. Paraskevaidis* (14:20-14:50)
7. Conclusion: *M. Arbyn* (14:50-15:00)

Chairmen: M. Steben & E. Paraskevaidis

Reporters: C. Simoens & I. Tsoumpou

M. Arbyn