Reviewer’s report

Title: Annual Papanicolaou screening for 5 years among human papillomavirus-negative women

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Reviewer: Marc Arbyn

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GENERAL COMMENTS
The authors have followed a cohort of women with double negative screening result (normal cytology and negative HC2 test for hrHPV) over about 5 years who were recommend to have a yearly Pap test. A representative control subgroup was chosen for testing with colposcopy, cytology and HPV at the end of the follow-up period. No cervical cancer or precursor lesions (CIN2+) were identified, indicating that the screening can be extended safely for five years. Moreover, extending the interval to 5 years will decrease low-grade cytology results which do not correspond to cervical precancer (CIN2+). Probably, HPV-testing will soon become the standard cervical cancer screening method in several industrialised countries. The reported findings are relevant for expected future policies of HPV-based screening in Germany and elsewhere in Europe.

SPECIFIC COMMENTS

ABSTRACT
1. Objective
Change “efficient” by “effective”

INTRODUCTION
2. Change “efficient” by “effective”

3. European guidelines discourage screening intervals <3 years. Make clear that these EU guidelines concern cytology-based screening.

MATERIALS AND METHODS
4. Study population:
The authors should mention whether an upper age limit was defined for enrollment;

Screening tests.
5. The authors mention where cytology interpretation was performed but not where HPV was done.

Cytological diagnoses.
6. It is recommended to explain here the equivalent Bethesda cytology terminology for the German cytological categories. For the rest of the paper, the authors should use only the Bethesda terminology. It is not necessary to use other terms derived from British cytology classification (borderline or mild). Use of just ASC-US or LSIL facilitates understanding (as recommended in EU guidelines (Herbert et al Cytopathol 2007).

Follow-up protocol

7. Selection of every 7th women clearly is NOT random. The authors could write: a “representative” subgroup of women with double-neg tests (every seventh participant) was invited...

8. Page 8, just before topic statistics.
The aim… determine the “proportion of women with abnormal cytology, the incidence of HR-HPV infection”, ....

9. In the result section, the authors present proportions having developed lesions (=cum incidence) but do not present incidences (=events per person years). Therefore, it is better to write: “the proportion of women developing abnormal cytology and the proportion with hrHPV infection at the end of the study”

10. Statistics
…to estimate reliably … To estimate “with sufficient precision” is more correct.

RESULTS
11. As mentioned earlier, it is recommended to use only equivalent Bethesda terminology to allow non-German readers to understand the cytological categories.

12. Page 9 line 2: Change “consistent” increase into “continuous” increase.

13. …“the incidence of a positive smear of LSIL or more (Table 1).”
“The cumulative proportion developing a LSIL or worse lesion (Table 1)” is more correct.
Change also “incidence” into “proportion developing” in the title of Table 1.

14. Given the very unstable cum incidence near the end of the observations (small population still under follow-up with one event having a huge impact at 68 months) it is better to truncate before: for instance at 60 or 66 months.

15. The age of the 3 hysterectomised women could be noted;

Proportion of abnormal Pap smears, HPV, and CIN at months 60–68

16. Mentioning % after each absolute number would facilitate reading.
FIGURES
17. Fig 1. Truncate at 66 months to diminish instability at the right end.
18. Fig 2. Delete the word “random”.
19. TABLE 1: “proportion developing” a positive smear is better than “incidence” of a positive smear.

COMMENT
20. Fist § We conclude … detection of all clinically relevant lesions….
   It is better to drop “all”, since follow-up was not complete.
21. In the same sentence: “…incidence of true hg lesions is low” Add “among women with double negative cotest (cytology & HPV) at baseline”
22. Page 10. Procedure related morbidity. The authors could refer to potential adverse obstetrical adverse effects (see Kyrgiou Lancet 2006 and Arbyn BMJ 2008.)

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests' regarding tests discussed in this manuscript