Reviewer's report

Title: Difference in overall and age-specific prevalence of human papillomavirus infection in Italy: evidence from NTCC trial

Version: 2 Date: 14 August 2012

Reviewer: BEIBEI LU

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The authors assessed differences in age trends of oncogenic HPV prevalence across nine regions of Italy using a well chosen statistical method. The study contributes important regional age-specific HPV prevalence information.

Major revision

1. The statement in the background, “…the impossibility of simply inferring the natural history of HPV from age distribution and…”, is somewhat out of place as providing inference on HPV natural history is not the focus of the study. Please consider removing the statement.

2. A briefly statement with respect to the following in page 5 first paragraph will be necessary to describe the study population: (1) study design of the NTCC study (randomized controlled trial?) and its endpoints/main objectives; (2) the source of study population – the type of institutions from which the participants were recruited.

3. Hybrid Capture 2 (HC2) assays was used to detect 13 oncogenic HPV types in the current study. Please provide the definition of a valid HC2 test (page 6 first paragraph). I would also like for the authors to consider the potential impact of undetected non-oncogenic HPV types on the overall age-specific HPV prevalence in the current study and discuss how it may affect the comparability of findings between the current study and previous studies.

4. The authors raised an interesting discussion to explain the higher HPV prevalence observed among young-to-middle-aged women in Northern Italy in page 8 second paragraph. The authors appeared to suggest (1) the increasing delay in age at first marriage could result in more sexual promiscuity before marriage and thus increased HPV exposures; (2) the birth cohort effect was mainly due to sexual behavioral changes in younger birth cohorts, for instance, earlier initiation of sexual activity. If so, the relationships need to be clarified in the text.

5. The authors suggested in page 8 last paragraph that the steeper decline in HPV prevalence reported by the study conducted in Central and Southern Italy compared to the findings of the current study was likely due to more recent change in sexual behaviors among youngest group of women in Southern Italy. Please explain the type of sexual behavioral changes that recently took place in Southern Italy and discuss how the changes might have affected the age-specific HPV exposures.
6. The authors stated in the discussion “The largest migration to Turin from Southern and North-eastern Italy, however, had occurred in the 1960s. Almost half the women migrated to Turin from Southern Italy arrived during such period and would have not fallen in the age range eligible for the NTCC study [39].” The relevance of internal migration to possible population mixing in Turin and resulting heterogeneous HPV prevalence observed in the current study is unclear in the statements. Please clarify.

Minor essential corrections
1. Page 3, Background: Please specify the observation was made among women.
2. Page 4 second paragraph line 4: it should be “…cohort studies suggesting that…”; Line 8: “by” should be removed.
3. Page 6 second paragraph: I believe the R package used for this analysis is “ljr” not “lrj”.
4. Page 6 second paragraph first sentence: “Age trends for the prevalence of 13 oncogenic HPV types were assessed for each recruitment centre using a logistic joinpoint regression analysis.”

Suggested changes
1. Page 5 second paragraph line 6: “Seventy-four percent of eligible women consented to the study and were randomized.”
2. Page 5 third paragraph second sentence: “The Hybrid Capture 2 (HC2) hybridization assay (Qiagen, Hilden, Germany) targeting HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68, was used to determine HPV presence with a cut point of 1 relative light unit (RLU) for HPV positivity, as recommended by the manufacturer.”
3. Page 6 first paragraph second sentence: “HPV prevalence was standardized to the 2004 Italian female population aged 25-60 years.”
4. Page 6 last paragraph last sentence: “…and studied differences between centres as suggested by the intercepts and the slopes.”
5. Page 7 third paragraph first sentence: “No significant join-points were observed in six of the nine centres…”; last sentence: “While HPV prevalence showed a steeper decline with age in Bologna, Florence and Imola than in Trento, Verona and Viterbo…, the test for heterogeneity of age slopes did not reach statistical significance (p=0.08).”
6. Page 7 fourth paragraph line 2: “In Ravenna HPV prevalence decreased linearly until 45 years of age and reached a plateau thereafter, with a slightly higher prevalence observed in the oldest women. In Turin two significant join-points were observed: HPV prevalence remained high up to age 30 years, decreased steeply between age 30 and 38 and maintained a very slow decline after age 38. In Padua, HPV prevalence showed a very slow decline between age 25 and 39, with a higher prevalence for women aged 35-39 than in any other centre (14.1% vs. 9.5% on average), and subsequently had a steep downturn with the lowest prevalence observed in the oldest age groups.”
7. Page 8 first paragraph: “…with the highest age-standardized prevalence in Ravenna (close to a touristic sea resort area) nearly double the lowest prevalence in Trento…”

8. Page 8 second paragraph line 2: “…, notable age patterns were observed in three regions (Ravenna, Turin and Padua).”

9. Page 8 second paragraph last sentence: “The center in Ravenna had the highest overall HPV prevalence with a second peak in prevalence detected above age 45, …”

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no financial or non-financial competing interests.