Reviewer’s report

Title: Association between invasive cancer of the cervix and HIV-1 infection in Tanzania: the need for dual screening

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Reviewer: Stephen E Hawes

Reviewer’s report:

This paper is generally well-written and attempts to explore the relationship between HIV infection and cervical cancer, an important issue, especially in sub-Saharan Africa. The study design appears sound. However, as in any observational epidemiologic study, the main limitations of this study have to do with potential confounding. The crude OR for HIV-1 as it is associated with cervical cancer was 2.0, while in the final multivariable model, the adjusted OR for HIV-1 ended up at 7.0, so clearly, confounding was a big issue in this study. In the abstract, the authors state that confounding and interaction were assessed with logistic regression; however, in the methods section, it appears that a backward elimination model was used to come up with a final model, with no apparent assessment of confounding. The discussion does not address the reasons why such an important change in the risk estimate was observed. From what I read, no assessment of confounding or interaction was actually performed.

The other important limitation has to do with the discussion, especially with regards to accuracy. In many places, the discussion mixes the literature regarding factors associated with low or high grade neoplasia and those where cancer was studied. This distinction is extremely important, and needs to be clarified, especially when reviewing the literature regarding HIV and cervical cancer.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1 â## Introduction - The statement that â##40% to 50% of women in developed countries are screenedâ#¹ needs a reference or references. Additionally, this range is too narrow and too low, as in some Scandinavian countries, the percentage screened is in the range of 70-85% with Luxemburg at 93%. In the US, it is estimated that 93% of women have had a pap in their lifetime, and 80% have had a pap in the last 3 years, with over 50% getting yearly paps. See Sirovich, 2004; Breen 2001; Antilla 2004 for details.

2 â## Introduction - The information in the last paragraph needs clarification. First, many of the articles cited as assessing the relationship between HIV and cervical cancer (Didelot-Rousseau, La Ruche, Mayaud, and Chirenje) did not study cancer, but instead studied preinvasive conditions such as SIL. This important distinction needs to be made clear. Nearly all of the studies regarding
HIV and SIL have shown an association. However, the relationship between HIV and invasive cervical cancer is less known.

3 Introduction - The statement, the prevention and control of cervical cancer is parallel to that of HIV, needs explanation. What does this mean? - perhaps that rates of cervical cancer and HIV are associated with each other (see ecologic study by Drain, 2002). Perhaps what is meant is that screening of cervical cancer and HIV can be done together.

4 Methods - No mention of cervical cytology in the controls is noted here, although it is noted in the discussion. What was the procedure and what were the results? Were women with LSIL or HSIL included or excluded as controls?

5 Methods - With regards to the statistical methods, it is stated that ORs were assessed with logistic regression and a backwards selection method was used in the final model. What happened to evaluation of confounding and effect modification (interaction)? This is very important. The stepwise model will leave you with an inclusion of factors which are independently association with the outcome, but will not help you assess confounding in the relationship between HIV and cervical cancer. This needs to be done, especially as your point estimate ultimately moves from 2.0 to 7.0! When you have a factor specially of interest (such as HIV in this case), the analysis should focus on coming up with the best estimate for this relationship, after adjustment for other factors. Instead, you have performed a shotgun approach utilizing a model/factor selection method where all factors are considered equal, and where confounding/effect modification are not assessed.

6 Results/Tables Why were all factors dichotomized in the analysis? Age, for example, was grouped as 25-48 and 49+, while parity was grouped as 1-4 and 5+. First, how were these cutoffs chosen? Second, why were either continuous or multiple groups not considered? If these factors are being considered as risk factors, then it would be best to consider them in other groups, perhaps with age by 10 year age. If they are to be considered as confounders, then residual confounding may be present if these are not more finely assessed.

7 Results/Tables Further, with regards to age, in the text, it is stated that 55% were in the age group 41-60, but a different age grouping (age 25-48) is used in analysis. These groupings should be consistent.

8 In the results section, it is stated that A significant majority of the women with cervical cancer had ever smoked compared to the controls. You appear to have confused the concepts of significance and majority. According to Table 2, only 7.2% of cases and 1.5% of controls ever smoked, so this is clearly not a majority. A better sentence might be Women with cervical cancer were more likely to have reported ever smoking compared to the controls (p=0.03, Table 2).

9 Results/Tables In your final analysis, you have come up with a model of factors that were independently associated with cancer of the cervix.
However, your stated aim is to determine the association between cancer of the cervix and HIV (from the abstract). A more appropriate analysis would have been to include HIV in the logistic regression model and then assess the other factors as potential confounders and/or effect modifiers. The other factors (such as age, education, etc.) should be considered as continuous, dichotomous, and grouped and assessed individually and together to see how they effect the risk estimate for HIV. Clearly they do so greatly, as the crude estimate (OR=2.0) changes dramatically with adjustment for the other factors (OR=7.0 in multivariate analysis).

10 Discussion - As discussed above, you mention that 20% of the controls were not screened. This implies that most were screened. What were the findings? Did you include women with cytologic evidence of preinvasive disease? This should be noted in the methods and/or results.

11 Discussion - HPV as a confounder. This gets a bit tricky. In studies of invasive cervical cancer, it is now generally accepted and assumed that nearly 100% of the cases will be HPV+. However, current evidence would suggest that HPV is a cause of cervical cancer, not a risk factor, and as a cause, HPV can not generally be adjusted for in epidemiologic studies (since all are positive). One way around this would be to stratify by HPV status (that is, include only HPV+ controls). However, as HPV is associated with HIV infection, that may result in an underestimate of the risk.


13 Discussion of HIV as a confounder in the relationship between HPV and cervical cancer. This paragraph has some misinformation in it and needs to be rewritten. The adjusted OR in the association between HIV and HRHPV was 7.0, not 17.0 as stated in the discussion. The 17.0 states was the adjusted OR for HIV as a risk factor. However, as noted above, this was a study of HSIL, not invasive cancer. Further, in no place in the article did the authors of the Didelot-Rousseau present an OR of 5.0 for the relationship between HIV infection and SIL among HPV negative women. In looking over the numbers (Table 2), it would appear that 2 of 16 HPV- HIV+ women, and 7 of 102 HPV- HIV- women had LSIL (non with HSIL), for an OR=1.9, p=0.4 (not significant). Few, if any, studies have shown that HIV is a risk factor for SIL or cancer in the absence of HPV. You incorrectly state that they did not show data to allow evaluation of HIV-1 as a potential effect modifier in the HPV-SIL relationship. However, that is the subject of Table 2, which clearly shows that HIV is associated with an increased risk of SIL in the presence of HPV, as 15.7% of HIV- but 53.6% of HIV+ women with HPV had SIL.

14 Discussion - The authors suggest the screening for cervical cancer in Tanzania. However, there is no discussion of the costs of implementing a
cervical screening program, or the type of program that should be considered. Cytology? HPV testing? Visual screening? Is there infrastructure for any of these in place in Tanzania? Would it be cost-effective? These need to be discussed.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

15 â## Abstract - The results section mentions a â##separateâ## logistic regression. Itâ##s unclear what this means. Do you mean â##multivariableâ##?

16 â## Introduction - The statement that â##Cervical cancer is completely preventableâ## is not true. This statement should be rewritten to suggest that the majority of cervical cancer cases can be prevented by screening. A number of women who are appropriately screened still develop cervical cancer.

17 â## Introduction - The Chirenje article referenced also includes Southern Africa (p3).

18 â## Introduction - An apparent reference regarding risk factors for cervical cancer has not been added to the bottom of p3.

19 â## Methods - It is stated that the controls were â##without cancerâ##. Is this any cancer or just without cervical cancer?

20 - Results/Tables â## Throughout the paper, the precision of your percentages and risk estimates varies. Please keep them consistent. Might I suggest one digit for the percentages (63.0%, not 63% in Table 1), and also one digit for the odds ratios (2.0, not 2.03 in Table 2).

21 â## In Table 1, all percentages should be column percentages. The information for Residence has row percentages.

22 - Results/Tables â## Among the cases, 21.0% (not 21%)â#¦. (in order to keep precision similar throughout the paper)

23 â## Tables 2 and 3. Please use a similar level of precision for your odds ratios throughout (OR=2.0 for one factor, OR=2.03 for another). Also, use the same precision for the estimate and the confidence interval.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

24 â## Abstract - While the information regarding the ages of the cancers in HIV-infected and uninfected subjects is of interest, the subsequent information regarding the age of the HIV-infected and uninfected subjects without cancer is not. This should be deleted.

25 â## Conclusions. These seem fine, except I donâ##t think I would emphasize the smoking issue, as in your study, only 12 (4%) of 276 were smokers.

26 â## Methods - Sample size and power calculations. These are generally not necessary in a report, especially if they are post-hoc. These appear to be
post-hoc, since the HIV rate in those with cervical cancer was 21% (exactly that observed in your study), even though this is labeled as an ``estimate``. I would recommend the entire paragraph be deleted.

27 - Results/Tables With regards to education, a p-value (from an overall chi-square test?) is listed as 0.01 for the four categories (a test of trend would be better, as this is ordinal data), while in the text, a dichotomy with regards to lack of formal education (p=0.003) is listed. Again, if a test for trend is conducted, then a general statement of ``Cases were less educated than controls (p=0.xx)`` could be utilized, instead of necessitating you choosing a single category for the comparison.

28 - Results/Tables It is stated that age of first coitus was not associated with cervical cancer. This information is interesting but is not shown in Table 1 or 2. Please add.

29 Discussion - The second sentence of the discussion regarding the validity of the association, written as a question, should be reworded or deleted.

30 With regards to cervical cancer and HIV, it is stated that both are ``completely preventable diseases``. However, this is quite overstated. In sexually active women, neither is completely preventable. However, screening may indeed prevent most cervical cancer cases.

31 - Discussion - With regards to education (p13), the link between increasing literacy and preventing cervical cancer is not particularly direct. Education in general (especially with regards to health education regarding the need for screening and ways of prevention) may be more directly linked than literacy.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**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.