20-Dec-2018

Dear Miss Lei

Manuscript ID BMJ-2018-047292 entitled "Screening effectiveness of less common histological types of invasive cervical cancer: a population-based nested case-control study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that from 30 November 2018 BMJ is mandating ORCID iDs for corresponding authors for all research articles if accepted. Co-authors and reviewers are strongly encouraged to also connect their ScholarOne accounts to ORCID. We firmly believe that the increased use and integration of ORCiD iDs will be beneficial for the whole research community. For those who do not currently have an iD they will be required to register but this is free and takes a matter of seconds.

Best regards,

Daoxin Yin
dyin@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Sophie Cook (chair), Angela Wade (statistician), Elizabeth Loder, Wim Weber, Jose Merino, John Fletcher, Daoxin Yin, Tiago Villanueva
Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

It needs explanations and clarifications on the association between “screening and the risk of” other cancers. If screening doesn't or can't detect these cancers then why does screening appear to reduce the risk of developing the cancers? Do the author here mean the risk of having invasive cancer? The screening does not decrease the risk of having cancer (unless all rare cancers related to HPV and treatment of HPV eliminates the risk of cancer -but the study showed that not all RICC is associated with HPV infection) but rather decreases the risk of having advanced or invasive cancer at the time of diagnosis.

Highly invasive and aggressive cancers do not meet the criteria for screening programmes. The relevant criteria here are that the natural history should allow time for detection at an early stage and that there should be an effective treatment available that alters prognosis at the stage of detection. Table 1 shows that 88% of these cancers were not detected at screening and that's mostly because they progress so quickly that they go from nothing to nasty in the interval between screens.

It's an observational study and we know that people who attend screening also do other things that are beneficial for their health, so the apparent protective effect of screening is probably down to the other healthy behaviours of women who attend for screening and nothing to do with the screening itself. Consequently, these results don't provide strong evidence that screening prevents rare "other types" of cervical cancer.

Our statistician noted the authors could consider modelling age as a continuum.

The title might need revision to reflect the study better.

For some general readers, some terms might be confusing. For example, RICC or less-common ICC. Could author consider terming them in a clearer way and be consistent across the paper?

Could authors consider disseminating the findings to the public, patients, doctors, and allied groups as they might benefit from the study? The author may also want to thank those who made their data possible.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
There is undoubtedly a great amount of effort that went into this manuscript, and the authors should be commended for that. However, there are several points which could make this manuscript more informative:

1. This is one of the very few reports on RICC, and so I find it a missed opportunity not to include a thorough comparison with SCC and AC. This would provide the context for the results and help clarify whether and how RICC differ from the common CC types; the lack of these data in this paper is particularly regrettable as the authors do seem have access to the relevant records (see Supplementary Figure 1).
2. Today, official cancer registry data in Nordcan report 4430 cases of cervical cancer diagnosed in 2002-2011 in Sweden at ages 25-85+ (which, if I understood correctly, is approximately the age group that the authors used in the study [birth cohorts 1909-1986]). If we assume that Nordcan data are the golden standard, then Nordcan reports 176 cases more than what the authors considered to be confirmed primary ICC (N=4254). As a proportion of the total, the 176 cases represent a small minority. However, if the “missing” cases are not randomly selected and (potentially) represent RICC, then in the worst-case scenario they would represent about 50% of all the RICC studied in the paper. I expect that

the explanation for the "missing" cases is more benign, but I would welcome a report/discussion on these discrepancies.

3. The authors analysed screening participation during periods of exactly the recommended lengths of the screening intervals, 3 or 5 years. In cervical screening, it is known that women may participate in slightly longer intervals, and so many national monitoring reports evaluate participation in 0.5-1 year longer-than-recommended intervals (e.g. 3.5-4 years, and 5.5-6 years). How do the results change if this reasonable routine variability in screening intervals is considered?

4. Please explain the completeness and accuracy of the Swedish Patient Register and Longitudinal Integration Database […]. Please clarify which types of hysterectomies were excluded from the analysis. Is the proportion of women excluded because of a hysterectomy approximately the same as the prevalence of hysterectomy in the general population of the same age? What is the source data on education within the Longitudinal Integration Database […]? Were all these data linked on the individual level?

5. The risk of RICC was increased in women with at least one abnormal screening test, compared to unscreened women. Please clarify whether this was a consequence of insufficient follow-up after an abnormality.

6. Tables: data on controls should be added throughout, as should be crude IRRs – this would increase the transparency of the reporting and would help the readers follow the results.

7. Minor comment: page 6, line 43-46, please clarify whether controls were required to be alive until the date of diagnosis of the matched case or until a later date (this may be just a misunderstanding because of how the sentence is written).

8. Minor comment: page 12, lines 48-50, when the authors talk about "a smaller magnitude of risk reduction", what comparison did they have in mind?

9. Minor comment: Tables 2 and 3, although not statistically significant and based on small numbers, the IRRs for FIGO stage IA cases are oddly increased – please discuss.

Additional Questions:

Please enter your name: Matejka Rebolj

Job Title: Senior Epidemiologist

Institution: King's College London

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
I thank you for asking me to review this manuscript. No doubt this is a very interesting study. It has highlighted the importance the rare types of invasive cervical cancer especially as the incidences of the more common types are decreasing in the western countries.
HrHPV positivity was however very low in RICC compared with the common ICC and the relative distribution of the serotypes seem to be a reversal in the more common types of ICC, could this be attributed to the use of FFPE blocks?
Does the method of extraction lead to the reduced detection of hr HPV? It is important to clarify this with the increasing use of the HPV vaccine, does that mean that the vaccines will be less effective in the prevention of RICC whose relative incidence may increase because of the decreasing incidences of the more common types?

Additional Questions:
Please enter your name: Ajenifuja Kayode Olusegun

Job Title: Lecturer/Consultant

Institution: Obafemi Awolowo University /Teaching hospitals Complex

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:
This is a very good piece of research, the methods (laboratory, clinical confirmation, ascertainment of disease, statistical analysis) are well explained and applied, making the results very valid.
I only have two comments:

1) Although there might not be enough cases of adenosquamous cell carcinoma (ASC) or the other rare types (RICC), the age categories of 30 to 60 and above 60 are not intuitive, can the authors produce a table with at least three age-groups, for instance: 30-39, 40-49 and 50 over?, or better discuss the lack of power to conduct such analysis?
2) Only 12% (41 of 338 cases including 31 less than 30y) were screen-detected (Table 1) while 56% of ASC and RICC (172 of 307 cases over 30y) attended screening (Table 2), however most of them were not detected by the screening process since these types of cancers are more aggressive and progress rapidly. The main results show that there is a risk reduction of developing ASC and RICC on women who attend screening, however, most cases are symptomatic and not screen-detected, can the authors discuss this further?
Apart from these comments, I think the manuscript is very valuable for the scientific audience, and should be published.

Additional Questions:
Please enter your name: Maribel Almonte

Job Title: Head of Prevention and Implementation Group

Institution: International Agency for Research on Cancer

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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